Literature and Abstracts about Leptin & Inflammation

1: J Am Coll Cardiol 2008 Oct;52(15):1201-10

Leptin resistance a possible interface of inflammation and metabolism in obesity-related cardiovascular disease.

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Leptin is an adipocyte-derived hormone and cytokine that regulates energy balance through a wide range of functions, including several that are important to cardiovascular health. Increased circulating leptin, a marker of leptin resistance, is common in obesity and independently associated with insulin resistance and cardiovascular disease (CVD) in humans. The mechanisms of leptin resistance include genetic mutation, leptin self-regulation, limited tissue access, and cellular or circulating molecular regulation. Evidence suggests that central leptin resistance causes obesity and that obesity-induced leptin resistance injures numerous peripheral tissues, including liver, pancreas, platelets, vasculature, and myocardium. This metabolic- and inflammatory-mediated injury may result from either resistance to leptin's action in selective tissues, or excess leptin action from adiposity-associated hyperleptinemia. In this sense, the term "leptin resistance" encompasses a complex pathophysiological phenomenon. The leptin axis has functional interactions with elements of metabolism, such as insulin, and inflammation, including mediators of innate immunity, such as interleukin-6. Leptin is even purported to physically interact with C-reactive protein, resulting in leptin resistance, which is particularly intriguing, given C-reactive protein's well-studied relationship to cardiovascular disease. Given that plasma levels of leptin and inflammatory markers are correlated and also predict cardiovascular risk, it is conceivable that part of this risk may be mediated through leptin resistance-related insulin resistance, chronic inflammation, type II diabetes, hypertension, atherothrombosis, and myocardial injury. Leptin resistance and its interactions with metabolic and inflammatory factors, therefore, represent potential novel diagnostic and therapeutic targets in obesity-related cardiovascular disease.

PMID: 18926322 [found with GoPubMed]

2: Respir Med 2008 Jul;

Airway inflammation in obstructive sleep apnea: Is leptin the missing link?

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BACKGROUND: Local and systemic inflammation is implicated in the pathophysiology of Obstructive Sleep Apnea (OSA). Exhaled breath condensate (EBC) is a non-invasive sampling method for the lower airways. However, it is important to consider the potential effect of the systemic origin whereas systemic inflammation is significantly elevated. This prospective study was designed to investigate whether airway inflammation is significantly related to plasma leptin levels in OSA patients.

Simultaneously, it was designed to investigate whether inflammatory variables predict parameters expressing disease severity and finally whether smoking habit affect the above measurements. PATIENTS & METHODS: About 45 OSA patients (mean AHI 40+/-25, 28 smokers) and 25 healthy controls (AHI<5, 15 smokers) were studied and underwent overnight diagnostic polysomnography. We measured pH, 8-isoprostane, TNF-alpha and IL-6 in EBC and leptin in plasma. Plausible associations between leptin and inflammatory parameters were analyzed after adjustment for proper variables. Similar associations between inflammatory variables and parameters of disease severity were also performed. RESULTS: An increased level of leptin and respective increase of inflammatory variables was found. No significant association was observed between parameters of EBC and plasma leptin levels. A part of the parameters of disease severity is significantly associated with pH and 8-isoprostane. Smoking did not seem to be a critical confounding factor for evaluation of the above measurements. CONCLUSIONS: Increased levels of leptin were not associated with the observed airway inflammation in OSA. The observed airway inflammation seemed to be independent of smoking habit with limited association with disease severity.

PMID: 18606530 [found with GoPubMed]

3: J Ren Nutr 2008 Jul;18(4):332-7

Adipocytokines leptin and adiponectin, and measures of malnutrition-inflammation in chronic renal failure: is there a relationship?

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BACKGROUND: Serum levels of adipocytokines such as leptin and adiponectin are significantly elevated in patients with chronic renal failure (CRF). The effect of such adipocytokines on malnutrition in the CRF population has been of substantial interest. We sought to determine the relationship between plasma leptin and adiponectin levels and malnutrition-inflammation status in end-stage renal disease patients. METHODS: Thirty patients (15 women and 15 men; mean [+/-SD] age, 50 +/- 14 years) on hemodialysis, and 30 patients (12 women and 18 men; mean [+/-SD] age, 47 +/- 16) on continuous ambulatory peritoneal dialysis, were enrolled in this study. Adipocytokine levels were measured by enzyme-linked immunosorbent assay. Inflammatory markers, such as high-sensitivity serum C-reactive protein (hs-CRP), ferritin, and a nutritional inflammatory scoring system known as the malnutrition-inflammation score (MIS), were also measured in all patients. RESULTS: Serum leptin had negative correlations with ferritin (r = -0.33, P = .016) and MIS (r = -0.39, P = .003). Adiponectin had a weak positive correlation with MIS (r = 0.26, P = .050), indicating that an increased level of serum adiponectin was associated with a worse nutritional status. Levels of hs-CRP, serum albumin, cholesterol, and triglycerides did not correlate with nutritional status. CONCLUSIONS: Serum leptin concentration seems to be a marker of good nutritional status, rather than an appetite-suppressing uremic toxin, in patients with CRF. However, the positive correlation between serum adiponectin and worse nutritional-inflammatory status suggests that elevated adiponectin levels may contribute to the pathogenesis of malnutrition in such patients.

PMID: 18558297 [found with GoPubMed]

4: Cell Cycle 2008 Apr;7(12)

Leptin and mTOR: Partners in metabolism and inflammation.

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Leptin is both a hormone/cytokine that plays a major role in the regulation of feeding and energy expenditure. Beyond its central role in the hypothalamus, leptin modulates peripheral tissues' responses to growth and storage based on nutrient availability, and it regulates the innate and adaptive immune responses. mTOR (mammalian Target of Rapamycin) is a core component of intracellular signaling for cellular growth, mRNA translation, and metabolism. Here, we review recent findings on the cross talk between mTOR and leptin signaling. Important roles for mTOR on leptin signaling have been established both in hypothalamic centers to control food intake and in peripheral cells to regulate lipid metabolism and inflammation. Leptin directly activates resident macrophages to form ADRP-enriched lipid droplets and enhances eicosanoid production via a mechanism that is dependent on activation of the PI3K/mTOR pathway. Leptin-induced mTOR activation may have implications for obesity-related pathophysiological conditions such as diabetes, cardiovascular disease and cancer.

PMID: 18583936 [found with GoPubMed]

5: J Leukoc Biol 2008 Dec;

Role of leptin receptor-induced STAT3 signaling in modulation of intestinal and hepatic inflammation in mice.

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Leptin-deficient ob/ob mice are resistant to dextran sulfate sodium (DSS)-induced colitis and Con A-induced hepatitis. However, the signal transduction pathways involved have not been identified. The present study investigated the effect of leptin-induced STAT3 signaling in the DSS and Con A models. Mice carrying a leptin receptor (LEPR) gene mutant for Y1138 (s/s mice), with abrogated leptin-induced STAT3 signaling, were compared with wild-type (WT) and LEPR-deficient db/db mice. Administration of DSS to s/s mice resulted in a clinical score and colon shortening of intermediate severity compared with disease induced in WT and db/db mice-the latter group having the lowest disease severity. A comparable degree of inflammatory infiltrate and epithelial damage was observed in the colon of WT and s/s mice, and these parameters were reduced in db/db mice. Levels of IFN-gamma, IL-6, IL-10, and TNF-alpha were comparable in the colon of s/s and db/db mice, and a similar trend was observed for CXCL2. s/s and WT mice developed severe liver disease in response to Con A, whereas db/db mice were protected. However, Con A-induced serum IL-6 and TNF-alpha levels in s/s mice mimicked levels observed in db/db rather than WT mice. In conclusion, lack of leptin-induced STAT3 signaling is associated with reduced cytokine production following DSS and Con A administration, but it appears to sensitize mice to the effects of proinflammatory mediators.

PMID: 19052144 [found with GoPubMed]

6: Rheumatol Int 2008 Nov;

Serum and synovial fluid leptin levels and markers of inflammation in rheumatoid arthritis.

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This study was designed to investigate the serum and synovial fluid leptin levels, and inflammatory markers in rheumatoid arthritis (RA) patients. Serum and synovial fluid leptin levels were significantly higher ($P > 0.05$) in RA patients than control group; RA patients with moderate disease activity (DAS < 2.7) having significantly higher leptin levels ($P > 0.05$) than those with low disease activity (DAS < 2.7). Leukocytes and erythrocyte sedimentation rate (ESR) were found to be significantly higher in moderate disease activity RA group compared to low activity group ($P > 0.05$, $P < 0.001$, respectively). Serum leptin level is found to be independent of age and inflammatory markers. ESR is positively correlated with DAS activity and CRP values. Our finding of no correlation between leptin and BMI shows that regulation of leptinemia is complex, and leptin levels cannot be used to assess RA activity.

PMID: 19009296 [found with GoPubMed]

7: Br J Dermatol 2008 Jun;

Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation.

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Background Obesity is a significant risk factor for psoriasis and body mass index (BMI) correlates with disease severity. Objectives To investigate the relationship between obesity and psoriasis, focusing on the role of adipokines such as leptin and resistin. Patients/methods Patients with psoriasis (n = 30) were recruited and their BMI, waist circumference and disease severity [Psoriasis Area and Severity Index (PASI)] were recorded. Fasting serum samples were obtained on enrolment and after a course of ultraviolet (UV) B treatment. Age-, sex- and BMI-matched healthy controls were also recruited. Results On enrolment, serum leptin and soluble leptin receptor levels were not raised compared with the controls. However, resistin, interleukin (IL)-1beta, IL-6, and chemokines CCL2, CXCL8 and CXCL9 were all significantly elevated in the patient group and serum resistin correlated with disease severity ($r = 0.372$, $P = 0.043$). Improvement after UVB treatment was accompanied by decreased serum CXCL8. In vitro, both leptin and resistin could induce CXCL8 and tumour necrosis factor-alpha production by blood monocytes, and leptin could additionally induce IL-1beta and IL-1 receptor antagonist production. Leptin also dose dependently increased secretion of the growth factor amphiregulin by ex vivo-cultured lesional psoriasis skin. Conclusions These data support the view that leptin and resistin may be involved in the pathogenesis of

psoriasis in overweight individuals, possibly by augmenting the cytokine expression by the inflammatory infiltrate.

PMID: 18547319 [found with GoPubMed]

8: J Comp Neurol 2008 Sep;511(3):373-395

Selective contribution of interleukin-6 and leptin to brain inflammatory signals induced by systemic LPS injection in mice.

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This study aimed to address the relative contributions of the proinflammatory cytokine interleukin-6 (IL-6) and the cytokine-like hormone leptin to the genomic activation of brain cells during lipopolysaccharide (LPS)-induced systemic inflammation. Wildtype and IL-6KO mice were injected with LPS (50 mug/kg, intraperitoneally) and the brains analyzed by immunohistochemistry and reverse-transcriptase polymerase chain reaction (RT-PCR). LPS induced a pronounced nuclear translocation of the signal transducer and activator of transcription (STAT3) throughout the brains of wildtype mice, an effect that was significantly diminished, but not abolished, in the IL-6KOs. The remnant STAT3-activation, although still observed within some of the same areas activated by IL-6, was most intense in ependymal and meningial cells and along distinct blood vessels throughout the brain. This expression was almost totally abolished in the presence of an anti-leptin antiserum. Interestingly, the induction of cyclooxygenase 2 and microsomal prostaglandin E synthase (mPGES), the rate-limiting enzymes for synthesis of PGE2 by LPS, was diminished to a degree that correlated with the absence of IL-6 but not entirely with leptin. These results demonstrate that the induction of the inflammatory pathway in the brain is mediated by both IL-6 and leptin, which appear to work in tandem. Unlike IL-6, however, the contribution of leptin to this response was limited to distinct cell types/brain areas and STAT3-responsive target genes implicated in the brain-controlled sickness-type response. The physiological significance of leptin's action on meningeal and endothelial cells remains to be clarified but might reflect a role in LPS-induced immune cell infiltration into the brain. J. Comp. Neurol. 511:373-395, 2008. (c) 2008 Wiley-Liss, Inc.

PMID: 18803240 [found with GoPubMed]

9: Endocrinology 2008 Jun;

Leptin Enhances Human {beta}-Defensin-2 Production in Human Keratinocytes.

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Leptin, an adipocyte-derived cytokine/hormone, modulates innate and adaptive immunity. Human beta-defensin-2 (hBD-2) produced by epidermal keratinocytes promotes cutaneous antimicrobial defense, inflammation, and wound repair. We examined the in vitro effects of leptin on hBD-2 production in human keratinocytes. hBD-2 secretion and mRNA expression were analyzed by ELISA and RT-PCR, respectively. Although leptin alone was

ineffective, it enhanced IL-1beta-induced hBD-2 secretion and mRNA expression in keratinocytes. IL-1beta- and IL-1beta plus leptin-induced hBD-2 production both were suppressed by antisense oligonucleotides against nuclear factor-kappaB (NF-kappaB) p50 and p65; the latter was also suppressed by antisense signal transducer and activator of transcription (STAT)1 and STAT3. IL-1beta enhanced the transcriptional activity of NF-kappaB, while leptin enhanced STAT1 and STAT3 activity. The p38 MAPK inhibitor SB202190 suppressed IL-1beta- and IL-1beta plus leptin-induced hBD-2 production, IL-1beta-induced NF-kappaB activity, and leptin-induced STAT1 and STAT3 activity; contrastingly, the Janus kinase (JAK) 2 inhibitor AG490 suppressed IL-1beta plus leptin-induced hBD-2 production and leptin-induced STAT1 and STAT3 activity. IL-1beta induced serine phosphorylation of inhibitory kappaBalpha, STAT1, and STAT3. Leptin induced tyrosine and serine phosphorylation of STAT1 and STAT3, both of which were suppressed by AG490 and serine phosphorylation was also suppressed by SB202190. IL-1beta or leptin individually induced threonine/tyrosine phosphorylation of p38 MAPK, while only leptin induced tyrosine phosphorylation of JAK2, suggesting that leptin may enhance hBD-2 production in keratinocytes by activating STAT1 and STAT3 via JAK2 and p38 MAPK in cooperation with NF-kappaB, which is activated by IL-1beta. Leptin may promote cutaneous antimicrobial defense, inflammation, and wound repair via hBD-2.

PMID: 18556347 [found with GoPubMed]

10: J Endocrinol 2008 Jul;

Serum leptin concentrations and markers of immune function in overweight or obese postmenopausal women.

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Experimental studies and case reports suggest a multifunctional role of leptin in immune function. However, clinical studies of leptin in healthy individuals with a comprehensive assessment of immunity are lacking. This study investigated associations between serum leptin concentrations and multiple biomarkers of cellular immunity and inflammation among 114 healthy postmenopausal, overweight or obese women. Leptin was measured by radioimmunoassay. C-reactive protein (CRP) and serum amyloid A (SAA) were measured by nephelometry. Flow cytometry was used to measure natural-killer-cell cytotoxicity and to enumerate and phenotype lymphocyte subsets. T-lymphocyte proliferation was assessed in response to phytohemagluttinin, as well as to anti-CD3 antibodies by the flow-cytometric cell-division tracking method. Multiple-linear regression analysis with adjustment for confounding factors and log-transformation, where appropriate, was used. Serum leptin concentrations were positively associated with serum CRP, SAA, and IL-6 ($p < 0.0001$, $p=0.01$, and $p=0.04$, respectively), more strongly among women with a BMI <30 kg/m2. The associations were attenuated after adjustment for measured body composition, yet remained significant for CRP and SAA. No statistically significant associations were observed between leptin and NK cytotoxicity, lymphocyte subpopulations or T lymphocyte proliferation. This study fills an important gap in knowledge about the relationship between leptin concentrations and immune function in healthy individuals. Findings support an association between serum leptin and the inflammatory proteins CRP and SAA, which appears to be mediated only partly by adipose tissue. Our study does not support a link between leptin and other immune parameters among overweight or obese, but otherwise healthy, postmenopausal women, perhaps because such effects are only present at low or deficient leptin concentrations.

PMID: 18614715 [found with GoPubMed]

11: Clin Chim Acta 2008 May;

Leptin expression in Peripheral Blood Mononuclear Cells (PBMCs) is related with blood pressure variability.

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BACKGROUND: Leptin is an adipokine initially considered as a molecule related exclusively to obesity but advances in research revealed its multiple roles in other physio-pathological mechanisms and particularly in the inflammatory ones. The aim of the present study was to demonstrate the presence of leptin in human Peripheral Blood Mononuclear Cells (PBMCs) and to quantify its mRNA in this type of tissue, closely related to inflammation. METHODS: Leptin mRNA was present in PBMCs of healthy individuals. Its expression was further studied in 83 individuals in relation to constitutional factors, anthropometric variables, blood pressure, lipid profile, glucose and markers of inflammation (C-reactive protein, lymphocyte count). RESULTS: Expression levels were significantly associated with systolic blood pressure (SBP) ($p = 0.03$) and diastolic blood pressure (DBP) ($p = 0.003$). Using a multiple regression analysis model, we showed that leptin mRNA levels explained 11% of the variation of SBP ($p = 0.007$) and of DBP ($p = 0.003$). These percentages remained at the same magnitude for SBP (9%) and for DBP (10%), after introducing BMI in the model. CONCLUSION: We report here for the first time, leptin expression in human PBMCs of healthy individuals. The associations found with blood pressure suggest a possible role of leptin in blood pressure regulation via PBMCs.

PMID: 18501706 [found with GoPubMed]

12: Zhong Xi Yi Jie He Xue Bao 2008 Sep;6(9):921-7

Effects of puerarin on expressions of leptin receptor mRNA, phosphoryla-ted Janus kinase 2/phosphorylated signal transducers and activators of transcription 3 proteins in the liver of rats with non-alcoholic fatty liver.

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Objective: To observe the effects of puerarin on the expressions of leptin receptor mRNA and phosphorylated Janus kinase 2 / phosphorylated signal transducers and activators of transcription 3 (P-JAK2/P-STAT3) proteins in the liver of rats with non-alcoholic fatty liver (NAFLD).dz Methods: A rat model of NAFLD was successfully established by feeding high-fat diet. All SD rats were randomly divided into blank control group, untreated group, simvastatin-treated group and puerarin-treated group. After four-week treatment, the levels of hepatic triglyceride and total cholesterol were analyzed by using an automatic biochemical analyzer. The pathology of the liver tissue was observed by light microscopy. Serum leptin level was

detected by enzyme-linked immunosorbent assay, and the expressions of leptin receptor mRNA and P-JAK2/P-STAT3 proteins in the liver of NAFLD rats were quantified by reverse transcription polymerase chain reaction (RT-PCR) and Western blot analysis respectively.dz Results: Puerarin significantly decreased the levels of hepatic triglyceride and total cholesterol in NAFLD rats. Fat degeneration and inflammatory reaction in liver tissues of NAFLD rats were ameliorated after puerarin treatment. The serum leptin level was increased and the expressions of leptin receptor mRNA and P-JAK2/P-STAT3 proteins were up-regulated in puerarin-treated group. Conclusion: Puerarin can effectively attenuate liver lipid disorder and inflammation by improving the leptin resistance and enhancing the expressions of leptin receptor mRNA and P-JAK2/P-STAT3 proteins.

PMID: 18782535 [found with GoPubMed]

13: Free Radic Biol Med 2008 May;

Endurance training without weight loss lowers systemic, but not muscle, oxidative stress with no effect on inflammation in lean and obese women.

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Obesity is associated with oxidative stress. Endurance training (ET) in healthy individuals increases antioxidant enzyme activity and decreases oxidative stress, whereas its effects on oxidative status in obese humans have yet to be determined. We investigated the effects of obesity and ET on markers of oxidative stress, antioxidant defense, and inflammation. Obese (n=12) and lean (n=12) women underwent 12 weeks of ET with blood, 24-h urine, and muscle biopsies collected prior to and following training for determination of oxidative stress (urinary 8-hydroxy-2-deoxyguanosine and 8-isoprostanes, muscle protein carbonyls, and 4-hydroxynonenal), antioxidant enzyme protein content (muscle CuZnSOD, MnSOD, and catalase), and inflammation (C-reactive protein, leptin, adiponectin, interleukin-6). Obese women had elevated urinary 8-hydroxy-2-deoxyguanosine (P=0.03), muscle protein carbonyls (P=0.03), and 4-hydroxynonenal (P<0.001); serum C-reactive protein (P=0.01); and plasma leptin (P=0.0001) and interleukin-6 (P=0.03). ET decreased urinary 8-hydroxy-2-deoxyguanosine (P=0.006) and 8-isoprostanes (P=0.02) in all subjects and CuZnSOD protein content (P=0.04) in obese women, in the absence of changes in body weight or composition. ET without weight loss decreases systemic oxidative stress, but not markers of inflammation, in obese women.

PMID: 18502211 [found with GoPubMed]

14: Endocrinology 2008 May;

Role and regulation of adipokines during zymosan-induced peritoneal inflammation in mice.

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Adipokines, cytokines mainly produced by adipocytes, are active participants in the regulation of inflammation. Administration of zymosan (ZY) was used to investigate regulation and role of adipokines during peritonitis in mice. Injection of ZY lead to a significant increase in leptin levels in both serum and peritoneal lavage fluid (PLF), while a differential trend in local versus systemic levels was observed for both resistin and adiponectin. The role of leptin in ZY-induced peritonitis was investigated using leptin-deficient ob/ob mice, with and without reconstitution with exogenous leptin. Leptin-deficiency was associated with delayed resolution of peritoneal inflammation induced by ZY, since ob/ob mice had a more pronounced cellular infiltrate in the peritoneum as well as higher and prolonged local and systemic levels of IL-6, TNFalpha, IL-10 and CXCL2 compared to WT mice. Reconstitution with exogenous leptin exacerbated the inflammatory infiltrate and systemic IL-6 levels in ob/ob mice, while inhibiting production of TNFalpha, IL-10 and CXCL2. In contrast with the important role of leptin in regulating each aspect of ZY-induced peritonitis, adiponectin deficiency was only associated with a decreased inflammatory infiltrate, without affecting cytokine levels. These findings point to a complex role for adipokines in ZY-induced peritonitis and further emphasize the interplay between obesity and inflammation.

PMID: 18450950 [found with GoPubMed]

15: Mol Nutr Food Res 2008 Mar;

Leptin, adiponectin, resistin, and ghrelin - Implications for inflammatory bowel disease.

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Inflammatory bowel disease (IBD) is characterized by anorexia, malnutrition, altered body composition, and development of mesenteric white adipose tissue (WAT) hypertrophy. Increasing evidence suggests that adipokines synthesized either in WAT or in immune cells, are involved in these manifestations of IBD. Among adipokines leptin, adiponectin and resistin hold a fundamental role while the role of ghrelin in inflammation is not well established. Preliminary studies have shown overexpression of leptin, adiponectin, and resistin in mesenteric WAT of patients with Crohn's disease (CD) and significant alterations of circulating serum levels of these adipokines in IBD. It has also been demonstrated that intestinal inflammation causes an increase in endogenous ghrelin production. In animal models of intestinal inflammation, existing data suggest that leptin, adiponectin, and resistin are pivotal mediators of inflammation. Interesting therapeutic interventions based on these data have been suggested. A specific role for hypertrophic WAT has also been implicated in CD. Further efforts with experimental and clinical studies are needed to better understand the role of adipokines in IBD.

PMID: 18383234 [found with GoPubMed]

16: Schizophr Res 2008 Apr;

Coagulation and inflammation markers during atypical or typical antipsychotic treatment in schizophrenia patients and drug-free first-degree relatives.

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BACKGROUND: Clinical studies suggest that the second generation antipsychotics (APs) clozapine and olanzapine and to a lesser extent the typical antipsychotics may be associated with a procoagulant and proinflammatory state that promotes venous thromboembolism. We evaluated here several blood factors associated with coagulation and inflammation in AP-treated schizophrenia patients and their first-degree relatives. METHODS: Procoagulant factors (fibrinogen and plasminogen activator inhibitor [PAI-1]), the anticoagulant factor antithrombin III [AT-III], and inflammation-related factors (C-reactive protein [CRP] and leptin) were assessed in patients chronically treated with clozapine (n=29), olanzapine (n=29), typical APs (n=30) and first degree relatives of clozapine (n=23) and olanzapine subjects (n=11). RESULTS: The typical AP group had the highest CRP level (p=0.013) in spite of having the lowest body mass index (BMI). Patients as a single group had higher CRP levels than relatives (p=0.003). The typical AP group also had the highest AT-III levels (p=0.021). Fibrinogen levels did not differ between the groups (p=0.13). Olanzapine patients displayed the highest PAI-1 and leptin levels among the drug-treated subjects, but values were similar to those observed in their relatives, and were significantly correlated with the BMI. CONCLUSIONS: A homogeneous negative profile of high inflammation and procoagulant factors along with low levels of anticoagulants was not detected in any group. While preliminary, our results suggest that the observed abnormalities were not related to a direct drug effect, but to elevated BMI (high PAI-1 and leptin in olanzapine-treated patients). We speculate that the high CRP in the typical AP group might be related to poor lifestyle habits, but this must we confirmed in future studies.

PMID: 18436434 [found with GoPubMed]

17: Nat Clin Pract Cardiovasc Med 2008 Apr;

Relationships between leptin and C-reactive protein with cardiovascular disease in the adult general population.

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Background Leptin could be a key regulator of C-reactive protein (CRP) levels, which serve as a marker of systemic inflammation. Both leptin and CRP are predictors of cardiovascular disease (CVD). However, the interactions between leptin and CRP, and their association with CVD, remain unclear. We therefore studied them in a large, multiethnic population.Methods We analyzed leptin and CRP levels, anthropometric variables and cardiovascular risk factor data from 6,251 participants from the Third National Health and Nutrition Examination Survey (NHANES III). Logistic regression was used to estimate the association between leptin, CRP and CVD (defined as history of myocardial infarction or stroke). Receiver operating characteristic curves were created to study the additional value of leptin and CRP for the association with CVD.Results The mean age was 44.4 +/- 0.21 years (52.5% women). After adjustment for age, race, dyslipidemia, hypertension, diabetes, smoking, obesity and CRP, high

levels of leptin were significantly associated with CVD in men (odds ratio 2.47, 95% CI 1.19-5.19) and in women (odds ratio 3.30, 95% CI 1.47-7.99). After adjustment for leptin, CRP was not associated with CVD. There was a significant correlation between levels of leptin and CRP (Spearman correlation rho = 0.22 in men and rho = 0.32 in women, both P < 0.0001). The area under the curve, representing the association between cardiovascular risk factors and CVD, increased after the addition of high levels of both leptin and CRP together.Conclusion High leptin levels are independently associated with CVD even after adjustment for CRP; elevated CRP levels are not associated with CVD after adjustment for leptin. However, increased concentrations of both leptin and CRP confer the highest risk for CVD.

PMID: 18431365 [found with GoPubMed]

18: J Cell Mol Med 2008 Jun;

Interleukin-6 and leptin as markers of energy metabolic changes in advanced ovarian cancer patients.

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The progression of the neoplastic disease is characterised by specific alterations of energy metabolism and by symptoms like fatigue, anorexia, nausea, anemia, immunodepression and poor performance status (PS). The main cause of these symptoms and metabolic abnormalities is the chronic action of proinflammatory cytokines released both by tumor and immune cells. The present study aimed to assess the relationship between markers of inflammation (C-Reactive Protein, Fibrinogen, proinflammatory cytokines) and energy metabolic status (BMI, leptin, oxidative stress) according to clinical parameters in 104 ovarian cancer patients at different stage and, moreover, to evaluate prospectively the changes of these parameters in accordance to tumor response in a subgroup of 70 advanced stage ovarian cancer patients. Advanced stage and poor PS were associated to high grade inflammation and impaired energy metabolism. Among inflammatory mediators, interleukin (IL)-6 had a central role as predictive factor of leptin, reactive oxygen species and glutathione peroxidase. In turn, leptin considered the key marker of the nutritional status and energy metabolism, was independently determined from stage and IL-6, not only from BMI. Moreover, the evaluation of the changes of these parameters during the course of the neoplastic disease in the subgroup of advanced ovarian cancer patients clearly unveils the central role of IL-6 and leptin as early markers of the metabolic alterations and symptoms associated to disease progression in advanced stage ovarian cancer. Their assessment should be included in monitoring disease outcome, especially when cancer is no longer curable and quality of life becomes the primary endpoint.

PMID: 18624749 [found with GoPubMed]

19: Am J Physiol Lung Cell Mol Physiol 2008 Mar;

Effect of obesity on pulmonary inflammation induced by acute ozone exposure: role of interleukin-6.

Lang JE, Williams ES, Mizgerd JP, Shore SA

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To determine the role of interleukin (IL)-6 in the increased ozone (O3)-induced inflammation and injury observed in obese versus lean mice, lean wildtype and leptin-deficient obese (ob/ob) mice were injected with anti-IL-6 antibody (Ab) or an isotype control Ab 24 hours before exposure to either O3 (2 ppm for 3 h) or room air. Four or 24 hours after O3 exposure, bronchoalveolar lavage (BAL) was performed and the lungs were harvested for Western blotting. Anti-IL-6 Ab caused substantial reductions in O3-induced increases in BAL IL-6 in mice of both genotypes. Four hours following O3, ob/ob mice had increased BAL neutrophils compared to controls and anti-IL-6-Ab virtually abolished this difference. At 24 hours, O3-induced increases in BAL protein and BAL serum albumin were augmented in ob/ob versus wildtype mice and anti-IL-6-Ab ablated these obesity-related differences in epithelial barrier injury. O3 increased tyrosine phosphorylation of STAT-3 and STAT-1. There was no effect of obesity on STAT-3 phosphorylation, whereas obesity decreased STAT-1 expression, resulting in reduced STAT-1 phosphorylation. IL-6 neutralization did not alter STAT-3 or STAT-1 phosphorylation in ob/ob or wildtype mice. O3 increased BAL leukemia inhibitory factor (LIF) to a greater extent in obese than lean mice and LIF may account for effects on STAT phosphorylation. Our results suggest that IL-6 plays a complex role in pulmonary responses to O3, a role that differs between wildtype and ob/ob mice. Moreover, obesity-related differences in activation of STAT proteins may contribute to some of the differences in the response of obese versus lean mice. Key words: neutrophil, airway, inflammation, STAT-3, STAT-1.

PMID: 18359888 [found with GoPubMed]

20: Intern Emerg Med 2008 Dec;

Adipose tissue-mediated inflammation: the missing link between obesity and cardiovascular disease?

Calabrò P, Golia E, Maddaloni V, Malvezzi M, Casillo B, Marotta C, Calabrò R, Golino P

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Until relatively recently, the role of adipose tissue in the development of obesity and its consequences was considered to be a passive one. Mounting evidence highlights the role of adipose tissue in the development of a systemic inflammatory state that contributes to obesity-associated vasculopathy and cardiovascular risk. It is now clear that, in addition to storing calories as triglycerides, adipocytes secrete a large variety of cytokines, chemokines and hormone-like factors, such as leptin, resistin, and acute-phase proteins. In addition, insulin resistance, both in nondiabetic and diabetic subjects, is frequently associated with obesity, particularly with an excess of intraabdominal fat. This production of pro-atherogenic substances is of particular interest since an increase in the plasma levels of these mediators may provide a novel mechanistic link between obesity and its vascular complications.

PMID: 19052701 [found with GoPubMed]

21: Int J Obes (Lond) 2008 Dec;

Effects of feeding fish oil on mesenteric lymph node cytokine responses in obese leptin receptor-deficient JCR:LA-cp rats.

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Objective:Aberrant immune responses have been identified in obesity; however, immune cells of lymph nodes residing in the inflammatory environment of visceral adipose tissue have been largely overlooked. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can reduce inflammation and modify T-cell function and therefore may improve immune function in obesity. Thus, we determined the effects of feeding fish oil (FO) containing EPA and DHA on mesenteric lymph node (MLN) immune cell function.Methods:In this study, 14-week-old obese, leptin receptor-deficient JCR:LA-cp rats (cp/cp) (n=10 per group) were randomized to one of three nutritionally adequate diets for 3 weeks: control (ctl, 0% EPA+DHA), low FO (LFO, 0.8% w/w EPA+DHA) or high FO (HFO, 1.4% w/w EPA+DHA). Lean JCR:LA-cp (Cp/cp or Cp/Cp) rats (n=5) were fed ctl diet. MLN cell phospholipid (PL) fatty acid composition, phenotypes and cytokine production were measured.Results:Obese ctl rats produced more IL-1beta, IL-4 and IL-10, despite a higher proportion of (n-3) polyunsaturated fatty acids (PUFAs) and a lower (n-6):(n-3) PUFA ratio in MLN PL compared with lean ctl rats (P<0.05). Concanavalin A-stimulated IL-2 production did not differ from lean rats even though obese ctl rats had a lower proportion of CD4(+)CD25(+) cells (P<0.05). Feeding FO to obese rats increased the incorporation of (n-3) PUFA into MLN PL and normalized production of IL-1beta (HFO only), IL-4 and IL-10 to the levels similar to lean ctl rats (P<0.05).Conclusion:We demonstrate for the first time that obese JCR:LA-cp rats have impaired responses of MLN immune cells to mitogen stimulation and altered PL fatty acid composition. Feeding FO lowered the ex vivo inflammatory response (HFO only) and production of Th2 cytokines, without changing IL-2 production from ConA-stimulated splenocytes, which may occur independent of leptin signalling.International Journal of Obesity advance online publication, 2 December 2008; doi:10.1038/ijo.2008.227.

PMID: 19048014 [found with GoPubMed]

22: Mol Cell Biochem 2008 Nov;

Peroxisome proliferator-activated receptor-alpha modulates insulin gene transcription factors and inflammation in adipose tissues in mice.

Yessoufou A, Atègbo JM, Attakpa E, Hichami A, Moutairou K, Dramane KL, Khan NA

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We have recently reported that PPARalpha deficiency leads to hypoglycaemia and hypoinsulinemia in mice (Yessoufou et al. Endocrinology 147:4410-4418, 2006). Besides, these mice exhibited high adiposity with an inflammatory state. We, therefore, assessed, in this study, the effects of PPARalpha deficiency on the expression of mRNA encoding for the insulin gene transcription factors in pancreatic beta-cells along with those implicated in inflammation in adipose tissues. On fasting, the adult PPARalpha-null mice were hypoglycemic. Serum insulin concentrations and its pancreatic mRNA transcripts were downregulated in PPARalpha-null mice, suggesting that

PPARalpha gene deletion contributes to low insulin gene transcription. The PPARalpha gene deletion downregulates the mRNA expression of insulin gene transcription factors, i.e., Pdx-1, Nkx6.1, and MafA. Besides, the pancreatic function was diminished by PPARalpha deficiency as PPARalpha-null mice expressed low pancreatic Glut2 and glucokinase mRNA. PPARalpha-null mice also expressed high adiponectin and leptin mRNA levels compared to wild type animals. Adipose tissues of PPARalpha-null mice exhibited upregulation of CD14 and CD68 mRNA, generally expressed by macrophages. PPARalpha gene deletion downregulates the adipocyte mRNA of certain pro-inflammatory agents, like MCP-1, TNF-alpha, IL-1beta, IL-6, and RANTES, though pro-inflammatory TLR-2 and TLR-4 mRNAs were upregulated in the adipose tissues. Our results suggest that PPARalpha deficiency, in mice, is implicated in the modulation of insulin gene transcription and inflammatory status in adipose tissues.

PMID: 19039651 [found with GoPubMed]

23: Stroke 2008 Nov;

Leptin Is Induced in the Ischemic Cerebral Cortex and Exerts Neuroprotection Through NF-{kappa}B/c-Rel-Dependent Transcription.

Valerio A, Dossena M, Bertolotti P, Boroni F, Sarnico I, Faraco G, Chiarugi A, Frontini A, Giordano A, Liou HC, De Simoni MG, Spano P, Carruba MO, Pizzi M, Nisoli E

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BACKGROUND AND PURPOSE: Leptin is an adipose hormone endowed with angiopoietic, neurotrophic, and neuroprotective properties. We tested the hypothesis that leptin might act as an endogenous mediator of recovery after ischemic stroke and investigated whether nuclear transcription factors kappaB activation is involved in leptin-mediated neuroprotection. METHODS: The antiapoptotic effects of leptin were evaluated in cultured mouse cortical neurons from wild-type or NF-kappaB/c-Rel(-/-) mice exposed to oxygen-glucose deprivation. Wild-type, c-Rel(-/-) and leptin-deficient ob/ob mice were subjected to permanent middle cerebral artery occlusion. Leptin production was measured in brains from wild-type mice with quantitative reverse transcriptase-polymerase chain reaction and immunostaining. Mice received a leptin bolus (20 microg/g) intraperitoneally at the onset of ischemia. RESULTS: Leptin treatment activated the nuclear translocation of nuclear transcription factors kappaB dimers containing the c-Rel subunit, induced the expression of the antiapoptotic c-Rel target gene Bcl-xL in both control and oxygen-glucose deprivation conditions, and counteracted the oxygen-glucose deprivation-mediated apoptotic death of cultured cortical neurons. Leptin-mediated Bcl-xL induction and neuroprotection against oxygen-glucose deprivation were hampered in cortical neurons from c-Rel(-/-) mice. Leptin mRNA was induced and the protein was detectable in microglia/macrophage cells from the ischemic penumbra of wild-type mice subjected to permanent middle cerebral artery occlusion. Ob/ob mice were more susceptible than wild-type mice to the permanent middle cerebral artery occlusion injury. Leptin injection

significantly reduced the permanent middle cerebral artery occlusion-mediated cortical damage in wild-type and ob/ob mice, but not in c-Rel(-/-) mice. CONCLUSIONS: Leptin acts as an endogenous mediator of neuroprotection during cerebral ischemia. Exogenous leptin administration protects against ischemic neuronal injury in vitro and in vivo in a c-Rel-dependent manner.

PMID: 19023096 [found with GoPubMed]

24: Int J Cardiol 2008 May;

Contribution of adipocytokines to low-grade inflammatory state as expressed by circulating C-reactive protein in Japanese men: Comparison of leptin and adiponectin.

Sugiura K, Tamakoshi K, Yatsuya H, Otsuka R, Wada K, Matsushita K, Kondo T, Hotta Y, Mitsuhashi H, Murohara T, Toyoshima H

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BACKGROUND: Circulating C-reactive protein (CRP) is a marker of inflammation and is associated with the incidence of cardiovascular events. Although it has been known that adiponectin protects, whereas leptin accelerates, the development of atherosclerotic diseases, the comparative strength of their reciprocal effects on circulating CRP remains unclear. METHODS: We studied a population of 2049 Japanese men aged 35 to 66. For all subjects, multiple regression analysis performed with log-transformed CRP concentration as the dependent variable, and with log-transformed leptin, log-transformed adiponectin, age, BMI, smoking status, and components of metabolic syndrome as independent variables. RESULTS: Both leptin (positively) and adiponectin (negatively) were significantly and independently associated with CRP concentration. The absolute value of the standardized regression coefficient (st-beta) of leptin (st-beta=0.201) was higher than that of adiponectin (st-beta=-0.082). After subjects were stratified by current BMI level, both of the adipocytokines were significantly associated with CRP concentration among subjects with BMI <25 kg/m(2), whereas only leptin was significantly associated with CRP concentration among subjects with BMI >=25 kg/m(2). CONCLUSIONS: Both leptin and adiponectin were independently associated with CRP concentration. Leptin was more strongly related to CRP levels than adiponectin was, especially among obese subjects.

PMID: 18495270 [found with GoPubMed]

25: J Vasc Surg 2008 Sep;

Leptin receptor is elevated in carotid plaques from neurologically symptomatic patients and positively correlated with augmented macrophage density.

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BACKGROUND: Carotid artery lesions from symptomatic patients are characterized by inflammation and neovascularization. The adipokine leptin promotes angiogenesis and activates inflammatory cells, and the leptin receptor (ob gene-encoded receptor), ObR, is expressed in advanced atherosclerotic lesions. The present study quantitatively analyzed ObR messenger RNA (mRNA) expression and immunoreactivity in carotid artery plaques from symptomatic and asymptomatic persons. Plaque angiogenesis, gene expression of vascular endothelial growth factor (VEGF), and macrophage density were also analyzed. METHODS: Carotid endarterectomy specimens were collected from 26 patients undergoing surgery for hemispheric cerebrovascular symptoms (n = 13) or progressive asymptomatic internal carotid stenosis (n = 13). A representative sample, including part of the most active site, was collected from each lesion and evaluated by real-time polymerase chain reaction analysis for ObR(long) and ObR(common) isoforms, VEGF(165), and macrophage adhesion molecule-1 (Mac-1) mRNA, and by immunohistochemistry for ObR, von Willebrand factor (vWF), and CD68 antigen expression. RESULTS: All plaques exhibited advanced atherosclerosis (American Heart Association class IV through VI). Transcript levels were preferentially elevated in symptomatic plaques for ObR(long) (P = .0006) and ObR(common) (P = .033), with a simultaneous upregulation of VEGF(165) (P = .001) and Mac-1 mRNA expression (P = .003). Immunohistochemical analysis confirmed a significant increase of ObR antigen levels (P = .011) and CD68-positive inflammatory cells (P = .049) in symptomatic plaques, whereas neovascularization, evident in all plaques, was similar in both groups (P = .7). CONCLUSION: The ObR(long) and ObR(common) genes are upregulated and their protein preferentially synthesized in clinically symptomatic carotid plaques. Moreover, ObR expression is positively correlated with augmentation of gene transcripts related to macrophage density and neovascularization. These data suggest that ObR(long) and ObR(common) may be linked with histologic features of carotid plaque instability, which are associated with cerebral ischemic symptoms.

PMID: 18829234 [found with GoPubMed]

26: Int J Obes (Lond) 2008 Aug;

The increase of fatty acid-binding protein aP2 in overweight and obese children: interactions with dietary fat and impact on measures of subclinical inflammation.

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Background:In adults, circulating aP2 may link obesity, inflammation and the metabolic syndrome, but there are few data in children. Experimental models support that dietary factors, particularly dietary fat, may be major determinants of phenotype.Objective:The aim of this study was to investigate, in normal, overweight and obese children, the relationships among aP2, the metabolic syndrome, inflammation and diet.Design:This was a cross-sectional study conducted in Northern Switzerland.Subjects:Subjects for this study were 6- to 14-year-old, prepubertal and early pubertal, normal weight, overweight and obese children (n=124).Main outcome measures:Body mass index (BMI), body fat percent, waist-to-hip ratio, blood pressure, circulating aP2, fasting insulin, C-reactive protein (CRP), plasma lipids and dietary intakes of macro- and micronutrients were determined.Results:Circulating aP2 markedly increased with increasing central and total adiposity, and predicted measures of insulin resistance. Independent of BMI standard deviation scores and puberty, aP2 correlated

with intake of the antioxidant vitamins A, C and E as well as circulating concentrations of CRP, leptin and low-density lipoprotein cholesterol. Children with lower aP2 concentrations consuming high-fat diets did not show an increase in fasting insulin or CRP, whereas those with higher aP2 concentrations showed marked increases in these measures with high intakes of fat or saturated fat.Conclusions:Increased central and overall adiposity in children are associated with higher circulating aP2 concentrations. In children with high dietary intakes of total fat and saturated fat, but not those with low intakes, higher aP2 concentrations are associated with measures of insulin resistance and inflammation.International Journal of Obesity advance online publication, 5 August 2008; doi:10.1038/ijo.2008.128.

PMID: 18679408 [found with GoPubMed]

27: J Leukoc Biol 2008 Jun;

The intricate interface between immune and metabolic regulation: a role for leptin in the pathogenesis of multiple sclerosis?

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Over the last few years, a series of molecules known to play a function in metabolism has also been shown to play an important role in the regulation of the immune response. In this context, the adipocyte-derived hormone leptin has been shown to regulate the immune response in normal as well as in pathological conditions. More specifically, it has been shown that conditions of reduced leptin production (i.e., genetic leptin deficiency, anorexia nervosa, malnutrition) are associated with increased susceptibility to infections. Conversely, immune-mediated disorders such as autoimmune disorders are associated with increased secretion of leptin and production of proinflammatory, pathogenic cytokines. Leptin could represent the "missing link" among immune response, metabolic function, and nutritional status. Indeed, more recently, leptin-deficient mice have been shown to be resistant to a series of experimentally induced autoimmune disorders including experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis. Normal wild-type mice show increased secretion of leptin in serum upon EAE induction, and brain inflammatory infiltrates stain positive for leptin. Finally, leptin neutralization with leptin antagonists improves the EAE course by profoundly altering intracellular signaling of myelin-reactive T cells and increasing the number of regulatory forkhead/winged helix transcription factor 3(+)CD4(+) T cells. These data suggest that leptin can be considered as a link among immune tolerance, metabolic state, and autoimmunity and that strategies aimed at interfering with the leptin axis could represent innovative, therapeutic tools for autoimmune disorders.

PMID: 18552206 [found with GoPubMed]

28: Am J Physiol Endocrinol Metab 2008 Jun;

Voluntary Exercise Improves Insulin Sensitivity and Adipose Tissue Inflammation in Diet-Induced Obese Mice.

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Exercise promotes weight loss and improves insulin sensitivity. However, the molecular mechanisms mediating its beneficial effects are not fully understood. Obesity correlates with increased production of inflammatory cytokines, which in turn, contributes to systemic insulin resistance. To test the hypothesis that exercise mitigates this inflammatory response, thereby improving insulin sensitivity, we developed a model of voluntary exercise in mice made obese by feeding of a high fat/high sucrose diet (HFD). Over four weeks, mice fed chow gained 2.3 +/- 0.3 g, while HFD mice gained 6.8 +/- 0.5 g. After 4 weeks, mice were subdivided into four groups: chow-no exercise, chow-exercise, HFD-no exercise, HFD-exercise and monitored for an additional 6 weeks. Chow-no exercise and HFD-no exercise mice gained an additional 1.2 +/- 0.3 g and 3.3 +/- 0.5 g respectively. Exercising mice had higher food consumption, but did not gain additional weight. As expected, GTT and ITT showed impaired glucose tolerance and insulin resistance in HFD-no exercise mice. However, glucose tolerance improved significantly and insulin sensitivity was completely normalized in HFD-exercise animals. Furthermore, expression of TNF-alpha, MCP-1, PAI-1 and IKKbeta was increased in adipose tissue from HFD mice compared to chow mice, whereas exercise reversed the increased expression of these inflammatory cytokines. In contrast, expression of these cytokines in liver was unchanged among the four groups. These results suggest that exercise partially reduces adiposity, reverses insulin resistance and decreases adipose tissue inflammation in diet-induced obese mice, despite continued consumption of HFD. Key words: insulin resistance, cytokine, adiposity, high-fat diet.

PMID: 18577694 [found with GoPubMed]

29: Diabetes Res Clin Pract 2008 Jun;

Fatty liver and chronic inflammation in Chinese adults.

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OBJECTIVE: To investigate the significance of fatty liver as predictor of insulin resistance (IR) and chronic inflammation. RESEARCH DESIGN AND METHODS: This cross-sectional study included 450 adults of Han Chinese origin aged >/=35. Excluded were cases with hepatitis B or C, alcoholic liver disease, or currently using thiazolidinedione. The volunteers were screened for the presence of the components of metabolic syndrome (MtS). IR index was estimated by the homeostasis model assessment. The fatty liver index was evaluated by computed tomography, calculated as the liver/spleen (L/S) ratio arrived at by averaging Hounsfield values obtained for five 3-mm slices. Serum levels of adiponectin, C-reactive protein (CRP), leptin, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) were checked in 100 subjects with low-L/S ratio and 100 age- and sex-matched controls. RESULTS: Fatty liver index correlated with all MtS traits and IR index. The values of L/S ratios in subjects with 0, 1, 2, 3 and >/=4 traits of MtS were 1.25+/-0.13, 1.18+/-0.16, 1.12+/-0.21, 1.05+/-0.25 and 0.92+/-0.25, respectively ($p<0.001$). In our stepwise regression analysis to compare the L/S ratios to the conventional traits of MtS for association with adipokine dysregulation, we found L/S ratio to be independently associated with most of them: adiponectin ($p<0.001$), CRP ($p<0.001$), IL-6

(p=0.005) and TNF-alpha (p=0.014). CONCLUSION: In Chinese, fatty liver index correlated well with IR index and can be a better marker of chronic inflammation than the conventional components of MtS.

PMID: 18534708 [found with GoPubMed]

30: Physiol Res 2008 Jul;

The effect of pheochromocytoma treatment on subclinical inflammation and endocrine function of adipose tissue.

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The aim of our study was to evaluate the influence of surgical removal of pheochromocytoma on the endocrine function of adipose tissue and subclinical inflammation as measured by circulating C-reactive protein (CRP) levels. 18 patients with newly diagnosed pheochromocytoma were included into study. Anthropometric measures, biochemical parameters, serum CRP, leptin, adiponectin and resistin levels were measured at the time of diagnosis and 6 months after surgical removal of pheochromocytoma, respectively. Surgical removal of pheochromocytoma significantly increased body weight, decreased both systolic and diastolic blood pressure, fasting blood glucose and glycated hemoglobin levels. Serum CRP levels were decreased by 50 % six months after surgical removal of pheochromocytoma (0.49+/-0.12 mg/l vs. 0.23+/-0.05 mg/l, p<0.05) despite a significant increase in body weight. Serum leptin, adiponectin and resistin levels were not affected by the surgery. We conclude that increased body weight in patients after surgical removal of pheochromocytoma is accompanied by an attenuation of subclinical inflammation probably due to catecholamine normalization. We failed to demonstrate an involvement of the changes of circulating leptin, adiponectin or resistin levels in this process.

PMID: 18637714 [found with GoPubMed]

31: Obesity (Silver Spring) 2008 Jul;

beta-Aminoisobutyric Acid Prevents Diet-induced Obesity in Mice With Partial Leptin Deficiency.

Begriche K, Massart J, Abbey-Toby A, Igoudjil A, Lettéron P, Fromenty B

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beta-Aminoisobutyric acid (BAIBA), a thymine catabolite, increases fatty acid oxidation (FAO) in liver and reduces the gain of body fat mass in Swiss (lean) mice fed a standard chow. We determined whether BAIBA could prevent obesity and related metabolic disorders in different murine models. To this end, BAIBA (100 or 500 mg/kg/day) was administered for 4 months in mice totally deficient in leptin (ob/ob). BAIBA (100 mg/kg/day) was also given for 4 months in wild-type (+/+) mice and mice partially deficient in leptin (ob/+) fed a high-calorie (HC) diet. BAIBA did not limit obesity and hepatic steatosis in ob/ob mice, but reduced liver cytolysis and inflammation. In ob/+ mice fed the HC diet, BAIBA fully prevented, or limited, the gain of body fat, steatosis and necroinflammation, glucose intolerance, and hypertriglyceridemia. Plasma beta-hydroxybutyrate was

increased, whereas expression of carnitine palmitoyltransferase-1 was augmented in liver and white adipose tissue. Acetyl-CoA carboxylase was more phosphorylated, and de novo lipogenesis was less induced in liver. These favorable effects of BAIBA in ob/+ mice were associated with a restoration of plasma leptin levels. The reduction of body adiposity afforded by BAIBA was less marked in +/+ mice. Finally, BAIBA significantly stimulated the secretion of leptin in isolated ob/+ adipose cells, but not in +/+ cells. Thus, BAIBA could limit triglyceride accretion in tissues through a leptin-dependent stimulation of FAO. As partial leptin deficiency is not uncommon in the general population, supplementation with BAIBA may help to prevent diet-induced obesity and related metabolic disorders in low leptin secretors.Obesity (2008) doi:10.1038/oby.2008.337.

PMID: 18719655 [found with GoPubMed]

32: Am J Physiol Regul Integr Comp Physiol 2008 Apr;

Inflammation is associated with a decrease of lipogenic factors in omental fat in women.

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Obesity is characterized by systemic low-grade inflammation where adipose tissue, especially the omental depot, is thought to play a key role. We have previously shown that inflammation impairs 3T3-L1 preadipocyte cell line differentiation. To explore whether this interaction takes also place in vivo, the expression of several genes related to inflammation and adipocyte differentiation was assessed in human samples. Paired adipose tissue biopsies (from omental and subcutaneous depots) were obtained from 24 women: 6 lean normoglycaemic and 18 obese volunteers with different glycaemic states (normoglycaemic, glucose intolerant or type 2 diabetic). The expression levels of CD14, IL-18, leptin, adiponectin, SREBP1, PPARgamma, PBEF1 (visfatin), GPD1, LPL, FABP4 and HIF1alpha were determined by quantitative real time PCR. CD14 and IL-18 were overexpressed in omental adipose tissue as compared to the subcutaneous depot irrespective of the subjects obesity or diabetes status. A significant decrease of LPL, GPD1 and leptin expression was observed in omental tissue and an inverse correlation between expression of CD14 and IL-18 and that of PPARgamma, LPL and FABP4 was observed. The underexpression of omental lipogenic markers was more accentuated in the presence of glucose intolerance. Furthermore, adiponectin and SREBP1 expressions were also significantly decreased in omental tissue of type 2 diabetic patients. PBEF1 and HIF1alpha expressions remained comparable in all samples. Therefore, in humans, inflammation is increased in the omental depot as evidenced by CD14 and IL-18 expression. In this localisation, the inflammatory state is associated with a decreased expression of lipogenic markers, which is more pronounced in diabetic subjects. Key words: obesity, CD14, IL-18, subcutaneous and visceral adipose tissue, diabetes.

PMID: 18448614 [found with GoPubMed]

33: Endocr J 2008 May;

Oxidative Stress, Inflammation, and Atherosclerotic Changes in Retinal Arteries in the Japanese population;Results from the Mima Study.

Sakane N, Fujiwara S, Sano Y, Domichi M, Tsuzaki K, Matsuoka Y, Hamada T, Saiga K, Kotani K

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Oxidative stress, lifestyle and atherosclerosis in the general population. A population-based, cross-sectional study was made of 282 people (126 men and 156 women, mean age; 6513, mean BMI; 25.42.7 kg/m(2)) recruited from the Mima study in Tokushima Prefecture. Risk factors included age, sex, body mass index (BMI), cigarette smoking, systolic and diastolic pressure, fasting blood glucose, serum lipids, and high-sensitive C-reactive protein (hs-CRP). Oxidative stress in blood samples was measured by the diacron reactive oxygen metabolites (ROMs) test. The degree of sclerotic change was determined from fundus photographs according to Scheie's classification. After adjustment for age and sex, ROM levels positively correlated with hs-CRP levels, but not with ghrelin, leptin and adiponectin levels. Furthermore, ROM and hs-CRP levels positively and individually correlated with the grade of sclerotic change in the fundus oculi independent of age in a multiple regression analysis. These results suggest that oxidative stress and chronic inflammation promote atherosclerosis in the retinal arteries in the general population.

PMID: 18469484 [found with GoPubMed]

34: Endocrinology 2008 Apr;

CRH-deficiency is associated with reduced local inflammation in a mouse model of experimental colitis.

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CRH, the hypothalamic component of the HPA axis, attenuates inflammation through stimulation of glucocorticoid release, while peripherally expressed CRH acts as a proinflammatory mediator. CRH is expressed in the intestine and upregulated in patients with ulcerative colitis. However, its pathophysiological significance in intestinal inflammatory diseases has just started to emerge. In a mouse model of acute, trinitrobenzene sulfonic acid (TNBS) induced-experimental colitis we demonstrate that, despite low glucocorticoid levels, CRH deficient mice develop substantially reduced local inflammatory responses. These effects were shown by histological scoring of tissue damage and neutrophil infiltration. At the same time, CRH deficiency was found to be associated with higher serum leptin and IL-6 levels along with sustained anorexia and weight loss, although central CRH has been reported to be a strong appetite suppressor. Taken together, our results support an important proinflammatory role for CRH during mouse experimental colitis, and possibly in inflammatory bowel disease in humans. Moreover, they suggest that CRH is involved in homeostatic pathways that link inflammation and metabolism.

PMID: 18403481 [found with GoPubMed]

35: Endocrinology 2008 Apr;

Dietary Curcumin Significantly Improves Obesity-Associated Inflammation and Diabetes in Mouse Models of Diabesity.

Weisberg SP, Leibel R, Tortoriello DV

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Obesity is a major risk factor for the development of type 2 diabetes, and both conditions are now recognized to possess significant inflammatory components underlying their pathophysiologies. We tested the hypothesis that the plant polyphenolic compound curcumin, which is known to exert potent anti-inflammatory and anti-oxidant effects, would ameliorate diabetes and inflammation in murine models of insulin-resistant obesity. We found that dietary curcumin admixture ameliorated diabetes in high-fat diet induced obese (DIO) and leptin-deficient ob/ob male C57BL/6J mice as determined by glucose and insulin tolerance testing and hemoglobin A1c percentages. Curcumin treatment also significantly reduced macrophage infiltration of white adipose tissue, increased adipose tissue adiponectin production, and decreased hepatic nuclear NF-kappaB activity, hepatomegaly, and markers of hepatic inflammation. We therefore conclude that orally ingested curcumin reverses many of the inflammatory and metabolic derangements associated with obesity and improves glycemic control in mouse models of type 2 diabetes. This or related compounds warrant further investigation as novel adjunctive therapies for type 2 diabetes in man.

PMID: 18403477 [found with GoPubMed]

36: Headache 2008 Jun;

Low Leptin Levels in Migraine: A Case Control Study.

Guldiken B, Guldiken S, Demir M, Turgut N, Tugrul A

Trakya University—Neurology, Edirne, Turkey.

Background.- Obesity has been shown to be a risk factor for transformation of episodic migraine to chronic form, and adipocytokines have been implicated to modulate some of the cytokins such as interleukin-6 and tumor necrosis factor, which also act in the neurogenic inflammation in migraine. The aim of the study was to assess leptin levels, one of the adipocytokines, in headache-free period of migraine patients and investigate its relation to vascular risk factors. Material and Methods.- Sixty-one patients with episodic migraine headaches and 64 control subjects were enrolled in the study. Demographic data and anthropometric measurements were obtained from all participants; body mass index and fat mass values were calculated. Glucose and lipid parameters were measured by oxidase technique and cholesterol esterase enzymatic assays, and leptin levels were measured by ELISA in serum samples obtained after an overnight fasting. Results.- Leptin levels were found significantly lower in migraineurs than controls (40.1 +/- 21.2 ng/mL, 48.5 +/- 24.5 ng/mL; P < .05). Although body mass index did not differ between 2 groups, fat mass, and fat percentages were significantly lower in migraine patients (19.4 +/- 8.8 kg, 26.0 +/- 8.7 kg; P < .001 and 28 +/- 9%, 34 +/- 5%; P < .001, respectively). Conclusion.- Migraine patients have low leptin levels and fat mass which may be related to the pathogenesis of migraine. The importance and impact of our findings on the prevalence, characteristics, and treatment of migraine needs to be investigated in further detailed studies.

PMID: 18547265 [found with GoPubMed]

37: Metab Syndr Relat Disord 2008 May;

Association of Adiposity, Inflammation and Atherosclerosis: The Role of Adipocytokines and CRP in Asian Indian Subjects.

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Abstract Background: To reveal the exact link between adipose tissue, inflammation, and cardiovascular disease (CVD), we studied the association of C-reactive protein (CRP) with insulin resistance and adipocytokines in Asian Indian subjects. Methods: Forty-one controls, 40 obese, and 53 type 2 diabetes (T2DM) patients (total 134) were recruited. Enzyme-linked immunoassay (ELISA) technique was used to determine serum CRP and adipocytokine concentrations. Serum insulin was measured by radioimmune assay, and insulin resistance index was calculated by the homeostasis model assessment (HOMA). Association of CRP with different adipocytokines and insulin resistance was assessed with univariate regression analysis. Results: Serum leptin, resistin, and CRP levels were significantly increased and adiponectin levels were significantly reduced in obese subjects. In T2DM patients, CRP levels were increased and adiponectin levels were significantly decreased but no difference in leptin and resistin levels were found compared to controls. An important finding of this study was the significantly reduced levels of leptin, adiponectin, and resistin in nonobese T2DM patients compared to their BMI-matched controls. CRP in all subjects showed a significant correlation with obesity parameters like BMI ($P < 0.001$), waist circumference ($P < 0.01$), body fat percentage ($P < 0.01$), HOMA-IR ($P < 0.001$), leptin ($P < 0.05$), and resistin ($P < 0.01$). Conclusions: The association of CRP with insulin resistance, adipocytokines, and resistin reveals close links between inflammation, CVD, and adipose tissue. These findings provide an exciting therapeutic opportunity in cardiovascular disease by targeting various proinflammatory cascades in adipocytes.

PMID: 18484906 [found with GoPubMed]

38: Proc Natl Acad Sci U S A 2008 May;

Interleukin-18, together with interleukin-12, induces severe acute pancreatitis in obese but not in nonobese leptin-deficient mice.

Sennello JA, Fayad R, Pini M, Gove ME, Ponemone V, Cabay RJ, Siegmund B, Dinarello CA, Fantuzzi G

Departments of Kinesiology and Nutrition and.

Obesity is associated with increased severity of acute pancreatitis (AP). The cytokines IL-18 and IL-12 are elevated in patients with AP, and IL-18 levels are high in obesity. We aimed to develop a pathologically relevant model to study obesity-associated severe AP. Lean WT and obese leptin-deficient ob/ob mice received two injections of IL-12 plus IL-18. Survival, pancreatic inflammation, and biochemical markers of AP were measured. Dosing with IL-12 plus IL-18 induced 100% lethality in ob/ob mice; no lethality was observed in WT mice. Disruption of pancreatic exocrine tissue and acinar cell death as well as serum amylase and lipase levels were

significantly higher in ob/ob than in WT mice. Edematous AP developed in WT mice, whereas obese ob/ob mice developed necrotizing AP. Adipose tissue necrosis and saponification were present in cytokine-injected ob/ob but not in WT mice. Severe hypocalcemia and elevated acute-phase response developed in ob/ob mice. The cytokine combination induced high levels of regenerating protein 1 and pancreatitis-associated protein expression in the pancreas of WT but not of ob/ob mice. To differentiate the contribution of obesity to that of leptin deficiency, mice received short- and long-term leptin replacement therapy. Short-term leptin reconstitution in the absence of major weight loss did not protect ob/ob mice, whereas leptin deficiency in the absence of obesity resulted in a significant reduction in the severity of the pancreatitis. In conclusion, we developed a pathologically relevant model of AP in which obesity per se is associated with increased severity.

PMID: 18515422 [found with GoPubMed]

39: Diabetes 2008 Mar;

Kinin B1 receptor deficiency leads to leptin hypersensitivity and resistance to obesity.

Mori MA, Araújo RC, Reis FC, Sgai DG, Fonseca RG, Barros CC, Merino VF, Passadore M, Barbosa AM, Ferrari B, Carayon P, Castro CH, Shimuta SI, Luz J, Bascands JL, Schanstra JP, Even PC, Oliveira SM, Bader M, Pesquero JB

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Objective: Kinins mediate pathophysiological processes related to hypertension, pain and inflammation through the activation of two G protein-coupled receptors, named B(1) and B(2). Although these peptides have been related to glucose homeostasis, their effects on energy balance are still unknown. Research Design and Methods: Using genetic and pharmacological strategies to abrogate the kinin B(1) receptor in different animal models of obesity, we present here evidence of a novel role for kinins in the regulation of satiety and adiposity. Results: Kinin B(1) receptor deficiency in mice (B(1)(-/-)) resulted in less fat content, hypoleptinemia, increased leptin sensitivity and robust protection against high fat diet (HFD)-induced weight gain. Under HFD, B(1)(-/-) also exhibited reduced food intake, improved lipid oxidation and increased energy expenditure. Surprisingly, B(1) receptor deficiency was not able to decrease food intake and adiposity in obese mice lacking leptin (ob/ob-B(1)(-/-)). However, ob/ob-B(1)(-/-) mice were more responsive to the effects of exogenous leptin on body weight and food intake, suggesting that B(1) receptors may be dependent on leptin to display their metabolic roles. Finally, inhibition of weight gain and food intake by B(1) receptor ablation was pharmacologically confirmed by long term administration of the kinin B(1) receptor antagonist SSR240612 to mice under HFD. Conclusions: Our data suggest that kinin B(1) receptors participate in the regulation of the energy balance via a mechanism that could involve the modulation of leptin sensitivity.

PMID: 18332096 [found with GoPubMed]

40: J Endocrinol Invest 2008 Jun;31(6):499-504

Associations between serum uric acid and adipokines, markers of inflammation, and endothelial dysfunction.

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AIM: Serum uric acid is associated with the metabolic syndrome and its components, while its relationship with cardiovascular disease is controversial. The aim of the study was to evaluate the association between uric acid and adipokines, markers of inflammation, oxidative stress, and endothelial dysfunction, which are all linked to cardiovascular disease. METHODS: The associations between uric acid and adiponectin, resistin, leptin, high-sensitivity-C-reactive protein (hs-CRP), interleukin-6, tumor necrosis factor-alpha, nitrotyrosine, Total Antioxidant Status (TAS), E-selectin, vascular adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) were cross-sectionally evaluated in a randomly collected sample of 100 men from a population-based cohort. RESULTS: Subjects within the highest uric acid quartile showed a worse metabolic pattern and a higher prevalence of the metabolic syndrome [odds ratio (OR)=3.6; 95% confidence interval (CI) 1.6-8.2; p<0.001 for each 50 mumol/l uric acid increment in a logistic regression model after multiple adjustments]. Nitrotyrosine and adiponectin were significantly lower, while TAS, hs-CRP, E-selectin, ICAM-1, and VCAM-1 were higher in the groups with increased uric acid levels. In a multiple regression model, after adjustments for multiple confounders, uric acid levels were inversely associated with nitrotyrosine (p<0.001) and adiponectin (p=0.02), and directly with TAS (p<0.001), and E-selectin (p=0.006). CONCLUSION: Serum uric acid showed opposite relationships, being associated with both beneficial (inverse association with nitrotyrosine, direct association with TAS) and detrimental (inverse association with adiponectin, direct association with E-selectin) markers, thus providing a possible explanation for the previously reported controversial and not linear association between uric acid and cardiovascular disease.

PMID: 18591880 [found with GoPubMed]

41: Mol Endocrinol 2008 Feb;

The Role of Lipocalin 2 in the Regulation of Inflammation in Adipocytes and Macrophages.

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Adipose tissue-derived cytokines (adipokines) are associated with the development of inflammation and insulin resistance. However, which adipokine(s) mediate this linkage and the mechanisms involved during obesity are poorly understood. Through proteomics and microarray screening, we recently identified lipocalin 2 (LCN 2) as an adipokine that potentially connects obesity and its related adipose inflammation. Herein we show that the levels of LCN2 mRNA are dramatically increased in adipose tissue and liver of ob/ob mice and primary adipose cells isolated from Zucker obese rats, and thiazolidinedione (TZD) administration reduces LCN2 expression. Interestingly, addition of LCN2 induces mRNA levels of PPARgamma and adiponectin. Reducing LCN2 gene expression causes decreased expression of PPARgamma and adiponectin, slightly reduced insulin-stimulated Akt2

phosphorylation at Serine 473 in 3T3-L1 adipocytes. LCN2 administration to 3T3-L1 cells attenuated TNFalpha-effect on glucose uptake, expression of PPARgamma, IRS-1, and GLUT4, and secretion of adiponectin and leptin. When added to macrophages, LCN2 suppressed LPS-induced cytokine production. Our data suggest that LCN2 as a novel autocrine and paracrine adipokine, acting as an antagonist to the effect of inflammatory molecules on inflammation and secretion of adipokines.

PMID: 18292240 [found with GoPubMed]

42: Clin Endocrinol (Oxf) 2008 May;

High plasma C-reactive protein is related to low paraoxonase-I activity independently of high leptin and low adiponectin in Type 2 diabetes mellitus.

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Objectives: In type 2 diabetes mellitus, circulating C-reactive protein (CRP) is increased, whereas the high density lipoprotein (HDL)-associated, anti-oxidative and anti-inflammatory enzyme, paraoxonase-I, is decreased. Both high CRP and low paraoxonase-I activity may predict cardiovascular disease. It is unknown whether lower paraoxonase-I activity contributes to higher CRP levels in diabetes. In type 2 diabetic and control subjects, we determined the relationship of CRP with paraoxonase-I when taking account of plasma levels of pro- and anti-inflammatory adipokines. Design and patients: In 81 type 2 diabetic patients and 89 control subjects, plasma high-sensitive CRP, serum paraoxonase-I activity (arylesterase activity, assayed as the rate of hydrolysis of phenyl acetate into phenol), plasma leptin, adiponectin, resistin and lipids were determined. Results: Body mass index (BMI), waist, insulin resistance, triglycerides, CRP, leptin and resistin levels were higher ($P<0.05$ to $P<0.001$), whereas HDL cholesterol, paraoxonase-I activity and adiponectin levels were lower ($P=0.02$ to $P<0.001$) in diabetic compared to control subjects. Multiple linear regression analysis demonstrated that, after controlling for age and gender, CRP was inversely related to paraoxonase-I activity (ss=-0.15, $P=0.028$) and adiponectin (ss=-0.18, $P=0.009$), and positively to leptin (ss=0.33, $P<0.001$) and BMI (ss=0.22, $P=0.007$), independently of the diabetic state (or of fasting glucose or HbA1c), insulin resistance and lipids ($P>0.20$ for all). Conclusions: Low paraoxonase-I activity is related to higher CRP, independently of adipokines, as well as of obesity and lipids. Low paraoxonase-I activity in type 2 diabetes mellitus may contribute to increased cardiovascular risk via an effect on enhanced systemic low-grade inflammation.

PMID: 18505467 [found with GoPubMed]

43: J Biol Chem 2008 Feb;

Protein tyrosine phosphatase 1B (PTP1B) expression is induced by inflammation in vivo.

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PTP1B is a major negative regulator of insulin and leptin sensitivity. PTP1B overexpression in adipose tissue and skeletal muscle of humans and rodents may contribute to insulin-resistance and obesity. The mechanisms mediating PTP1B overexpression in obese and diabetic states have been unclear. We find that adipose tissue inflammation and the proinflammatory cytokine tumor necrosis factor alpha (TNFalpha) regulate PTP1B expression in vivo. High-fat feeding of mice increased PTP1B expression 1.5-7-fold in adipose tissue, liver, skeletal muscle, and arcuate nucleus of hypothalamus. PTP1B overexpression in high-fat fed mice coincided with increased adipose tissue expression of the macrophage marker CD68 and TNFalpha, which is implicated in causing obesity-induced insulin-resistance. TNFalpha increased PTP1B mRNA and protein levels by 2-5-fold in a dose- and time-dependent manner in adipocyte and hepatocyte cell lines. TNFalpha administration to mice increased PTP1B mRNA 1.4-4-fold in adipose tissue, liver, skeletal muscle, and hypothalamic arcuate nucleus and PTP1B protein 2-fold in liver. Actinomycin D treatment blocked, and high dose salicylate treatment inhibited by 80%, TNFalpha-induced PTP1B expression in adipocyte cell lines, suggesting TNFalpha may induce PTP1B transcription via nuclear factor kappaB (NFkappaB) activation. Chromatin immunoprecipitation from adipocyte cell lines and liver of mice demonstrated TNFalpha-induced recruitment of NFkappaB subunit p65 to the PTP1B promoter in vitro and in vivo. In mice with diet-induced obesity, TNFalpha deficiency also partly blocked PTP1B overexpression in adipose tissue. Our data suggest that PTP1B overexpression in multiple tissues in obesity is regulated by inflammation, and that PTP1B may be a target of anti-inflammatory therapies.

PMID: 18281274 [found with GoPubMed]

44: Cytokine 2008 May;42(2):156-60

Serum leptin levels in community acquired pneumonia (CAP) are related to nutritional status and not to acute phase reaction.

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To determine whether leptin in patients with CAP acts as a nutritional or as an inflammatory marker and whether leptin plays any role regarding survival, we included 222 patients diagnosed of CAP, 142 men and 80 women, median age 74 years. We did not find significant differences in serum leptin levels between CAP patients and healthy controls, even after adjusting by BMI. Serum leptin levels were directly related with BMI, body fat and muscle mass and inversely related with inflammatory markers, including pro- and anti-inflammatory cytokines. Patients with positive blood cultures showed lower serum leptin and raised inflammatory markers. Although patients who died showed lower values of serum leptin, multivariate analysis showed that the prognostic value of low serum leptin levels depends on impaired nutritional status. In conclusion, we suggest that in CAP patients, leptin does not act as an inflammatory reactant but as a nutritional marker.

PMID: 18396058 [found with GoPubMed]

45: Circ Res 2008 Jul;

Interferon-{gamma}, a Th1 Cytokine, Regulates Fat Inflammation. A Role for Adaptive Immunity in Obesity.

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Adipose tissue (AT) can accumulate macrophages and secrete several inflammatory mediators. Despite its pivotal role in the progression of chronic inflammatory processes such as atherosclerosis, the adaptive role of immunity in obesity remains poorly explored. Visceral AT of diet-induced obese C57BL/6 mice had higher numbers of both CD4(+) and CD8(+) T cells than lean controls, monitored by flow cytometry. When stimulated in vitro, T cells from obese AT produced more interferon (IFN)gamma than those from controls. AT from obese animals also had more cells expressing I-A(b), a mouse class II histocompatibility marker implicated in antigen presentation, as determined by immunostaining. Differentiated 3T3-L1 cells stimulated with recombinant IFNgamma or T-helper 1-derived supernatant produced several chemokines and their mRNAs. Obese IFNgamma-deficient animals had significantly reduced AT expression of mRNA-encoding inflammatory genes such as tumor necrosis factor-alpha and monocyte chemoattractant protein-1, decreased AT inflammatory cell accumulation, and better glucose tolerance than control animals consuming the same diet. Obese mice doubly deficient for IFNgamma receptor and apolipoprotein (Apo)E on a mixed 129SvEv/C57BL/6 (129/B6) genetic background, despite exhibiting similar AT mRNA levels of tumor necrosis factor-alpha and monocyte chemoattractant protein-1 as 129/B6-ApoE(-/-) controls, had decreased expression of important T cell-related genes, such as IP-10 (IFNgamma-inducible protein-10) and I-A(b), and lower plasma triglycerides and glucose. These results indicate a role for T cells and IFNgamma, a prototypical T-helper 1 cytokine, in regulation of the inflammatory response that accompanies obesity.

PMID: 18658050 [found with GoPubMed]

46: Int J Obes (Lond) 2008 Dec;

Emerging role of adipose tissue hypoxia in obesity and insulin resistance.

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Recent studies consistently support a hypoxia response in the adipose tissue in obese animals. The observations have led to the formation of an exciting concept, adipose tissue hypoxia (ATH), in the understanding of major disorders associated with obesity. ATH may provide cellular mechanisms for chronic inflammation, macrophage infiltration, adiponectin reduction, leptin elevation, adipocyte death, endoplasmic reticulum stress and mitochondrial dysfunction in white adipose tissue in obesity. The concept suggests that inhibition of adipogenesis and triglyceride synthesis by hypoxia may be a new mechanism for elevated free fatty acids in the circulation in obesity. ATH may represent a unified cellular mechanism for a variety of metabolic disorders and insulin resistance in patients with metabolic syndrome. It suggests a new mechanism of pathogenesis of insulin resistance and inflammation in obstructive sleep apnea. In addition, it may help us to understand the beneficial effects of caloric restriction,

physical exercise and angiotensin II inhibitors in the improvement of insulin sensitivity. In this review article, literatures are reviewed to summarize the evidence and possible cellular mechanisms of ATH. The directions and road blocks in the future studies are analyzed.International Journal of Obesity advance online publication, 9 December 2008; doi:10.1038/ijo.2008.229.

PMID: 19050672 [found with GoPubMed]

47: Clin Invest Med 2008;31(6):E386

Influence of obesity on the prevalence and clinical features of asthma.

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Obesity has been associated with an increased prevalence of asthma and poorer control of this disease. However, the mechanisms by which obesity can influence airway function and make asthma more difficult to control remain uncertain. The physiological changes associated with obesity can contribute to respiratory symptoms and these should be differentiated from those caused by asthma. Obesity can possibly influence the development of asthma through genetic, developmental, hormonal, neurogenic or mechanical influences. Breathing at low lung volumes and changes in the pattern of breathing in obese subjects may alter airway smooth muscle plasticity and airway function. The release by adipocytes of various cytokines and mediators such as Interleukin-6, TNF-α, eotaxin, and leptin, and the reduction of anti-inflammatory adipokines in obese subjects may possibly contribute to the development or increased clinical expression of asthma in promoting airway inflammation. Reduced asthma control and impaired response to asthma therapy have been reported in obese patients. Obesity-related co-morbidities such as Sleep Apnea and Gastro-esophageal reflux may also contribute to this poor control. Weight loss improves asthma control and reduces medication needs. Research is needed to better define the optimal management of obese asthmatic patients.

PMID: 19032910 [found with GoPubMed]

48: Cell 2008 Oct;135(1):20-2

Stressing the brain, fattening the body.

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Obesity is characterized by chronic activation of inflammatory pathways in peripheral tissues. In this issue, Zhang et al. (2008) demonstrate that inflammation also occurs in the central nervous system where it disrupts activity of the hypothalamus leading to resistance to leptin that is mediated by activation of IKK and the endoplasmic reticulum stress response.

PMID: 18854151 [found with GoPubMed]

49: Endocrinology 2008 Jun;

A new organotypic culture of adipose tissue fragments maintains viable mature adipocytes for a long term, together with development of immature adipocytes and mesenchymal stem cell-like cells.

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Adipose tissue that consists of mature and immature adipocytes is suggested to contain mesenchymal stem cells (MSCs), but a culture system for analyzing their cell types within the tissue has not been established. Here we show that three-dimensional collagen gel culture of rat subcutaneous adipose tissue fragments maintained viable mature adipocytes for a long term, producing immature adipocytes and MSC-like cells from the fragments, using immunohistochemistry, ELISA and real time RT-PCR. Bromodeoxyuridine uptake of mature adipocytes was detected. Adiponectin and leptin, and adipocyte-specific genes of adiponectin, leptin and PPAR-gamma were detected in culture assembly, while the lipogenesis factor insulin (20 mU/ml) and inflammation-related agent tumor necrosis factor-alpha (2 nM) increased and decreased, respectively, all of their displays. Both spindle-shaped cell types with oil red O-positive lipid droplets and those with expression of MSC markers (CD105 and CD44) developed around the fragments. The data indicate that adipose tissue-organotypic culture retains unilocular structure, proliferative ability and some functions of mature adipocytes, generating both immature adipocytes and CD105+/CD44+ MSC-like cells. This suggests that our method will open up a new way for studying both multiple cell types within adipose tissue and the cell-based mechanisms of obesity and metabolic syndrome.

PMID: 18535101 [found with GoPubMed]

50: Metabolism 2008 Oct;57(10):1414-21

Adipokines influencing metabolic and cardiovascular disease are differentially regulated in maintenance hemodialysis.

Ziegelmeier M, Bachmann A, Seeger J, Lossner U, Kratzsch J, Blüher M, Stumvoll M, Fasshauer M

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Adipokines including leptin, adiponectin, visfatin, resistin, and interleukin (IL)-6 significantly influence energy metabolism, insulin sensitivity, and cardiovascular health. In the current study, we investigated serum levels of these adipokines in diabetic and nondiabetic patients on maintenance hemodialysis (MD) as compared with controls with a glomerular filtration rate greater than 50 mL/min. Serum leptin, adiponectin, high-molecular-weight (HMW) adiponectin, visfatin, resistin, and IL-6 were determined by enzyme-linked immunosorbent assay in control (n = 60) and MD (n = 60) patients and correlated to clinical and biochemical measures of renal function, glucose, and lipid metabolism, as well as

inflammation. Adiponectin, visfatin, resistin, and IL-6 were significantly elevated in MD patients as compared with controls. In multivariate analyses, sex and body mass index were independently correlated with serum leptin levels in both controls and MD patients. Furthermore, insulin resistance was independently and negatively associated with adiponectin and HMW adiponectin in both groups. Moreover, circulating resistin levels were independently correlated with serum visfatin concentrations in control and MD patients. However, various independent associations were only found in either controls or patients on MD. Thus, serum IL-6 levels were strongly and independently associated with C reactive protein and resistin in MD patients but not control subjects. We show that levels of various adipokines are significantly increased in MD patients. Furthermore, regulation of adipokines in vivo strongly depends on renal function. Regulation of HMW adiponectin is similar as compared with total adiponectin in the patients studied.

PMID: 18803947 [found with GoPubMed]

51: Perit Dial Int 2008;28(5):527-32

Concentration of adipokines in peritoneal effluent: a new marker of acute peritonitis in peritoneal dialysis patients?

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BACKGROUND: An early and reliable diagnostic procedure for acute peritonitis in patients on peritoneal dialysis (PD) without typical clinical symptoms remains an important challenge in modern nephrology. During the first days of peritonitis, establishing the diagnosis based on peritoneal effluent pleocytosis and inflammatory markers [C-reactive protein (CRP) or interleukin-6] is not efficient in all cases. Increased peritoneal membrane permeability is a well-known consequence of peritonitis. Therefore, we evaluated the concentrations of selected circulating adipose tissue-derived proteins in the peritoneal effluent of PD patients with episodes of acute peritonitis. Material and METHODS: Concentrations of adiponectin and leptin, in both plasma and peritoneal effluent, were assessed in 24 adult PD patients with peritonitis episodes confirmed by clinical symptoms and/or microbiological tests, and in 23 PD patients without signs and symptoms of inflammation (control group). RESULTS: In peritoneal effluent collected from patients with acute peritonitis (also without pleocytosis or increased CRP), both adiponectin and leptin concentrations were markedly elevated: adiponectin 744.1 (344.2 - 1144.1) ng/mL vs 4.8 (3.1 - 6.5) ng/mL; leptin 16.3 (9.4 - 23.1) ng/mL vs 5.1 (0.5 - 9.6) ng/mL. Receiver operating characteristic analyses revealed that peritoneal effluent adiponectin concentration >180 ng/mL has 100% sensitivity and 100% specificity, while peritoneal effluent leptin concentration >11.0 ng/mL has 58.3% sensitivity and 95.5% specificity for the diagnosis of acute peritonitis. The increases in adiponectin and leptin concentrations in peritoneal effluent were not consequences of changes in their plasma levels. A positive correlation between peritoneal effluent and plasma concentrations of adiponectin and leptin in patients with peritonitis was found. CONCLUSION: Increased concentration of leptin and especially adiponectin in peritoneal effluent seems to be a valuable and new early marker of high peritoneal membrane permeability due to acute peritonitis.

PMID: 18708547 [found with GoPubMed]

52: Int J Cardiol 2008 Aug;

A new frame in thromboembolic cardiovascular disease: Adipocytokine.

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Recent researches have shown that adipocytokines secreted by adipose tissue play an important role in inflammation which is considered to be a crucial step in the pathogenesis of atherosclerosis. Leptin, one of the earlier adipocytokines, is known to play a major role in cardiovascular disease and recent observations suggest that leptin is an independent risk factor for coronary heart disease. Resistin, another recently discovered adipocytokine, has been related to risk factors of atherosclerosis, and in diabetic individuals serum resistin levels correlate well with inflammatory markers and are predictive for the development of cardiovascular disease. Adiponectin, another adipocytokine of interest in recent years, seems to be the most promising one studied to date. In contrast to leptin and resistin, adiponectin seems to be beneficial for health and it is a protective factor and decreased in obesity. However, many other factors derived from adipose tissue have also been discovered, such as interleukin-6, tumor necrosis factor alpha, monocyte chemoattractant protein 1, apelin, visfatin and probably others awaiting discovery in the near future. In this paper, we discussed the role of adipocytokines in the pathogenesis of atherosclerotic cardiovascular disease.

PMID: 18723235 [found with GoPubMed]

53: Br J Nutr 2008 Apr;:1-9

Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity?

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White adipose tissue is a key endocrine and secretory organ, releasing multiple adipokines, many of which are linked to inflammation and immunity. During the expansion of adipose tissue mass in obesity there is a major inflammatory response in the tissue with increased expression and release of inflammation-related adipokines, including IL-6, leptin, monocyte chemoattractant protein-1 and TNF-alpha, together with decreased adiponectin production. We proposed in 2004 (Trayhurn & Wood, Br J Nutr 92, 347-355) that inflammation in adipose tissue in obesity is a response to hypoxia in enlarged adipocytes distant from the vasculature. Hypoxia has now been directly demonstrated in adipose tissue of several obese mouse models (ob/ob, KKAy, diet-induced) and molecular studies indicate that the level of the hypoxia-inducible transcription factor, hypoxia-inducible factor-1alpha, is increased, as is expression of the hypoxia-sensitive marker gene, GLUT1. Cell- culture studies on murine and human adipocytes show that hypoxia (induced by low O2 or chemically) leads to stimulation of the expression and secretion of a number of inflammation-related adipokines, including angiopoietin-like protein 4, IL-6, leptin, macrophage migration inhibitory factor and vascular endothelial growth factor. Hypoxia also stimulates the inflammatory response of macrophages and inhibits adipocyte differentiation from preadipocytes. GLUT1 gene expression,

protein level and glucose transport by human adipocytes are markedly increased by hypoxia, indicating that low O2 tension stimulates glucose utilisation. It is suggested that hypoxia has a pervasive effect on adipocyte metabolism and on overall adipose tissue function, underpinning the inflammatory response in the tissue in obesity and the subsequent development of obesity-associated diseases, particularly type 2 diabetes and the metabolic syndrome.

PMID: 18397542 [found with GoPubMed]

54: J Am Coll Cardiol 2008 Jul;52(3):231-6

Adipokines, insulin resistance, and coronary artery calcification.

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OBJECTIVES: We evaluated the hypothesis that plasma levels of adiponectin and leptin are independently but oppositely associated with coronary artery calcification (CAC), a measure of subclinical atherosclerosis. In addition, we assessed which biomarkers of adiposity and insulin resistance are the strongest predictors of CAC beyond traditional risk factors, metabolic syndrome, and plasma C-reactive protein (CRP). BACKGROUND: Adipokines are fat-secreted biomolecules with pleiotropic actions that converge in diabetes and cardiovascular disease. METHODS: We examined the association of plasma adipocytokines with CAC in 860 asymptomatic, nondiabetic participants in the SIRCA (Study of Inherited Risk of Coronary Atherosclerosis). RESULTS: Plasma adiponectin and leptin levels had opposite and distinct associations with adiposity, insulin resistance, and inflammation. Plasma leptin was positively (top vs. bottom quartile) associated with higher CAC after adjustment for age, gender, traditional risk factors, and Framingham risk scores (tobit regression ratio 2.42 (95% confidence interval [CI]: 1.48 to 3.95; p = 0.002) and further adjustment for metabolic syndrome and CRP (tobit regression ratio: 2.31; 95% CI: 1.36 to 3.94; p = 0.002). In contrast, adiponectin levels were not associated with CAC. Comparative analyses suggested that levels of leptin, interleukin-6, and soluble tumor necrosis factor receptor-2, as well as the homeostasis model assessment of insulin resistance (HOMA-IR) index, predicted CAC scores, but only leptin and HOMA-IR provided value beyond risk factors, metabolic syndrome, and CRP. CONCLUSIONS: In SIRCA, although both leptin and adiponectin levels were associated with metabolic and inflammatory markers, only leptin was a significant independent predictor of CAC. Of several metabolic markers, leptin and the HOMA-IR index had the most robust, independent associations with CAC.

PMID: 18617073 [found with GoPubMed]

55: Clin Appl Thromb Hemost 2007 Dec;

Adipokines, Linking Adipocytes and Vascular Function in Hemodialyzed Patients, May Also Be Possibly Related to CD146, a Novel Adhesion Molecule.

Malyszko J, Malyszko JS, Kozminski P, Pawlak K, Mysliwiec M

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Possible correlations between adiponectin, leptin, CD146, a novel adhesion molecule localized at the endothelial junction, and other markers of endothelial cell injury, von Willebrand factor, thrombomodulin, vascular cell adhesion molecule, and intracellular adhesion molecule, and markers of inflammation, tumor necrosis factor-alpha, interleukin-6, and high-sensitivity C-reactive protein in nondiabetic hemodialyzed patients with and without coronary artery disease were studied. Markers of endothelial dysfunction were elevated in hemodialyzed patients, predominantly with coronary artery disease. In multivariate analysis, kinetic urea modeling and plasminogen activator inhibitor-1 remained the only positive predictors of adiponectin. In multivariate analysis, predictors of leptin were triglycerides, tissue plasminogen activator, CD146, and coronary artery disease. In multivariate analysis, predictors of CD146 were age, hemoglobin, and adiponectin. Elevated adiponectin correlated to CD146 may be the expression of a counterregulatory response aimed at mitigating the consequences in endothelial damage and increased cardiovascular risk in renal failure. The data provide further support for a link between adipocytokines, endothelial dysfunction, cardiovascular risk, and renal failure.

PMID: 18160586 [found with GoPubMed]

56: J Clin Endocrinol Metab 2008 Apr;

Insulin sensitivity is correlated with subcutaneous but not visceral body fat in overweight and obese prepubertal children.

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Aim: to explore the relationship between insulin sensitivity, body fat distribution, ectopic (liver and skeletal muscle) fat deposition, adipokines (leptin and adiponectin) and inflammation markers (hsCRP, IL-6, IL-10 and TNF-alpha) in prepubertal children. Subjects and methods: Thirty overweight and obese children (M/F:16/14; BMI z-score range: 1.1-3.2) were recruited. Body fat distribution and fat accumulation in liver and skeletal muscle were measured using Magnetic Resonance imaging (MRI). Insulin sensitivity was assessed by IVGTT. Results: Insulin sensitivity was associated with subcutaneous abdominal adipose tissue ($r= -0.52$; $P<0.01$) and liver fat content ($r= -0.44$; $P<0.02$), but not with visceral abdominal adipose tissue (VAT) ($r= -0.193$; P=NS) and fat accumulation in skeletal muscle ($r= -0.210$; P=NS). Adipokines, but not inflammation markers, were significantly correlated to insulin sensitivity. VAT correlated with CRP ($r = 0.55$; $P<0.01$) as well as adiponectin ($r = -0.53$; $P<0.01$). Multiple regression analysis showed that only subcutaneous adipose tissue and fat liver content were independently correlated to insulin sensitivity ($p<0.01$; 20% and 16% of explained variance, respectively). Conclusions: In overweight and moderately obese prepubertal children, insulin sensitivity was negatively correlated with subcutaneous abdominal adipose tissue (SAT) and liver fat content. Furthermore, contrary to adults, VAT and inflammation markers were not correlated with insulin sensitivity in children.

PMID: 18397988 [found with GoPubMed]

57: Arch Gerontol Geriatr 2008 Jan;

Adipocytokines in Down's syndrome, an atheroma-free model: Role of adiponectin.

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Down's syndrome (DS) is the most frequent chromosomal aberration in men. Moreover DS is considered an atheroma-free model. Plasma levels of interleukin-6 (IL-6), tumor necrosis factor-alpha high sensitivity (hsTNF-alpha), leptin and adiponectin from non-demented DS subjects of three different age cohorts (2-14, 20-50 and above 60 years) and healthy controls were measured. No clinical and sub-clinical inflammation was apparent in DS patients. Plasma levels of hsTNF-alpha, IL-6 and leptin were higher in children than in adult and old DS subjects. Instead, serum levels of adiponectin were increased in older DS patients than in DS children and adults. High levels of circulating adiponectin might protect DS from clinical complications of atherosclerosis.

PMID: 18207581 [found with GoPubMed]

58: Biochem Biophys Res Commun 2008 Oct;

SOCS-1 deficiency does not prevent diet-induced insulin resistance.

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Obesity is associated with inflammation and increased expression of suppressor of cytokine signaling (SOCS) proteins, which inhibit cytokine and insulin signaling. Thus, reducing SOCS expression could prevent the development of obesity-induced insulin resistance. Using SOCS-1 knockout mice, we investigated the contribution of SOCS-1 in the development of insulin resistance induced by a high-fat diet (HFD). SOCS-1 knockout mice on HFD gained 70% more weight, displayed a 2.3-fold increase in epididymal fat pads mass and increased hepatic lipid content. This was accompanied by increased mRNA expression of leptin and the macrophage marker CD68 in white adipose tissue and of SREBP1c and FAS in liver. HFD also induced hyperglycemia in SOCS-1 deficient mice with impairment of glucose and insulin tolerance tests. Thus, despite the role of SOCS proteins in obesity-related insulin resistance, SOCS-1 deficiency alone is not able to prevent insulin resistance induced by a diet rich in fat.

PMID: 18929539 [found with GoPubMed]

59: Dig Dis Sci 2008 Dec;

Adipose Tissue: The New Endocrine Organ? A Review Article.

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Fat is either white or brown, the latter being found principally in neonates. White fat, which comprises adipocytes, pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes, actively participates in hormonal and inflammatory systems. Adipokines include hormones such as leptin, adiponectin, visfatin, apelin, vaspin, hepcidine, chemerin, omentin, and inflammatory cytokines, including tumor necrosis factor alpha (TNF), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator protein (PAI). Multiple roles in metabolic and inflammatory responses have been assigned to adipokines; this review describes the molecular actions and clinical significance of the more important adipokines. The array of adipokines evidences diverse roles for adipose tissue, which looms large in the mediators of inflammation and metabolism. For this reason, treating obesity is more than a reduction of excess fat; it is also the treatment of obesity's comorbidities, many of which will some day be treated by drugs that counteract derangements induced by adipokine excesses.

PMID: 19052866 [found with GoPubMed]

60: Clin Invest Med 2008;31(6):E373

The relationship of inflammatory cytokines with asthma and obesity.

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Objectives: Obesity is considered a risk factor for asthma. However, the mechanism that connects the two is not well understood. In this study we investigated the relationship between inflammatory cytokines and acute phase reactants in obesity, and asthma. Method: Asthmatic and control subjects were divided into 2 sub-groups: obese and non-obese. Anthropomorphic parameters, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leptin, tumour necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) were compared between obese, asthmatics and control subjects of normal weight. Respiratory function tests and allergy skin tests were also performed in the patients with asthma. Results: ESR, CRP, TNF-α, IL-6, and leptin levels in obese asthma patients were higher than in the healthy controls (P < 0.01). TNF-α, IL-6, and leptin levels were higher in obese asthma patients than in non-obese asthma patients (P < 0.01). Inflammatory markers were related to parameters of obesity. No association was found between allergy test results and obesity (P > 0.05). Conclusion: We identified a relationship between acute phase reactants and inflammatory cytokines, and the criteria for obesity in obese asthma patients. Inflammation markers were at their highest levels in obese asthma patients. Leptin levels were considerably higher in obese patients than in normal weight controls. Like obesity, leptin is suggested to play a role in the pathogenesis of asthma.

PMID: 19032908 [found with GoPubMed]

61: Lab Invest 2008 Sep;

Critical role of the NADPH oxidase subunit p47(phox) on vascular TLR expression and neointimal lesion formation in high-fat diet-induced obesity.

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Reactive oxygen species (ROS) formation is associated with inflammation and vasculature dysfunction. We investigated the potential role of the NADPH oxidase on vascular Toll-like receptor (TLR) expression and carotid neointimal formation in high-fat (HF) diet-induced obesity (DIO) model. Using mice DIO and common carotid artery flow cessation-induced lesion formation models, we examined vascular TLR2 and TLR4 expression and neointimal formation in NADPH oxidase subunit p47(phox)-deficient (p47(phox-/-)) mice. Feeding C57BL/6J mice an HF diet for 22 weeks resulted in significant increases in p47(phox), TLR2 and TLR4 expression in vascular tissues compared with mice fed a low-fat (LF) diet. Minimal changes in TLR2 and TLR4 expression was detected in p47(phox-/-) DIO mice. Furthermore, flow cessation-induced angiogenic and inflammatory response and neointimal formation were significantly attenuated in p47(phox-/-) DIO mice compared with wild-type DIO mice. In addition, exposure of endothelial cells to leptin led to ROS formation; this was accompanied by upregulation of TLR2, TLR4 expression and its downstream signaling. Leptin also increased endothelial cell migration and proliferation. Pharmacological inhibition of NADPH oxidase or genetic deletion of p47(phox) significantly diminished these alterations. Obesity increases neointimal formation via a mechanism involving p47(phox)-TLRs signaling, suggesting that the NADPH oxidase may represent a potential novel therapeutic target for the treatment of obesity-associated vascular inflammation and dysfunction.Laboratory Investigation advance online publication, 8 September 2008; doi:10.1038/labinvest.2008.92.

PMID: 18779779 [found with GoPubMed]

62: J Lipid Res 2008 Nov;

Effect of dietary monosodium glutamate on trans fat-induced nonalcoholic fatty liver disease.

Collison KS, Maqbool Z, Saleh SM, Inglis A, Makhoul NJ, Bakheet R, Al-Johi M, Al-Rabiah R, Zaidi MZ, Al-Mohanna FA

The effect of dietary Monosodium Glutamate (MSG) on Trans-Fatty Acid (TFA)-induced nonalcoholic fatty liver disease (NAFLD) are addressed in an animal model. We used Affymetrix microarray to investigate hepatic gene expression and the contribution of visceral White Adipose Tissue (WAT) to diet-induced NAFLD. Trans-fat feeding increased serum leptin, Free Fatty Acid (FFA), HDL-C and total cholesterol (T-CHOL) levels, whilst robustly elevating the expression of genes involved in hepatic lipogenesis including the transcription factor SREBP1c. Histological examination revealed hepatic macrosteatosis in TFA-fed animals. Conversely, dietary MSG at doses similar to human average daily intake caused hepatic microsteatosis and the expression of ss-oxidative genes. Serum Triglyceride (Tg), FFA and insulin levels were elevated in MSG-treated animals. The abdominal cavities of TFA or MSG-treated animals had increased WAT deposition compared to control animals fed ad lib standard chow. WAT adipocytes were enlarged by TFA or MSG treatment, and microarray analysis of WAT gene expression revealed increased lipid biosynthetic gene expression, together with a 50% decrease in the key transcription factor Ppargc1a. A combination of TFA+MSG resulted

in the highest levels of serum HDL-C, T-CHOL and Leptin. Microarray analysis of TFA+MSG-treated livers showed elevated expression of markers of hepatic inflammation, lipid storage, cell damage and cell cycle impairment. TFA+MSG mice also had a high degree of WAT deposition and lipogenic gene expression. Levels of Ppargc1a were further reduced to 25% by TFA+MSG treatment. Conclusion: MSG exacerbates TFA induced NAFLD.

PMID: 19001666 [found with GoPubMed]

63: Am J Obstet Gynecol 2008 Jun;

Differential placental gene expression in preeclampsia.

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OBJECTIVE: Candidate genes that are associated with preeclampsia have not been described fully. We conducted microarray and confirmatory quantitative real time polymerase chain reaction studies to investigate global placental gene expression in preeclampsia. STUDY DESIGN: RNA was extracted from placental samples that were collected from 18 preeclampsia cases and 18 normotensive control subjects. Oligonucleotide probes that represented 22,000 genes were used to measure gene expression in each sample. Differential gene expression was evaluated with the Student t test, fold change assessment, and significance analysis of microarrays. Functions and functional relationships of differentially expressed genes were evaluated. RESULTS: Genes (n = 58) that participated in immune system, inflammation, oxidative stress, signaling, growth, and development pathways were expressed differentially in preeclampsia. These genes included previously described candidate genes (such as leptin), potential candidate genes with related functions (such as CYP11A) and novel genes (such as CDKN1C). CONCLUSION: Expression of genes (both candidate and novel) with diverse functions is associated with preeclampsia risk, which reflects the complex pathogenesis.

PMID: 18533121 [found with GoPubMed]

64: Am J Physiol Endocrinol Metab 2008 Sep;

In situ profiling of adipokines in subcutaneous microdialysates from lean and obese individuals.

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Adipose tissue (AT) emerges as an endocrine organ and a key regulator of the metabolically triggered inflammation. The aims of this study were: 1) to investigate the usefulness of a multiplexed bioassay at characterizing a panel of adipokines in subcutaneous (sc) microdialysate samples; and 2) to determine whether lean and obese individuals differ in their interstitial adipokines levels following microdialysis (MD) probe insertion. Ultrafiltrating MD membranes were inserted in opposite sites of the sc abdominal AT of six lean (L) and six obese (OB) males at the beginning (M1) and during the last 120 min (M2) of the study. Interstitial (i) and serum (s) concentrations of adipokines were quantified by Luminex technique and

ELISA at 60-min intervals for 5 h. In comparison with L, OB subjects exhibited elevated (i)leptin (p<0.001), (i)IL-8 (p<0.05) and (i)IL-18 levels (p=0.05), as well as higher serum concentrations of leptin (p<0.0001), (s)IL-6 (p<0.0001), (s)TNF-alpha (p<0.001), (s)IL-8 (p=0.01) and (s)IP-10 (p<0.05). In samples from the M1 membranes, leptin decreased, IL-1alpha, IL-18 and RANTES remained relatively stable, while IL-6, IL-8 and MCP-1 significantly increased after the first hour (p<0.0001 vs basal). Notably, either the magnitude of increase from the initial values or the time pattern of all the adipokines in M1 and M2 dialysates were similar between the groups. In conclusion, the current work provides valuable information on the optimal time frame to collect in situ AT microdialysate samples. Further studies are however needed to unravel the intricate interplay of cytokines in AT interstitial fluid. Key words: adipose tissue, inflammation, subcutaneous microdialysis.

PMID: 18780773 [found with GoPubMed]

65: J Clin Endocrinol Metab 2008 Nov;93(11 Suppl 1):S64-73

Adipocytokines and the metabolic complications of obesity.

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CONTEXT: Adipose tissue is increasingly recognized as an active endocrine organ with many secretory products and part of the innate immune system. With obesity, macrophages infiltrate adipose tissue, and numerous adipocytokines are released by both macrophages and adipocytes. Adipocytokines play important roles in the pathogenesis of insulin resistance and associated metabolic complications such as dyslipidemia, hypertension, and premature heart disease. EVIDENCE ACQUISITION: Published literature was analyzed with the intent of addressing the role of the major adipose secretory proteins in human obesity, insulin resistance, and type 2 diabetes. EVIDENCE SYNTHESIS: This review analyzes the characteristics of different adipocytokines, including leptin, adiponectin, pro-inflammatory cytokines, resistin, retinol binding protein 4, visfatin, and others, and their roles in the pathogenesis of insulin resistance. CONCLUSIONS: Inflamed fat in obesity secretes an array of proteins implicated in the impairment of insulin signaling. Further studies are needed to understand the triggers that initiate inflammation in adipose tissue and the role of each adipokine in the pathogenesis of insulin resistance.

PMID: 18987272 [found with GoPubMed]

66: Mol Med 2008;14(11-12):741-51

Adipokines and insulin resistance.

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Obesity is associated with an array of health problems in adult and pediatric populations. Understanding the pathogenesis of obesity and its metabolic sequelae has advanced rapidly over the past decades. Adipose tissue represents an active endocrine organ that, in addition to regulating fat mass and nutrient homeostasis, releases a large number of bioactive

mediators (adipokines) that signal to organs of metabolic importance including brain, liver, skeletal muscle, and the immune system-thereby modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis. In the present review, we summarize current data on the effect of the adipose tissue-derived hormones adiponectin, chemerin, leptin, omentin, resistin, retinol binding protein 4, tumor necrosis factor-alpha and interleukin-6, vaspin, and visfatin on insulin resistance.

PMID: 19009016 [found with GoPubMed]

67: Eur J Endocrinol 2008 Oct;

Serum levels of adipocyte fatty acid binding protein are increased in gestational diabetes mellitus.

Kralisch S, Stepan H, Kratzsch J, Verlohren M, Verlohren HJ, Drynda K, Lossner U, Bluher M, Stumvoll M, Fasshauer M

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Objective: Adipocyte fatty acid binding protein (AFABP) was recently introduced as a novel adipokine, serum levels of which independently correlate with the development of the metabolic syndrome and cardiovascular disease in humans. In the current study, we investigated serum concentrations of AFABP in patients with gestational diabetes mellitus (GDM) as compared to healthy pregnant controls matched for gestational age and fasting insulin. Design and Methods: AFABP was determined by ELISA in control (n=80) and GDM (n=40) patients and correlated to clinical and biochemical measures of renal function, glucose and lipid metabolism, as well as inflammation, in both groups. Results: Median serum AFABP concentrations were significantly elevated in subjects with GDM (22.9 mug/l) as compared to healthy pregnant controls (18.3 mug/l) ($p < 0.05$). Furthermore, GDM was independently associated with AFABP concentrations in multiple regression analysis ($p < 0.05$). In addition, markers of adiposity (body mass index, serum leptin), triglycerides, and serum creatinine were independently associated with circulating AFABP ($p < 0.05$). Conclusions: Maternal AFABP concentrations are significantly increased in GDM. The adipokine might contribute to the increased metabolic and cardiovascular risk of the disease.

PMID: 18849305 [found with GoPubMed]

68: Cell 2008 Oct;135(1):61-73

Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity.

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Overnutrition is associated with chronic inflammation in metabolic tissues. Whether metabolic inflammation compromises the neural regulatory systems and therefore promotes overnutrition-associated diseases remains unexplored. Here we show that a mediator of metabolic inflammation, IKKbeta/NF-kappaB, normally remains inactive although enriched in hypothalamic neurons. Overnutrition atypically activates hypothalamic

IKKbeta/NF-kappaB at least in part through elevated endoplasmic reticulum stress in the hypothalamus. While forced activation of hypothalamic IKKbeta/NF-kappaB interrupts central insulin/leptin signaling and actions, site- or cell-specific suppression of IKKbeta either broadly across the brain or locally within the mediobasal hypothalamus, or specifically in hypothalamic AGRP neurons significantly protects against obesity and glucose intolerance. The molecular mechanisms involved include regulation by IKKbeta/NF-kappaB of SOCS3, a core inhibitor of insulin and leptin signaling. Our results show that the hypothalamic IKKbeta/NF-kappaB program is a general neural mechanism for energy imbalance underlying obesity and suggest that suppressing hypothalamic IKKbeta/NF-kappaB may represent a strategy to combat obesity and related diseases.

PMID: 18854155 [found with GoPubMed]

69: Am J Clin Nutr 2008 Oct;88(4):950-8

Positive energy balance is associated with accelerated muscle atrophy and increased erythrocyte glutathione turnover during 5 wk of bed rest.

Biolo G, Agostini F, Simunic B, Sturma M, Torelli L, Preiser JC, Deby-Dupont G, Magni P, Strollo F, di Prampero P, Guarnieri G, Mekjavic IB, Pisot R, Narici MV

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BACKGROUND: Physical inactivity is often associated with positive energy balance and fat gain. OBJECTIVE: We aimed to assess whether energy intake in excess of requirement activates systemic inflammation and antioxidant defenses and accelerates muscle atrophy induced by inactivity. DESIGN: Nineteen healthy male volunteers were studied before and at the end of 5 wk of bed rest. Subjects were allowed to spontaneously adapt to decreased energy requirement (study A, n = 10) or were provided with an activity-matched diet (study B, n = 9). Groups with higher (HEB) or lower (LEB) energy balance were identified according to median values of inactivity-induced changes in fat mass (DeltaFM, assessed by bioelectrical impedance analysis). RESULTS: In pooled subjects (n = 19; median DeltaFM: 1.4 kg), bed rest-mediated decreases in fat-free mass (bioelectrical impedance analysis) and vastus lateralis thickness (ultrasound imaging) were significantly greater (P < 0.03) in HEB(AB) (-3.8 +/- 0.4 kg and -0.32 +/- 0.04 cm, respectively) than in LEB(AB) (-2.3 +/- 0.5 kg and -0.09 +/- 0.04 cm, respectively) subjects. In study A (median DeltaFM: 1.8 kg), bed rest-mediated increases in plasma leptin, C-reactive protein, and myeloperoxidase were greater (P < 0.04) in HEB(A) than in LEB(A) subjects. Bed rest-mediated changes of glutathione synthesis rate in eythrocytes (l-[3,3-(2)H(2)]cysteine incorporation) were greater (P = 0.03) in HEB(A) (from 70 +/- 19 to 164 +/- 29%/d) than in LEB(A) (from 103 +/- 23 to 84 +/- 27%/d) subjects. CONCLUSIONS: Positive energy balance during inactivity is associated with greater muscle atrophy and with activation of systemic inflammation and of antioxidant defenses. Optimizing caloric intake may be a useful strategy for mitigating muscle loss during period of chronic inactivity.

PMID: 18842781 [found with GoPubMed]

70: Ann Allergy Asthma Immunol 2008 Oct;101(4):350-7

Obstructive sleep apnea syndrome and asthma: the role of continuous positive airway pressure treatment.

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OBJECTIVE: To review the concept of a possible link between asthma and obstructive sleep apnea syndrome (OSAS) and the impact on asthma symptoms of treatment of OSAS with continuous positive airway pressure (CPAP) in patients with both conditions. DATA SOURCES: The Ovid, MEDLINE, and PubMed databases from 1950 to the present were searched for relevant articles regarding a possible relationship between asthma and OSAS and the effectiveness of CPAP in treating OSAS. STUDY SELECTION: Articles describing pathophysiologic conditions occurring in OSAS that may be linked to asthma pathogenesis were used for this review. RESULTS: The data suggest that OSAS is an independent risk factor for asthma exacerbations. CPAP has been shown in prospective clinical studies to have a positive impact on asthma outcome in patients with concomitant OSAS. Ameliorative mechanisms of treatment with CPAP include mechanical and neuromechanical effects, gastroesophageal acid reflux suppression, local and systemic anti-inflammatory effects (including suppression of increased serum levels of inflammatory cytokines, chemokines, and vascular endothelial growth factor), cardiac function improvements, leptin level suppression, weight reduction, and sleep restoration. CONCLUSIONS: Asthma and OSAS are increasingly troublesome public health issues. Mounting evidence implicates OSAS as a risk factor for asthma exacerbations, thereby linking these 2 major epidemics. We describe potential mechanisms whereby CPAP, the first line of therapy for OSAS, might modify airway smooth muscle function and asthma control in patients with both disorders. Despite the ever-increasing population of patients with both disorders, large, prospective, randomized controlled studies are necessary to more fully evaluate CPAP and asthma outcomes.

PMID: 18939721 [found with GoPubMed]

71: Arch Physiol Biochem 2008 Oct;114(4):267-76

Hypoxia and the endocrine and signalling role of white adipose tissue.

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White adipose tissue is a major endocrine and signalling organ. It secretes multiple protein hormones and factors, termed adipokines (such as adiponectin, leptin, IL-6, MCP-1, TNFalpha) which engage in extensive cross-talk within adipose tissue and with other tissues. Many adipokines are linked to inflammation and immunity and these include cytokines, chemokines and acute phase proteins. In obesity, adipose tissue exhibits a major inflammatory response with increased production of inflammation-related adipokines. It has been proposed that hypoxia may underlie the inflammatory response in adipose tissue and evidence that the tissue is hypoxic in obesity has been obtained in animal models. Cell culture studies have demonstrated that the expression and secretion of key adipokines, including leptin, IL-6 and VEGF, are stimulated by hypoxia, while adiponectin (with an anti-inflammatory action) production falls. Hypoxia

also stimulates glucose transport by adipocytes and may have a pervasive effect on cell function within adipose tissue.

PMID: 18946787 [found with GoPubMed]

72: Arch Physiol Biochem 2008 Oct;114(4):237-43

Metabolic syndrome in children and adolescents - risk for sleep-disordered breathing and obstructive sleep-apnoea syndrome?

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The clinical relevance of the term "metabolic syndrome", the definition criteria, and predictive power are being disputed. Inclusion of sleep-disordered breathing and sleep apnoea into a definition of metabolic syndrome is also controversial once children and/or adolescents are affected. Nevertheless, along with the increasing prevalence of childhood obesity, the prevalence of the metabolic syndrome in obese children is reported at 30%, irrespective of the definition applied. Moreover, childhood obesity is associated with sleep-disordered breathing. Adipocytokines, cytokines secreted from adipose tissue, are thought to play a major role in the pathophysiology of metabolic syndrome. Leptin was initially suggested as a promising "anti-obesity" hormone. New concepts indicate that in humans leptin and its soluble receptor may be more important in states of energy deficiency rather than a predictor of the metabolic syndrome. Adiponectin, on the other hand, is not only related to obesity and insulin resistance, but appears to be the strongest predictor for metabolic syndrome, even in children. In newborns and infants, both adipocytokines occur in high concentrations, even though this cannot completely explain the increased risk for ensuing metabolic disease later in life. Finally, low-grade systemic inflammation may underlie the clustering of metabolic risk factors. Overall factors from the adipose tissue may constitute not only markers but also mediators of metabolic sequelae of obesity.

PMID: 18946784 [found with GoPubMed]

73: Atherosclerosis 2008 Feb;

Dietary salt restriction increases plasma lipoprotein and inflammatory marker concentrations in hypertensive patients.

Nakandakare ER, Charf AM, Santos FC, Nunes VS, Ortega K, Lottenberg AM, Mion D, Nakano T, Nakajima K, D'Amico EA, Catanozi S, Passarelli M, Quintão EC

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BACKGROUND: Dietary salt restriction has been reported to adversely modify the plasma lipoprotein profile in hypertensive and in normotensive subjects. We investigated the effects of the low sodium intake (LSI) on the plasma lipoprotein profile and on inflammation and thrombosis biomarkers during the fasting and postprandial periods. METHODS: Non-obese, non-treated hypertensive adults (n=41) were fed strictly controlled diets. An

initial week on a control diet (CD, Na=160mmol/day) was followed by 3 weeks on LSI (Na=60mmol/day). At admission and on the last day of each period, the 24-h ambulatory blood pressure was monitored and blood was drawn after an overnight fasting period and after a fat-rich test meal. RESULTS: The dietary adherence was confirmed by 24-h urinary sodium excretion. Fasting triglyceride (TG), chylomicron-cholesterol, hsC-reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) concentrations, renin activity, aldosterone, insulin, and homeostasis model assessment insulin resistance (HOMA-IR) values were higher, but non-esterified fatty acids (NEFA) were lower on LSI than on CD. For LSI, areas under the curve (AUC) of TG, chylomicron-cholesterol, apoB and the cholesterol/apoB ratio were increased, whereas AUC-NEFA was lowered. LSI did not modify body weight, hematocrit, fasting plasma cholesterol, glucose, adiponectin, leptin, fibrinogen and factor VII (FVII), and AUC of lipoprotein lipase and of lipoprotein remnants. CONCLUSION: LSI induced alterations in the plasma lipoproteins and in inflammatory markers that are common features of the metabolic syndrome.

PMID: 18262533 [found with GoPubMed]

74: Can J Cardiol 2008 Oct;24(10):e65-9

A randomized, controlled trial of the effects of rosiglitazone on adipokines, and inflammatory and fibrinolytic markers in diabetic patients: study design and protocol.

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BACKGROUND: Although rosiglitazone may offer vascular benefits beyond lowering glucose, recently, concern has been raised that this drug may paradoxically increase cardiovascular risk. OBJECTIVE: To assess the effects of rosiglitazone compared with standard oral hypoglycemic therapies on adipokines, and inflammatory and fibrinolytic markers in subjects with type 2 diabetes. METHODS: A 12-week, randomized, open-label, parallel-group study will be conducted on 100 type 2 diabetic subjects with suboptimal glycemic control (glycosylated hemoglobin 0.075 or greater) despite management with lifestyle alone (drug-naive) or with monotherapy (either metformin or sulfonylurea). Drug-naive patients will be randomly assigned to receive either rosiglitazone (4 mg/day to 8 mg/day) or metformin (500 mg/day to 2000 mg/day). Patients on pre-existing monotherapy will be randomly assigned to the addition of rosiglitazone (4 mg/day to 8 mg/day), or to either metformin (500 mg/day to 2000 mg/day) or glyburide (5 mg/day to 20 mg/day) (depending on background treatment). The primary end point of the study is the change in adiponectin level (from baseline to 12 weeks) in the rosiglitazone versus metformin or sulfonylurea arms. Secondary end points include changes in leptin, high-sensitivity C-reactive protein, interleukin-6, tumour necrosis factor-alpha, matrix metalloproteinase-9, vascular cell adhesion molecule-1, plasminogen activator inhibitor type 1, insulin sensitivity, glycosylated hemoglobin and lipid levels. Additionally, all patients will be required to be treated with an inhibitor of the renin-angiotensin system, namely an angiotensin receptor antagonist, as per national diabetes treatment guidelines, to a target systolic blood pressure of less than 130 mmHg and a diastolic blood pressure of less than 80 mmHg, or for the optimal suppression of microalbuminuria.

PMID: 18841263 [found with GoPubMed]

75: Chest 2008 Jul;

Effects of CPAP on Cardiovascular Risk Profile in Patients with Severe Obstructive Sleep Apnea and Metabolic Syndrome.

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Background The increased risk of atherosclerotic morbidity and mortality in patients with obstructive sleep apnea (OSA) has been linked to arterial hypertension, insulin resistance, systemic inflammation, and oxidative stress in previous studies. We aimed to determine the effects of 8-weeks therapy with continuous positive airway pressure (CPAP) on glucose and lipid profile, systemic inflammation, oxidative stress, and the global cardiovascular disease (CVD) risk in patients with severe OSA and metabolic syndrome. Methods In 32 patients, serum cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, fibrinogen, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB), high sensitivity C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), leptin, malondialdehyde (MDA) and erythrocytic glutathione peroxidase (GPx) activity were measured at baseline and after 8 weeks of CPAP. Insulin resistance index (HOMA-IR) was based on the homeostasis model assessment method, the CVD risk was calculated using the multivariable risk factor algorithm. Results In patients who used CPAP for >/=4 h.night(-1) (n=16), CPAP therapy reduced systolic and diastolic blood pressure (p=0.001; p=0.006, respectively), total cholesterol (p=0.002), ApoB (p=0.009), HOMA-IR (p=0.031), MDA (p=0.004), and TNF-alpha (p=0.037), and increased erythrocytic GPx activity (p=0.015), in association with reductions in the global CVD risk (from 18.8+/-9.8 to 13.9+/-9.7%, p=0.001). No significant changes were seen in patients who used CPAP for <4 h.night(-1). Mask leak was the strongest predictor of compliance with CPAP therapy. Conclusions In patients with severe OSA and metabolic syndrome, good compliance to CPAP may improve insulin sensitivity, reduce systemic inflammation and oxidative stress, and reduce the global CVD risk. Study registered at www.clinicaltrials.gov,No NCT00635674.

PMID: 18625666 [found with GoPubMed]

76: Diabetologia 2008 Aug;

Longitudinal changes in pancreatic and adipocyte hormones following Roux-en-Y gastric bypass surgery.

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AIMS/HYPOTHESIS: Bariatric surgery is an effective treatment for severe obesity, as in addition to dramatic weight loss, co-morbidities such as type 2 diabetes are frequently resolved. Although altered gastrointestinal peptide hormone secretion and its relationship with post-surgical improvements in insulin sensitivity has been studied, much less is known about long-term changes in pancreatic and adipose tissue-derived hormones. Our objective was to conduct a comprehensive longitudinal investigation of the endocrine changes following Roux-en-Y gastric bypass surgery (RYGBP),

focusing on pancreatic and adipocyte hormones and systemic markers of inflammation. METHODS: Nineteen severely obese women (BMI 45.6 +/- 1.6 kg/m(2)) were studied prior to RYGBP, and at 1, 3, 6, and 12 months after RYGBP. Body composition was assessed before surgery and at 1 and 12 months. RESULTS: Pre-surgical adiposity was correlated with circulating adipocyte hormones (leptin, visfatin) and inflammatory molecules (IL-6, high sensitivity C-reactive protein [hsCRP], monocyte chemoattractant protein-1). As expected, RYGBP reduced fat mass and fasting insulin and glucose concentrations. In addition, reductions of fasting pancreatic polypeptide (PP) and glucagon concentrations were observed at 1 and 3 months, respectively. In the 12 months following RYGBP, concentrations of most adipocyte hormones (leptin, acylation-stimulating hormone and visfatin, but not retinol-binding hormone-4) and inflammatory molecules (IL-6, hsCRP and soluble intracellular adhesion molecule-1) were significantly reduced. Reductions of insulin resistance (measured by homeostasis model assessment of insulin resistance) were independently associated with changes of glucagon, visfatin and PP. Pre-surgical HMW adiponectin concentrations independently predicted losses of body weight and fat mass. CONCLUSIONS/INTERPRETATION: These results suggest that pancreatic and adipocyte hormones may contribute to the long-term resolution of insulin resistance after RYGBP.

PMID: 18704364 [found with GoPubMed]

77: J Leukoc Biol 2008 Aug;

Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis.

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Calorie restriction (CR) prevents many age-associated diseases and prolongs the lifespan. CR induces multiple metabolic and physiologic modifications, including anti-inflammatory, antioxidant, and neuroprotective effects that may be beneficial in multiple sclerosis (MS). The present studies sought to determine whether CR or increased calorie intake alters the course of experimental autoimmune encephalomyelitis (EAE), the leading animal model for MS. SJL and C57BL/6 mice were subjected to 40% CR beginning at 5 weeks of age. After 5 weeks of CR, EAE was induced by immunizing with proteolipid protein in SJL mice and with myelin oligodendrocyte glycoprotein in C57BL/6 mice. Clinical, histologic, and immunologic features of EAE were compared with mice fed ad libitum and to SJL mice fed a high-fat, high-calorie diet. CR ameliorated clinical EAE in both mouse strains with less severe inflammation, demyelination, and axon injury. No suppression of immune function was observed. A high-calorie diet did not alter the EAE course. CR was associated with increased plasma levels of corticosterone and adiponectin and reduced concentrations of IL-6 and leptin. The CR-induced hormonal, metabolic, and cytokine changes observed in our studies suggest a combined anti-inflammatory and neuroprotective effect. CR with adequate nutrition and careful medical monitoring should be explored as a potential treatment for MS.

PMID: 18678605 [found with GoPubMed]

78: Metabolism 2008 Oct;57(10):1434-44

Renal and metabolic effects of tempol in obese ZSF(1) rats-distinct role for superoxide and hydrogen peroxide in diabetic renal injury.

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Oxidative stress, that is, overproduction of reactive oxygen species and reduced antioxidant system activity, is implicated in the pathogenesis of diabetic complications; and therefore, superoxide dismutase (SOD) mimetic tempol should be protective in diabetic kidney. However, the effects of tempol in metabolic syndrome-associated renal injury have not been thoroughly examined. In this study, we examined the effects of 9 weeks of treatment with tempol on metabolic status, renal oxidative stress, and kidney function and structure in obese, diabetic, hypertensive ZSF(1) rats and their nondiabetic, hypertensive, lean littermates. The obese rats had significantly reduced total SOD and catalase activity, increased peroxidase activity and lipid peroxidation, and higher level of protein oxidation in renal cortical tissue compared with their lean littermates. These changes were accompanied by renal injury (proteinuria; reduced excretory function; and markedly increased glomerular and interstitial inflammation, proliferation, and collagen IV synthesis). Tempol treatment slightly increased total SOD activity, significantly reduced lipid peroxidation and peroxidase activity, but had no effect on catalase and protein oxidation. Tempol had no effects on blood pressure, renal hemodynamics and excretory function, and proteinuria in obese rats, yet improved insulin sensitivity and reduced renal inflammatory, proliferative, and fibrotic changes. Because tempol possesses no catalase activity and, in diabetes, not only SOD but also catalase is inhibited, it is possible that the toxicity of hydrogen peroxide (H(2)O(2)) remains unaltered under tempol treatment. This study suggests that superoxide and H(2)O(2) may have distinct roles in the pathogenesis of diabetic renal injury, with superoxide mainly being involved in inflammatory, proliferative, and fibrotic changes, and H(2)O(2) in glomerular hemodynamics and proteinuria.

PMID: 18803950 [found with GoPubMed]

79: Metabolism 2008 Oct;57(10):1315-22

Independent and opposite associations of hip and waist circumference with metabolic syndrome components and with inflammatory and atherothrombotic risk factors in overweight and obese women.

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Recent studies have shown independent and opposite associations of hip circumference (HC) and waist circumference (WC) with glucose intolerance, insulin resistance, and type 2 diabetes mellitus. However, no studies have simultaneously considered the independent contributions of both markers to metabolic proinflammatory and atherosclerotic risk factors. In this study, we examine the independent associations of WC and HC with metabolic syndrome and with proinflammatory and atherothrombotic features. Independent associations of thigh muscle and adipose tissue (AT) compartments with metabolic features were also studied. Abdominal and thigh muscle and AT distributions were assessed by computed tomography in 140

overweight and obese women (mean +/- SD: age, 38.3 +/- 0.5 years; body mass index, 30.4 +/- 0.3 kg/m(2)). Blood lipids and inflammatory and atherothrombotic markers were measured. For a given WC, a larger HC was inversely associated with fasting insulin (beta = -0.288, P = .008), hemoglobin A(1c) (beta = -0.246, P = .041), and plasminogen activator inhibitor-1 concentrations (beta = -0.241, P = .023). Contrarily, WC was related with an unfavorable metabolic profile. For a given WC, higher total thigh AT and total thigh subcutaneous AT masses were associated with lower hemoglobin A(1c) (beta = -0.244, P = .049; beta = -0.233, P = .049) and low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (beta = -0.252, P = .040; beta = -0.245, P = .037). In addition, total thigh AT was related with leptin (beta = 0.310, P = .012), whereas total thigh subcutaneous AT revealed opposite associations with fasting insulin concentrations (beta = -0.239, P = .034). Total thigh muscular tissue mass was related with lower plasminogen activator inhibitor-1 (beta = -0.164, P = .049) and fibrinogen concentrations (beta = -0.222, P = .018). In conclusion, HC revealed independent and opposite associations with insulin resistance and atherothrombotic disturbances. Contrarily, a larger WC predicted an increased metabolic risk. These contrasting effects in diabetogenic and atherothrombotic disturbances were, respectively, mediated by gluteofemoral AT and thigh muscle tissue. Besides body mass index and WC screening relevance, HC can contribute to additionally predict health risk in overweight and obese women.

PMID: 18803932 [found with GoPubMed]

80: Dyn Med 2008 Sep;7(1):13

Femoral artery remodeling after aerobic exercise training without weight loss in women.

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ABSTRACT: BACKGROUND: It is currently unclear whether reductions in adiposity mediate the improvements in vascular health that occur with aerobic exercise. The purpose of this longitudinal study of 13 healthy women (33 +/- 4 years old) was to determine whether 14 weeks of aerobic exercise would alter functional measures of vascular health, namely resting aortic pulse wave velocity (aPWV, an index of arterial stiffness), femoral artery diameter (DFA), and femoral artery blood flow (BFFA) independent of changes in adiposity. Methods: Aerobic fitness was assessed as VO2peak normalized to fat-free mass, and adiposity (percent body fat) was determined by dual energy x-ray absorptiometry. Serum concentrations of proteins associated with risk for cardiovascular disease, including C-reactive protein (CRP), soluble intercellular adhesion molecule-1 (sICAM-1), and leptin, were also measured. Subjects cycled for 50 minutes, 3 times per week. Results: Aerobic fitness normalized to fat-free mass increased 6% (P=0.03) whereas adiposity did not change. Resting DFA increased 12% (P<0.001) and resting shear rate decreased 28% (P=0.007). Aortic PWV, and serum sICAM-1, CRP and leptin did not change with training. Conclusion: Significant reductions in adiposity were not necessary for aerobic exercise training to bring about improvements in aerobic fitness and arterial remodeling. Peripheral arterial remodeling occurred without changes in central arterial stiffness or markers of inflammation.

PMID: 18775082 [found with GoPubMed]

81: Eur Heart J 2008 Sep;

Adipose tissue dysfunction in obesity, diabetes, and vascular diseases.

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The classical perception of adipose tissue as a storage place of fatty acids has been replaced over the last years by the notion that adipose tissue has a central role in lipid and glucose metabolism and produces a large number of hormones and cytokines, e.g. tumour necrosis factor-alpha, interleukin-6, adiponectin, leptin, and plasminogen activator inhibitor-1. The increased prevalence of excessive visceral obesity and obesity-related cardiovascular risk factors is closely associated with the rising incidence of cardiovascular diseases and type 2 diabetes mellitus. This clustering of vascular risk factors in (visceral) obesity is often referred to as metabolic syndrome. The close relationship between an increased quantity of visceral fat, metabolic disturbances, including low-grade inflammation, and cardiovascular diseases and the unique anatomical relation to the hepatic portal circulation has led to an intense endeavour to unravel the specific endocrine functions of this visceral fat depot. The objective of this paper is to describe adipose tissue dysfunction, delineate the relation between adipose tissue dysfunction and obesity and to describe how adipose tissue dysfunction is involved in the development of diabetes mellitus type 2 and atherosclerotic vascular diseases. First, normal physiology of adipocytes and adipose tissue will be described.

PMID: 18775919 [found with GoPubMed]

82: Brain Res 2008 Jun;

Long-term cigarette smoke exposure increases uncoupling protein expression but reduces energy intake.

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The appetite suppressing effect of tobacco is a major driver of smoking behaviour; however few studies have addressed the effects of chronic cigarette smoke exposure (SE) on appetite, body weight and metabolic markers. We compared the effects of SE to equivalent food restriction (pair-fed, PF), against sham-exposure, on body weight, adiposity, cytokines, and levels of uncoupling proteins (UCP) and brain neuropeptide Y (NPY) in male Balb/C mice. SE rapidly induced anorexia, and after 12 weeks, SE and PF groups were lighter than control animals (23.9+/-0.2, 25.5+/-0.5, 26.8+/-0.4 g respectively, P<0.05). White fat (WAT) masses were reduced by both SE and PF. Plasma leptin and insulin were reduced in SE mice; insulin was further reduced by PF. Brown fat UCP1 and 3 mRNA were increased in SE animals relative to PF animals, possibly promoting thermogenesis. WAT mRNA expression of the inflammatory cytokine, TNFalpha was doubled by SE, while IL-6 was reduced by both PF and SE. Hypothalamic NPY content was increased by SE (89.3+/-2.8 vs. 75.9+/-2.4 ng control, P<0.05), and more by PF (100.7+/-3.4 ng, P<0.05 compared to both groups), suggesting disinhibition due to reduced adipose derived leptin. In contrast to equivalent food restriction, cigarette smoke exposure reduced body weight and total hypothalamic NPY, and increased thermogenesis and markers of inflammation. The suppressed hypothalamic NPY and increased UCPs may contribute to the spontaneous hypophagia and extra weight loss in SE animals. These findings

contribute to our understanding of weight loss in smoking-related lung disease, suggesting a greater impact than that due to anorexia alone.

PMID: 18619427 [found with GoPubMed]

83: Atherosclerosis 2008 Sep;

Vaspin serum concentrations in patients with carotid stenosis.

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Obesity is associated with accelerated atherosclerosis. Adipokines may directly influence vessel wall homeostasis by influencing the function of endothelial cells, arterial smooth muscle cells, and modulating inflammation. Recently, visceral adipose tissue-derived serpin (vaspin) was identified as a novel adipokine related to obesity and its metabolic consequences. However, the regulation of vaspin serum concentrations in human atherosclerosis is unknown. We therefore assessed vaspin serum concentrations in 107 consecutive patients with carotid stenosis undergoing carotid endarterectomy (CEA) in relation to severity of atherosclerosis, measures of obesity and circulating markers of obesity and atherosclerosis. Vaspin serum concentrations were significantly lower in patients with carotid stenosis who experienced an ischemic event within 3 months before surgery compared to asymptomatic patients. However, circulating vaspin was not associated with measures of atherosclerosis severity as maximum percentage stenosis. Vaspin serum concentrations were indistinguishable before and after CEA. We found a significant correlation between vaspin and leptin serum concentrations supporting previous results that vaspin closely reflects body fat mass. In conclusion, our data show that low vaspin serum concentrations correlate with recently experienced ischemic events in patients with carotid stenosis despite the lack of an association between circulating vaspin and parameters of atherosclerosis severity.

PMID: 18848328 [found with GoPubMed]

84: Endocr Metab Immune Disord Drug Targets 2008 Sep;8(3):220-30

Critical role of the endocannabinoid system in the regulation of food intake and energy metabolism, with phylogenetic, developmental, and pathophysiological implications.

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The endocannabinoid system (ECS) consists of two receptors (CB(1) and CB(2)), several endogenous ligands (primarily anandamide and 2-AG), and over a dozen ligand-metabolizing enzymes. The ECS has deep phylogenetic roots and regulates many aspects of embryological development and homeostasis, including neuroprotection and neural plasticity, immunity and inflammation, apoptosis and carcinogenesis, pain and emotional memory, and the focus of this review: hunger, feeding, and metabolism. The ECS controls

energy balance and lipid metabolism centrally (in the hypothalamus and mesolimbic pathways) and peripherally (in adipocytes and pancreatic islet cells), acting through numerous anorexigenic and orexigenic pathways (e.g., ghrelin, leptin, orexin, adiponectin, endogenous opioids, and corticotropin-releasing hormone). Obesity leads to excessive endocannabinoid production by adipocytes, which drives CB(1) in a feed-forward dysfunction. Phylogenetic research suggests the genes for endocannabinoid enzymes, especially DAGLalpha and NAPE-PLD, may harbor mildly deleterious alleles that express disease-related phenotypes. Several CB(1) inverse agonists have been developed for the treatment of obesity, including rimonabant, taranabant, and surinabant. These drugs are efficacious at reducing food intake as well as abdominal adiposity and cardiometabolic risk factors. However, given the myriad beneficial roles of the ECS, it should be no surprise that systemic CB(1) blockade induces various adverse effects. Alternatives to systemic blockade include CB(1) partial agonists, pleiotropic drugs, peripherally restricted antagonists, allosteric antagonists, and endocannabinoid ligand modulation. The ECS offers several discrete targets for the management of obesity and its associated cardiometabolic sequelae.

PMID: 18782018 [found with GoPubMed]

85: Pflugers Arch 2008 Aug;

Endotoxaemia leads to major increases in inflammatory adipokine gene expression in white adipose tissue of mice.

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The proposition that white adipose tissue is involved in the inflammatory response and metabolic dysregulation of endotoxaemia has been examined. Mice were injected with lipopolysaccharide (LPS; 25 mg/kg) and epididymal, perirenal and subcutaneous adipose tissue removed 4 or 24 h later. The expression of genes encoding key inflammation-related adipokines was measured by real-time polymerase chain reaction. At 24 h after the administration of LPS, there was no change in leptin mRNA level, and adiponectin mRNA fell. However, major increases in TNFalpha, MCP-1 (up to 40-fold) and IL-6 (up to 250-fold) mRNA levels were evident; a substantial elevation in these mRNAs occurred by 4 h, and adipose tissue IL-6 protein also increased (three- to eightfold). At 24 h, the responses in the subcutaneous depot were much lower than in epididymal and perirenal adipose tissue, but at 4 h, the subcutaneous tissue showed major increases in IL-6, MCP-1 and TNFalpha gene expression. In contrast to the inflammatory adipokines, the mRNA level of two macrophage markers, F4/80 and MAC-1, was unaltered in adipose tissue during endotoxaemia. Expression of the hypoxia-sensitive transcription factor, HIF-1alpha, gene was increased at both 4 and 24 h, and HIF-1alpha protein was elevated at 4 h, suggesting that the tissue was hypoxic. It is concluded that white adipose tissue may play an important role in the production of inflammatory mediators in endotoxaemia.

PMID: 18677510 [found with GoPubMed]

86: Arthritis Rheum 2008 Jul;58(8):2318-2328

Inhibition of experimental Sjögren's syndrome through immunization with HSP60 and its peptide amino acids 437-460.

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OBJECTIVE: To investigate a potential immunomodulatory effect of the 60-kd heat-shock protein (Hsp60) on experimental spontaneous Sjögren's syndrome (SS). METHODS: Seven-week-old nonobese diabetic (NOD) mice were immunized with eukaryotic Hsp60 or an Hsp60-derived peptide (amino acid residue [aa] 437-460). At 21 weeks of age, nondiabetic mice were investigated for salivary gland inflammation, exocrine function, and extraglandular disease manifestations. In addition, biomarker profiles comprising 87 analytes in serum and 75 in saliva were analyzed. RESULTS: In mice immunized with Hsp60 and aa 437-460, SS-related histopathologic features were significantly reduced compared with NOD controls. In addition, 50% of Hsp60-injected mice and 33% of aa 437-460-injected mice retained normal exocrine function. Both treatments induced similar changes in biomarker profiles. Notably, levels of circulating interferon-gamma-inducible 10-kd protein (IP-10) and eotaxin were decreased significantly after treatment. Anti-type 3 muscarinic acetylcholine receptor (anti-M3R) IgG1, interleukin-10, and leptin discriminated best between the different treatment groups. Successful prevention of hyposalivation was accompanied by quantitative alterations in 36 biomarkers, of which 19 mediators of inflammation declined to levels comparable with those found in BALB/c mice. Low secreted vascular endothelial growth factor A was the most accurate predictor of successful prevention of hyposalivation. Low salivary granulocyte chemotactic protein 2 was identified as the best predictor of normal secretory function across the strains. CONCLUSION: Immunization with Hsp60 and its peptide aa 437-460 led to inhibition of SS in NOD mice. Comprehensive analyses revealed specific biomarker signatures capable of predicting treatment group and treatment outcome. Molecules involved in inflammatory chemotaxis, neovascularization, and regulatory pathways caused the differences displayed by the biomarker profiles.

PMID: 18668586 [found with GoPubMed]

87: J Clin Endocrinol Metab 2008 May;

CALORIE RESTRICTION MODULATES INACTIVITY-INDUCED CHANGES IN THE INFLAMMATORY MARKERS CRP AND PTX3.

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Context. Energy balance and physical activity potentially influence systemic inflammation. Objective. To test the hypothesis that moderate energy restriction may prevent activation of inactivity-induced inflammatory response. Design. Participants were studied four times at the end of 14-day periods of experimental bed rest or controlled ambulation, after receiving eucaloric or hypocaloric diets. Setting. Clinical research center of German Space Agency. Subjects. Nine healthy young volunteers. Interventions. Energy intake was calibrated to physical activity and decreased by about 20% in hypocaloric conditions. Main Outcome Measures.

Changes in body fat by DXA as well as plasma inflammatory markers and cytokine mRNA levels in blood cells. Results. Fat mass did not change significantly in eucaloric conditions and decreased in hypocaloric periods (-1.0+/-0.3 and -1.0+/-0.3 kg in ambulatory and bed rest, respectively). Bed rest in eucaloric conditions increased plasma C-reactive protein (CRP) (+143+/-53%) and both the ratios between plasma interleukin-6 (IL-6) and interleukin-10 (IL-10) (4+/-1 times) and white blood cell IL-6 and IL-10 mRNAs (5+/-1 times). Energy restriction prevented bed rest-mediated increases in CRP and IL-6-to-IL-10 ratio. Bed rest increased (P=0.03) long pentraxin-3 (PTX3) plasma concentration, without significant activity-by-diet interaction. In all conditions (n=36), CRP and PTX3 were inversely correlated (r=-0.61, p<0.001). Changes in fat mass, leptin and IL-6 directly correlated with CRP and inversely correlated with PTX3. IL-10 inversely correlated with CRP and directly correlated with PTX3 (r=0.52, P<0.01). Conclusions. Calorie restriction prevents the inflammatory response induced by 14 days of bed rest. We suggest an inverse regulation of CRP and PTX3 in response to changes in energy balance.

PMID: 18492758 [found with GoPubMed]

88: J Neuroimmunol 2008 Jun;

How cytokines can influence the brain: A role for chemokines?

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Following inflammation or infection, cytokines are released in the blood. Besides their effect on the immune system, cytokines can also act in the brain to modulate our behaviors, inducing for example anorexia when produced in large amount. This review focuses on our current knowledge on how cytokines can influence the brain and the behaviors through several possible pathways: modulating peripheral neurons which project to the brain through the vagus nerve, modulating the levels of hormones such as leptin which can act to the brain through the humoral pathway and possibly acting directly in the brain, through the local production of cytokines and chemokines such as SDF-1alpha/CXCL12.

PMID: 18547650 [found with GoPubMed]

89: Cardiovasc Res 2008 May;

Signaling mechanisms underlying the metabolic and other effects of adipokines on the heart.

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Adipokines represent a family of proteins released by adipocytes that affect various biological processes including metabolism, satiety, inflammation and cardiovascular function. The first adipokine to be identified is leptin, a product of the obesity gene whose primary function is to act as a satiety factor. However, it is now recognized that leptin and many of the newly discovered adipokines produce effects on numerous organ systems including the heart. Indeed, various adipokines including

leptin, adiponectin and apelin exert potent and diverse cardiovascular effects which are mediated by their specific receptors and involve complex and multifaceted cell signaling pathways. Among these are effects on the heart as well as blood pressure where leptin has been proposed to potentially contribute to obesity-related hypertension. In this review we focus primarily on the diverse effects of adipokines on the heart and discuss the potential cell signaling mechanisms underlying their actions. The potential role of adipokines in the regulation of cardiac metabolism and function is discussed. Discussion is also presented on the emerging role, both deleterious and salutary, of various adipokines in heart disease with an examination of the possible underlying mechanisms which contribute to these effects.

PMID: 18474523 [found with GoPubMed]

90: Clin Chem 2008 May;

Retinol-Binding Protein 4 and Lipocalin-2 in Childhood and Adolescent Obesity: When Children Are Not Just "Small Adults"

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BACKGROUND: Although there is much evidence regarding the physiologic and pathogenic roles of the newly described adipokines retinol-binding protein 4 (RBP4) and lipocalin-2 as potential promoters of insulin resistance in obese adults, relatively little information exists regarding their roles in obese children. METHODS: We investigated the circulating concentrations of RBP4 and lipocalin-2 in 80 obese girls (ages 9- 15 years) and their relationships with high-sensitivity C-reactive protein (hs-CRP) and the adipokines leptin and adiponectin. We divided participants by their body mass index standard deviation scores (BMI SDSs) into 4 groups of 20 girls each: overweight [mean BMI SDS (SD), 1.8 (0.4)], obese [2.2 (0.4)], morbidly obese [3.6 (0.4)], and lean controls [-0.11 (0.4)]. We measured plasma-soluble RBP4, the RBP4-binding protein transthyretin, lipocalin-2, hs-CRP, leptin, and adiponectin and calculated the homeostatic assessment model (HOMA) index from fasting glucose and insulin concentrations. RESULTS: Unexpectedly, plasma RBP4 and lipocalin-2 concentrations were correlated negatively with BMI SDS values ($P = 0.005$, and $P < 0.03$, respectively). These results were different from those of adults and were not correlated with the HOMA index. In contrast, hs-CRP and leptin concentrations were positively correlated with BMI SDS values ($P < 0.0001$, and $P < 0.00001$, respectively), as expected, whereas the adiponectin concentration was negatively correlated ($P = 0.008$). CONCLUSIONS: Although the correlations of leptin, adiponectin, and hs-CRP concentrations with BMI in children are similar to those of adults, the correlations of RBP4 and lipocalin-2 with BMI in children are the inverse of those observed in adults. Thus, although systemic inflammation and mild insulin resistance are present in childhood obesity, RBP4 and lipocalin-2 concentrations are not increased in children as they are in obese adults with long-standing severe insulin resistance and type 2 diabetes.

PMID: 18487287 [found with GoPubMed]

91: Diabetes 2008 Apr;

Blockade of {alpha}4 integrin Signaling Ameliorates the Metabolic Consequences of High Fat Diet-Induced Obesity.

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Objective: Many prevalent diseases of advanced societies, such as obesity-induced Type 2 diabetes, are linked to indolent mononuclear cell-dependent inflammation. We previously proposed that blockade of alpha4 integrin signaling can inhibit inflammation, while limiting mechanism-based toxicities of loss of alpha4 function. Thus, we hypothesized that mice bearing an alpha4(Y991A) mutation, which blocks signaling, would be protected from development of high fat diet (HFD)-induced insulin resistance. Research Design and Methods: 6-8 weeks old wild-type (WT) and alpha4(Y991A) C57Bl/6 male mice were placed on either a HFD that derived 60% calories from lipids, or a chow diet. Metabolic testing was performed after 16 to 22 weeks of diet. Results: alpha4(Y991A) mice were protected from development of HFD-induced insulin resistance. This protection was conferred on WT mice by alpha4(Y991A) bone marrow transplantation. In the reverse experiment, WT bone marrow renders HFD-fed alpha4(Y991A) acceptor animals insulin-resistant. Furthermore, fat-fed alpha4(Y991A) mice showed a dramatic reduction of monocyte/macrophages in adipose tissue. This reduction was due to reduced monocyte/macrophage migration rather than reduced monocyte chemoattractant protein-1 (MCP-1) production. Conclusions: alpha4 integrins contribute to the development of HFD-induced insulin resistance by mediating the trafficking of monocytes into adipose tissue; hence, blockade of alpha4 integrin signaling can prevent the development of obesity-induced insulin resistance.

PMID: 18426864 [found with GoPubMed]

92: Endocrinology 2008 Apr;

Low Frequency Electro-Acupuncture and Physical Exercise Improve Metabolic Disturbances and Modulate Gene Expression in Adipose Tissue in Rats with Dihydrotestosterone-Induced Polycystic Ovary Syndrome.

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Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder associated with ovulatory dysfunction, hyperandrogenism, abdominal obesity and insulin resistance. Pharmacotherapy is often unsatisfactory. This study evaluates the effects of low-frequency electro-acupuncture (EA) and physical exercise on metabolic disturbances and adipose tissue mRNA expression of selected genes in a rat PCOS model characterized by insulin resistance and adiposity. Dihydrotestosterone (inducing PCOS) or vehicle (control) was administrated continuously, beginning before puberty. At age 10 wk, PCOS rats were randomly divided into three groups; PCOS, PCOS EA and PCOS exercise. PCOS EA rats received 2-Hz EA (evoking muscle twitches) 3 times/wk during 4-5 wk. PCOS exercise rats had free access to a running wheel for 4-5 wk. EA and exercise improved insulin sensitivity, measured by clamp, in PCOS rats. Exercise also reduced adiposity, visceral adipocyte size, and plasma leptin. EA increased plasma IGF-1. Real-time RT-PCR revealed increased expression of leptin and IL-6 and decreased expression

of uncoupling protein 2 (UCP2) in visceral adipose tissue of PCOS rats compared with controls. EA restored the expression of leptin and UCP2 while exercise normalized adipose tissue leptin and IL-6 expression in PCOS rats. Thus, EA and exercise ameliorate insulin resistance in rats with PCOS. This effect may involve regulation of adipose tissue metabolism and production since EA and exercise each partly restore divergent adipose tissue gene expression associated with insulin resistance, obesity, and inflammation. In contrast to exercise, EA improves insulin sensitivity and modulates adipose tissue gene expression without influencing adipose tissue mass and cellularity.

PMID: 18388196 [found with GoPubMed]

93: J Periodontol 2008 Jul;79(7):1208-1216

Effect of Periodontitis on Insulin Resistance and the Onset of Type 2 Diabetes Mellitus in Zucker Diabetic Fatty Rats.

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Background: Studies indicate that an association exists between periodontitis and type 2 diabetes mellitus (T2DM) and/or obesity, with chronic inflammation hypothesized as the common denominator. The purpose of this study was to determine the causal effect of periodontitis and the concomitant impact of diet on the onset of insulin resistance (IR) and T2DM using a rat model system that simulates human obesity and T2DM. Methods: Twenty-eight, 5-week-old female Zucker diabetic fatty (ZDF, fa/fa) rats were divided into four groups of seven animals: high-fat fed-periodontitis (HF/P), high-fat fed-no periodontitis (HF/C), low-fat fed-periodontitis (LF/P), and low-fat fed-no periodontitis (LF/C). Periodontitis was induced by ligature placement. Fasting plasma insulin and glucose levels were measured, and glucose tolerance tests were performed to assess glucose homeostasis, IR, and the onset of T2DM. The level of tumor necrosis factor-alpha (TNF-alpha), leptin, triglycerides, and free fatty acids were determined in week 13 at sacrifice. Results: HF/P rats developed more severe IR compared to HF/C rats ($P < 0.01$) and LF/P or LF/C rats ($P < 0.001$) as measured by fasting insulin levels and homeostasis model assessment analysis. The onset of severe IR occurred approximately 3 weeks earlier in HF/P rats compared to HF/C rats. HF/P rats developed impaired (110 to 125 mg/dl) and frank fasting hyperglycemia (>125 mg/dl) 2 weeks earlier than HF/C rats. There was no difference in the severity and onset of IR and T2DM between LF/P and LF/C rats. The level of TNF-alpha was significantly higher in HF/P rats compared to HF/C rats ($P < 0.01$). Conclusion: Periodontitis accelerated the onset of severe IR and impaired glucose homeostasis in high-fat fed ZDF rats.

PMID: 18597603 [found with GoPubMed]

94: Clin Endocrinol (Oxf) 2008 Jun;

Relationships between vascular resistance and energy deficiency, nutritional status and oxidative stress in oestrogen deficient physically active women.

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Objective: Oestrogen deficiency contributes to altered cardiovascular function in premenopausal amenorrheic physically active women. We investigated whether other energy deficiency-associated factors might also be associated with altered cardiovascular function in these women. Design: A prospective observational study was completed at a research facility at the University of Toronto. Participants: Thirty-two healthy premenopausal women (18-35 years old) were studied: 9 sedentary and ovulatory; 14 physically active and ovulatory; and 8 physically active and amenorrheic. Measurements: We measured calf vascular resistance, resting heart rate, dietary energy intake, resting energy expenditure and serum measures of homocysteine, high-sensitivity C-reactive protein, oxidized low-density lipoproteins, total T(3), ghrelin, leptin, and insulin. Results: Groups were similar (P>0.05) in age (25.1+/-0.8 years; mean +/- SEM), weight (57.3+/-1.1 kg), and BMI (21.4+/-0.3 kg/m(2)). Resting vascular resistance and ghrelin were highest (P<0.05, main effect), and total T(3) and energy expenditure adjusted for fat free mass lowest (P<0.05, main effect) in oestrogen deficient women. Using pooled data for stepwise multiple regression modeling: ghrelin and resting energy expenditure adjusted for fat free mass were associated with resting vascular resistance (R(2)=0.398, P=0.018); adjusted dietary energy intake was associated with peak-ischemic vascular resistance (R(2)=0.231, P=0.015). Adjusted resting energy expenditure (r=0.624, P<0.001) and total T(3) correlated (r=0.427, P=0.019) with resting heart rate. Homocysteine, high-sensitivity C-reactive protein and oxidized low-density lipoproteins were similar (P>0.05, main effect) among the groups, and were unrelated to cardiovascular measures. Conclusion: Altered resting vascular resistance in premenopausal oestrogen deficient physically active amenorrheic women is not associated with vascular inflammation or oxidative stress, but rather with parameters that reflect metabolic allostasis and dietary intake, suggesting a potential role for chronic energy deficiency in vascular regulation.

PMID: 18616718 [found with GoPubMed]

95: Ann Surg 2008 Jun;247(6):909-915

Barrett Esophagus: Prevalence of Central Adiposity, Metabolic Syndrome, and a Proinflammatory State.

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BACKGROUND:: Obesity is a risk factor for esophageal adenocarcinoma, with a pathway through inflammation and metaplasia secondary to reflux the dominant hypothesis. The proinflammatory impact of adipocytokines associated with the metabolic syndrome of central adiposity may also be relevant. The objective of this study was to explore this profile in Barrett esophagus. METHODS:: Patients with specialized intestinal metaplasia were invited to attend the metabolic syndrome screening where they underwent anthropometry, segmental bioelectrical impedance analysis,

and blood pressure measurement, and had blood taken for quantification of fasting lipids, insulin, glucose, C-reactive protein, and adipocytokines. RESULTS:: One hundred two patients were studied. Forty-six percent of Barrett patients had metabolic syndrome and 78% were centrally obese. Patients with metabolic syndrome were significantly more obese by body mass index, had a 9.4 cm greater waistline, were more hypertensive, and were insulin resistant with 25% having fasting hyperinsulinemia compared with Barrett patients without metabolic syndrome. Metabolic syndrome was associated with elevated C-reactive protein, leptin, and a trend toward decreased adiponectin levels. Sixty percent of patients with long-segment Barrett had metabolic syndrome, and 92% were centrally obese compared with 23.8% and 62%, respectively (P = 0.007 and 0.005) in short-segment Barrett. Long-segment Barrett was associated with hyperinsulinemia and significantly increased levels of interleukin-6 compared with short-segment Barrett. CONCLUSIONS:: The prevalence of metabolic syndrome in Barrett far exceeds population norms, and the syndrome was significantly associated with the length of specialized intestinal metaplasia. The data do suggest that the metabolic syndrome may be relevant to the continuum of metaplasia within the Barrett cohort.

PMID: 18520215 [found with GoPubMed]

96: Maturitas 2008 Apr;

Metabolic syndrome after menopause and the role of hormones.

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OBJECTIVES: The purpose of this review is to focus on the importance of metabolic syndrome (MBS) and its increased prevalence in postmenopausal (PM) women. Also the role of hormonal therapy in PM women with MBS will be discussed. METHODS: Review of the relevant literature and results from recent clinical trials. RESULTS: MBS may occur in 40% of PM women and is largely determined by overweight status and obesity. Weight gain, particularly an increase in central fat mass increases in PM women, beginning a few years prior to menopause. Hormonal Therapy (HT) in normal PM women, generally decreases abdominal fat, but the effect of transdermal estrogen is preferable to oral therapy in this regard. In women with MBS, oral therapy was found to increase leptin and the leptin/adiponectin ratio, while transdermal therapy showed no changes. HT has been found to improve insulin resistance in PM women, although the data are mixed. In women with MBS, oral therapy was found to worsen parameters of insulin resistance, while transdermal therapy had minimal effects overall. Women with MBS have elevations in several inflammation and coagulation factors. Both oral and transdermal HT reduce inflammation markers except for levels of CRP and MMP-9, which increase with oral therapy, but are unaffected by the transdermal route. Oral estrogen has a small pro-coagulant effect, not observed with transdermal therapy, in both normal PM women and those with MBS. The beneficial effects of HT on lipids occur in PM women with and without MBS, although the changes in the latter are minimal. Blood pressure was not affected by HT in women with MBS. CONCLUSIONS: Weight gain and obesity largely drives the increased prevalence of MBS in PM women. Use of HT is beneficial overall for reducing many of the parameters of MBS. Our own data would suggest that in MBS, transdermal therapy may be preferable to oral therapy, at least in standard doses.

PMID: 18407440 [found with GoPubMed]

97: Am J Hum Genet 2008 May;82(5):1185-92

Loci related to metabolic-syndrome pathways including LEPR,HNF1A, IL6R, and GCKR associate with plasma C-reactive protein: the Women's Genome Health Study.

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Although elevated levels of C-reactive protein (CRP) independently predict increased risk of development of metabolic syndrome, diabetes, myocardial infarction, and stroke, comprehensive analysis of the influence of genetic variation on CRP is not available. To address this issue, we performed a genome-wide association study among 6345 apparently healthy women in which we evaluated 336,108 SNPs as potential determinants of plasma CRP concentration. Overall, seven loci that associate with plasma CRP at levels achieving genome-wide statistical significance were found (range of p values for lead SNPs within the seven loci: 1.9 x 10(-)(8) to 6.2 x 10(-)(28)). Two of these loci (GCKR and HNF1A) are suspected or known to be associated with maturity-onset diabetes of the young, one is a gene-desert region on 12q23.2, and the remaining four loci are in or near the leptin receptor protein gene, the apolipoprotein E gene, the interleukin-6 receptor protein gene, or the CRP gene itself. The protein products of six of these seven loci are directly involved in metabolic syndrome, insulin resistance, beta cell function, weight homeostasis, and/or premature atherothrombosis. Thus, common variation in several genes involved in metabolic and inflammatory regulation have significant effects on CRP levels, consistent with CRP's identification as a useful biomarker of risk for incident vascular disease and diabetes.

PMID: 18439548 [found with GoPubMed]

98: Am J Hypertens 2008 May;21(5):582-6

Serum Levels of the Adipokine Adipocyte Fatty Acid-binding Protein Are Increased in Preeclampsia.

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BackgroundPreeclampsia (PE) is a serious complication of pregnancy which is associated with an increased future metabolic and cardiovascular risk for both mother and newborn. Recently, adipocyte fatty acid-binding protein (AFABP) was introduced as a novel adipokine, serum levels of which independently correlate with the development of the metabolic syndrome and cardiovascular disease in humans. In this study, we investigated serum concentrations of the adipokine AFABP in patients with PE as compared to healthy controls of similar gestational age.MethodsAFABP serum levels were quantified by enzyme-linked immunosorbent assay (ELISA) in control (n = 20) and PE (n = 16) patients. Furthermore, AFABP was correlated to clinical and biochemical measures of renal function, glucose, and lipid metabolism, as well as inflammation.ResultsMean maternal AFABP concentrations were

significantly elevated in PE (24.5 +/- 9.7 mug/l) as compared to controls (14.8 +/- 7.1 mug/l). Furthermore, AFABP serum levels correlated positively with age, body mass index (BMI), blood pressure, serum creatinine, free fatty acids (FFAs), leptin, and C-reactive protein (CRP). In multivariate analyses, BMI and serum creatinine remained independently associated with AFABP concentrations and explained 58% of the variation in AFABP levels.ConclusionWe demonstrate that maternal AFABP serum concentrations are significantly increased in PE. Furthermore, BMI and serum creatinine are independent predictors of circulating AFABP.American Journal of Hypertension (2008); 21, 5, 582-586. doi:10.1038/ajh.2008.23American Journal of Hypertension (2008); 21, 5, 582-586. doi:10.1038/ajh.2008.23.

PMID: 18437151 [found with GoPubMed]

99: Am J Physiol Regul Integr Comp Physiol 2008 Mar;

Peripheral Ghrelin Treatment Stabilizes Body Weights of Senescent Male Brown Norway Rats at Baseline and After Surgery.

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Unintentional weight loss may occur spontaneously in older humans and animals. Further weight losses after surgery or illness in the older patients result in increased morbidity, mortality, and hospital readmission rate. A growing body of work has shown increased appetite and weight gain in response to administration of ghrelin. We conducted two studies in senescent male Brown Norway rats to assess the ability of peripheral administration of ghrelin to increase body weight and food intake. One study assessed the effect of 2 weeks of daily subcutaneous ghrelin administration (1mg/kg/d) to senescent rats in a baseline condition; a second study used the same administration protocol in an interventional experiment with aged rats subjected to a surgery with 10-15% blood loss, as a model of elective surgery. In both studies, animals receiving ghrelin maintained their body weights, while control animals lost weight. Body weight stability was achieved in ghrelin-treated animals despite a lack of increase in daily or cumulative food intake in both experiments. Hormone and pro-inflammatory cytokine levels were measured before surgery and after 14 days of treatment. Ghrelin treatment appeared to blunt declining ghrelin levels and also to blunt cytokine increases seen in the surgical control group. The ability of peripheral ghrelin treatment to maintain body weights of senescent rats without concomitant increases in food intake may be due to its known ability to decrease sympathetic activity and metabolic rate, perhaps by limiting cytokine-driven inflammation. Key words: energy balance, anorexia of aging, cytokine, postoperative.

PMID: 18337314 [found with GoPubMed]

100: Postepy Hig Med Dosw (Online) 2008;62:249-57

[Obesity as inflammatory disease]

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Studies of the role of immune system activation in the pathogenesis of obesity and its concomitant diseases have been conducted for some years. Numerous recent studies revealed an association between increased immune activation in obesity and the development of insulin resistance. On the other hand there is the hypothesis that immune activation in obesity is a homeostatic mechanism to protect the organism from reaching the point at which the over-accumulation of fat decreases the possibility to move. The aim of the present study was to review the current literature on immune activation in obesity and the participation of adipokines produced by adipose tissue in the development of insulin resistance. Attention is drawn to the similarities in function and gene expression of adipocytes and macrophages.

PMID: 18542045 [found with GoPubMed]