Attenuation of acute pancreatitis by peroxisome proliferator-activated receptor-α in rats: the effect on toll-like receptor signaling pathways

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OBJECTIVES: The peroxisome proliferator-activated receptor-α (PPAR-α) has attracted considerable attention for its anti-inflammatory properties; however, Toll-like receptor (TLR) pathways have an essential proinflammatory role in acute pancreatitis (AP). This study aimed to evaluate the attenuation of inflammation by PPAR-α and to investigate the interaction between PPAR-α and TLR pathways in AP.

METHODS: Acute pancreatitis was induced in rats by administration of cerulein. The PPAR-α agonist WY14643 and/or antagonist MK886 was administered. The severity of AP was determined by measuring serum amylase, lipase, Ca, pathological changes, myeloperoxidase activity, serum levels of interleukin (IL)-6, and intercellular adhesion molecule-1 (ICAM-1). The TLR2 and TLR4 messenger RNA (mRNA) and proteins were determined by real-time reverse transcriptase polymerase chain reaction and Western blotting, respectively. The mRNA expressions of target molecules of TLR pathways, including IL-6, IL-10, ICAM-1, and tumor necrosis factor α were also measured. RESULTS: Treatment with WY14643 significantly decreased amylase, lipase, myeloperoxidase activity, pathological scores, IL-6, and ICAM-1 levels. The TLR2 and TLR4 mRNA and proteins were determined by real-time reverse transcriptase polymerase chain reaction and Western blotting, respectively. The mRNA expressions of target molecules of TLR pathways, including IL-6, IL-10, ICAM-1, and tumor necrosis factor α were also measured. RESULTS: Treatment with WY14643 significantly decreased amylase, lipase, myeloperoxidase activity, pathological scores, IL-6, and ICAM-1 levels. The TLR2 and TLR4 mRNA and proteins were markedly decreased after treatment with WY14643, along with IL-6, ICAM-1, and tumor necrosis factor α mRNA levels. However, these effects were completely reversed by the coadministration of MK886. CONCLUSIONS: Activation of PPAR-α played a protective role in AP, partially mediated by modulation of TLR pathways.

Factors associated with intolerance after refeeding in mild acute pancreatitis

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OBJECTIVES: This study aimed to describe the mode of refeeding, frequency of intolerance, and related factors in mild acute pancreatitis (AP). METHODS: The authors included all cases of mild AP between January 2007 and December 2009 in an observational, descriptive, and retrospective study. The authors analyzed demographic and etiological data, admission variables, treatment, refeeding mode, intolerance frequency, and treatment. Intolerance-related variables were determined using a Cox regression. RESULTS: Two-hundred thirty-two patients were included (median age, 74.3 years, bedside index for severity in AP score, 1). Oral diet was reintroduced at 3 days (range, 0-11 days) in 90.9% of cases with a liquid diet. Intolerance to refeeding appeared in 28 patients (12.1%) at a median time of 1 day (range, 0-14 days). Oral diet was reduced or suspended in 71.4% and 35.7% of patients, respectively. The variables independently associated with intolerance to refeeding were choledocholithiasis (hazard ratio (HR), 12.35; 95% confidence interval (CI), 2.98-51.19; P=0.001), fasting time (HR, 1.33; 95% CI, 1.09-1.63; P=0.005), refeeding with complete diet (HR, 4.93; 95% CI, 1.66-14.66; P=0.04), length of symptoms before admission (HR, 1.004; 95% CI, 1.001-1.006; P=0.012), and metamizole dose (HR, 1.11; 95% CI, 1.02-1.21; P=0.014). CONCLUSIONS: Intolerance to refeeding is an infrequent event. The authors have identified several factors independently associated with intolerance.

Proteomic analysis of the soluble and the lysosomal+mitochondrial fractions from rat pancreas: implications for cerulein-induced acute pancreatitis

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Alterations in protein expression within the initiation phase of acute pancreatitis (AP) might play an important role in the development of this disease, lysosomes being involved in its pathophysiology. The use of pancreatic subcellular fractions in proteomic analysis, simplifies protein maps and helps in the identification of new protein changes and biomarkers characterizing tissue damage. The present study aims to determine the differentially expressed acidic proteins in the pancreatic soluble and lysosomal+mitochondrial
Subcellular pancreatic extracts from diseased and control rats were analyzed by 2-DE (3-5.6 pH range) and MALDI-TOF/TOF MS. Comparative analysis afforded the conclusive identification of 13 (soluble fraction) and 7 (L+M fraction) proteins or protein fragments occurring in different amounts between diseased and control pancreas, some of them being newly described in AP. In the soluble fraction, the authors detected changes related to inflammation and apoptosis (α1-inhibitor-3, α-1 antitrypsin, α-1 macroglobulin, haptoglobin, STRAP), oxidative stress and stress response (peroxiredoxin-2, thioredoxin-like 1, GRP94/TRA1, heat shock cognate 71kDa protein), digestive proteases (elastase 3B), serine protease inhibition (serpins B6 and A3L) and translation processes (EF 1-α). In the L+M fraction, the authors detected changes mainly related to energy generation or cellular metabolism (ATP synthase β subunit, chymotrypsinogen B, triacylglycerol lipase), cell redox homeostasis (iodothyronine 5’monodeiodinase) and digestive proteases (carboxypeptidase B1). The data should provide valuable information for unraveling the early pathophysiologic mechanisms of Cer-induced AP.

Utility of the computed tomography severity index (Balthazar score) in children with acute pancreatitis

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BACKGROUND: Previous studies in children with acute pancreatitis have demonstrated that clinical scoring systems such as the Ranson, modified Glasgow, and pediatric acute pancreatitis scores are of value in predicting severity of the disease. The aim of this study was to determine the predictive value of the computed tomography severity index (CTSI or Balthazar score) in pediatric patients. METHODS: All children (≤18 years) admitted to their institution with acute pancreatitis from 2000 through 2009 were reviewed. Contrast-enhanced computed tomographic (CT) images at presentation were retrospectively reviewed by two pediatric radiologists. Peripancreatic fluid and the extent of necrosis were assessed to determine the CTSI. The predictive value of the CTSI was calculated and compared with clinical scoring systems. RESULTS: Of 211 children with acute pancreatitis, 64 underwent contrast-enhanced CT at presentation. The median age was 12.3 years. Etiology of pancreatitis was idiopathic (35.9%), gallstone (17.2%), medication-induced (20.3%), posttransplant (9.4%), traumatic (6.3%), structural (1.6%), and other (9.4%). The sensitivity, specificity, positive predictive value, and negative predictive value of the CTSI (using a cutoff score of 4+) were 81%, 76%, 62%, and 90%, respectively, which compared favorably to the results of the pediatric acute pancreatitis (53%, 72%, 41%, 80%), Ranson (71%, 87%, 67%, 89%), and modified Glasgow (71%, 87%, 67%, 89%) scores. CONCLUSION: The CTSI is superior to clinical scoring systems for identifying children with acute pancreatitis at heightened risk for developing serious complications.

The role of chronic inflammation: chronic pancreatitis as a risk factor of pancreatic cancer

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Pancreatic carcinoma is a condition with late diagnosis and one for which there is no effective screening method. One possible diagnostic approach of so-called early adenocarcinoma is the identification and systematic examination of individuals at risk for this condition. Between 1992 and 2005 the authors systematically observed 223 individuals diagnosed with chronic pancreatitis. In this 14-year period the authors performed classical biochemical tests, endoscopic ultrasound, CT scans and ERCP. The authors also asked about the number of cigarettes smoked per year and classified individuals consuming regularly more than 80 g of alcohol per day for 5 years for men and 50 g of alcohol per day for 5 years for women as having the alcoholic form of chronic pancreatitis. The remaining patients were classified according to the TIGARO classification. Alcohol-related etiology was detected in 73.1% of patients, 21.5% had the chronic obstructive form and only 5.4% were classified as idiopathic pancreatitis. Pancreatic carcinoma was detected in 13 patients with chronic pancreatitis (5.8%), 3 patients were diagnosed with gastric carcinoma and 1 with esophageal carcinoma. Pancreatic malignancy developed mainly in patients with the alcoholic form of pancreatitis (4.5%). In the 14-year period 11 subjects died, out of which 8 cases were related to pancreatic carcinoma. Pancreatic and extrapancreatic cancer localized in the gastrointestinal tract are serious complications of chronic nonhereditary pancreatitis. Systematic observation of patients with chronic pancreatitis must be performed with the aim of early diagnosis of pancreatic malignancies (but also including other types).
The daily practice of pancreatic enzyme replacement therapy after pancreatic surgery: a Northern European survey: enzyme replacement after surgery

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INTRODUCTION: After pancreatic surgery, up to 80% of patients will develop exocrine insufficiency. For enzyme supplementation to be effective, prescribing an adequate dose of pancreatic enzymes is mandatory but challenging because the required dose varies. Data on the practice of enzyme replacement therapy after surgery are lacking, and therefore, the authors conducted this analysis. METHODS: An anonymous survey was distributed to members of the Dutch and German patient associations for pancreatic disorders. The target population consisted of patients with chronic pancreatitis or pancreatic cancer who had undergone pancreatic surgery and were using enzymes to treat exocrine insufficiency. Results were compared to a similar group of non-operated patients. RESULTS: Ninety-one cases were analyzed (84% underwent a resection procedure). The median daily enzyme dose was 6, and 25% took three or less capsules. Despite treatment, 68% of patients reported steatorrhea-related symptoms, 48% adhered to a non-indicated dietary fat restriction, and only 33% had visited a dietician. The outcome was equally poor for the 91 non-operated patients. CONCLUSION: Most patients suffering from exocrine insufficiency after pancreatic surgery are undertreated. To improve efficacy, physicians should be more focused on treating exocrine insufficiency and educate patients to adjust the dose according to symptoms and their diet.

Changes in 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D are associated with maturation of regulatory T lymphocytes in patients with chronic pancreatitis: a randomized controlled trial

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OBJECTIVES: The authors studied the impact of changes in 25-hydroxyvitamin D (25OHD) and 1,25-dihydroxyvitamin D (1,25(OH)2D) on regulatory T lymphocytes (Tregs) in patients with chronic pancreatitis (CP) and fat malabsorption in a prospective clinical trial. METHODS: The patients were randomized to 1 of 3 treatments during 10 weeks: weekly UV-B in a tanning bed (group A), 1,520-IU/d vitamin D supplement (group B), or placebo (group C). A placebo tanning bed was used in groups B and C. The authors determined the levels of CD4 Tregs (CD3CD4CD25CD127lowFoxP3) and CD8 Tregs (CD3CD8CD25CD127lowFoxP3), together with 25OHD and 1,25(OH)2D. For baseline comparisons, the authors included 8 healthy individuals. Of the 30 included patients, 27 (group A, 7 patients; group B, 9 patients; and group C, 11 patients) completed the protocol. RESULTS: The baseline levels of CD4 Tregs relative to total CD4 count were higher in 22 patients with CP compared with healthy controls (2.8% vs. 1.9%, P < 0.05) and were comparable for CD8+ Tregs (0.13% vs. 0.05%, P=0.3). Increases in levels of CD4 Tregs correlated to changes in 1,25(OH)2D (2% per 100 pmol/L, P=0.002) and 25OHD (3% per 100 nmol/L, P=0.01). CONCLUSIONS: Patients with CP have elevated relative levels of CD4 Tregs. Increases in 25OHD and 1,25(OH)2D were both related with increases in levels of Tregs.

Selected cancers with increasing mortality rates by educational attainment in 26 states in the United States, 1993-2007

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BACKGROUND: Mortality rates continue to increase for liver, esophagus, and pancreatic cancers in non-Hispanic whites and for liver cancer in non-Hispanic blacks. However, the extent to which trends vary by socioeconomic status (SES) is unknown. METHODS: The authors calculated age-standardized death rates for liver, esophagus, and pancreas cancers for non-Hispanic whites and non-Hispanic blacks aged 25-64 years by sex and level of education (≤12, 13-15, and ≥16 years, as a SES proxy) during 1993-2007 using mortality data from 26 states with consistent education information on death certificates. Temporal trends were evaluated using log-linear regression, and rate ratios (RRs) with 95% confidence intervals (CIs) compared death rates in persons with ≤12 versus ≥16 years of education. RESULTS: Generally, death rates increased for cancers of the liver, esophagus, and pancreas for non-Hispanic whites and non-Hispanic blacks aged 25-64 years by sex and level of education (≤12, 13-15, and ≥16 years, as a SES proxy) during 1993-2007 using mortality data from 26 states with consistent education information on death certificates. Temporal trends were evaluated using log-linear regression, and rate ratios (RRs) with 95% confidence intervals (CIs) compared death rates in persons with ≤12 versus ≥16 years of education. RESULTS: Generally, death rates increased for cancers of the liver, esophagus, and pancreas in non-Hispanic whites and non-Hispanic blacks (liver cancer only) with ≤12 and 13-15 years of education, with steeper increases in the least educated group. In contrast, rates remained stable in persons with ≥16 years of education. During 1993-2007, the RR (rates in ≤12 versus ≥16 years of education) increased for all
Pancreatic cancer is almost always fatal, in part because of its delayed diagnosis, poor prognosis, rapid progression and chemoresistance. Oncogenic proteins are stabilized by the Hsp90, making it a potential therapeutic target. The authors investigated the oxidative stress-mediated dysfunction of Hsp90 and the hindrance of its chaperonc activity by a carbazole alkaloid, mahanine, as a strategic therapeutic in pancreatic cancer. Mahanine exhibited anti-proliferative activity against several pancreatic cancer cell lines through apoptosis. It induced early accumulation of reactive oxygen species (ROS) leading to thiol oxidation, aggregation and dysfunction of Hsp90 in MIA PaCa-2. N-acetyl-L-cysteine prevented mahanine-induced ROS accumulation, aggregation of Hsp90, degradation of client proteins and cell death. Mahanine disrupted Hsp90-Cdc37 complex in MIA PaCa-2 as a consequence of ROS generation. Client proteins were restored by MG132, suggesting a possible role of ubiquitinylated protein degradation pathway. Surface plasmon resonance study demonstrated that the rate of interaction of mahanine with recombinant Hsp90 is in the range of seconds. Molecular dynamics simulation showed its weak interactions with Hsp90. However, no disruption of the Hsp90-Cdc37 complex was observed at an early time point, thus ruling out that mahanine directly disrupts the complex. It did not impede the ATP binding pocket of Hsp90. Mahanine also reduced in vitro migration and tube formation in cancer cells. Further, it inhibited orthotopic pancreatic tumour growth in nude mice. Taken together, these results provide evidence for mahanine-induced ROS-mediated destabilization of Hsp90 chaperone activity resulting in Hsp90-Cdc37 disruption leading to apoptosis, suggesting its potential as a specific target in pancreatic cancer.

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Targeting pancreatic cancer stem cells for cancer therapy

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Pancreatic cancer (PC) is the fourth most frequent cause of cancer death in the United States. Emerging evidence suggests that pancreatic cancer stem cells (CSCs) play a crucial role in the development and progression of PC. Recently, there is increasing evidence showing that chemopreventive agents commonly known as nutraceuticals could target and eliminate CSCs that has been proposed as the root of the tumor progression, which could be partly due to attenuating cell signaling pathways involved in CSCs. Therefore, targeting pancreatic CSCs by nutraceuticals for the prevention of tumor progression and treatment of PC may lead to the development of novel strategy for achieving better treatment outcome of PC patients. In this review article, the authors have summarized the most recent advances in the pancreatic CSCs field, with particular emphasis on nutraceuticals to target CSCs for fighting this deadly disease.

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Health disparities in endocrine disorders: biological, clinical, and nonclinical factors: an Endocrine Society Scientific Statement


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The aim was to provide a scholarly review of the published literature on biological, clinical, and nonclinical contributors to race/ethnic and sex disparities in endocrine disorders and to identify current gaps in knowledge as a focus for future research needs. Participants in Development of Scientific Statement: The Endocrine Society’s Scientific Statement Task Force (SSTF) selected the leader of the statement development group. She selected an eight-member writing group with expertise in endocrinology and health disparities, which was approved by the Society. All discussions regarding the scientific statement content occurred via teleconference or written correspondence. No funding was provided to any expert or peer reviewer, and all participants volunteered their time to prepare this Scientific Statement. Evidence: The primary sources of data on
global disease prevalence are from the World Health Organization. A comprehensive literature search of PubMed identified U.S. population-based studies. Search strategies combining Medical Subject Headings terms and keyword terms and phrases defined two concepts: 1) racial, ethnic, and sex differences including specific populations; and 2) the specific endocrine disorder or condition. The search identified systematic reviews, meta-analyses, large cohort and population-based studies, and original studies focusing on the prevalence and determinants of disparities in endocrine disorders. Consensus Process: The writing group focused on population differences in the highly prevalent endocrine diseases of type 2 diabetes mellitus and related conditions (prediabetes and diabetic complications), gestational diabetes, metabolic syndrome with a focus on obesity and dyslipidemia, thyroid disorders, osteoporosis, and vitamin D deficiency. Authors reviewed and synthesized evidence in their areas of expertise. The final statement incorporated responses to several levels of review: 1) comments of the SSTF and the Advocacy and Public Incorporation responses to several levels of review: 1) comments of the SSTF and the Advocacy and Public

**Metformin reverses hexokinase and phosphofructokinase downregulation and intracellular distribution in the heart of diabetic mice**

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Diabetes mellitus is characterized by hyperglycemia and its associated complications, including cardiomyopathy. Metformin, in addition to lowering blood glucose levels, provides cardioprotection for diabetic subjects. Glycolysis is essential to cardiac metabolism and its reduction may contribute to diabetic cardiomyopathy. Hexokinase (HK) and phosphofructokinase (PFK), rate-limiting enzymes of glycolysis, are downregulated in cardiac muscle from diabetic subjects, playing a central role on the decreased glucose utilization in the heart of diabetic subjects. Thus, the aim of this study was to determine whether metformin modulates heart HK and PFK from diabetic mice. Diabetes was induced by streptozotocin injection on male Swiss mice, which were treated for three consecutive days with 250 mg/kg metformin before evaluating HK and PFK activity, expression, and intracellular distribution on the heart of these subjects. The authors show that metformin abrogates the downregulation of HK and PFK in the heart of streptozotocin-induced diabetic mice. This effect is not correlated to alteration on the enzymes’ transcription and expression. However, the intracellular distribution of both enzymes is altered in diabetic hearts that show increased activity of the soluble fraction when compared to the particulate fraction. Moreover, this pattern is reversed upon the treatment with metformin, which is correlated with the effects of the drug on the enzymes activity. Altogether, these results support evidences that metformin alter the intracellular localization of HK and PFK augmenting glucose utilization by diabetic hearts and, thus, conferring cardiac protection to diabetic subjects.

**Increased risk of diabetes following perianal abscess: a population-based follow-up study**

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PURPOSE: It remains unclear whether perianal abscess is a prediabetes condition or the initial presentation of type 2 diabetes. Using a population-based dataset, this study aimed to explore the risk of type 2 diabetes following perianal abscess. METHODS: The authors used data sourced from the Longitudinal Health Insurance Database 2000. In total, there were 1,419 adult patients with perianal abscess in the study group and 7,095 randomly selected subjects in the

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comparison group. Stratified Cox proportional hazards regressions were carried out to evaluate the association between being diagnosed with perianal abscess and receiving a subsequent diagnosis of diabetes within 5 years. RESULTS: Of the total 8,514 sampled subjects, the incidence rate of diabetes per 100 person-years was 1.87 (95% confidence interval (CI)=1.74-2.01); the rate among patients with perianal abscess was 3.00 (95% CI=2.60-3.43) and was 1.65 (95% CI=1.52-1.79) among comparison patients. Stratified Cox proportional hazards analysis revealed that patients with perianal abscess were more likely to have received a diagnosis of diabetes than comparison patients (hazard ratio=1.80, 95% CI=1.50-2.16, P<0.001) during the 5-year follow-up period after censoring cases that died from nondiabetes causes and adjusting for patient geographic location, urbanization level, monthly income, hypertension, coronary heart disease, hyperlipidemia, obesity, and alcohol abuse/alcohol dependence syndrome at baseline. CONCLUSIONS: These results suggest that patients with perianal abscess have a higher chance of contracting type 2 diabetes mellitus within the first 5 years following their diagnosis.

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**Mitochondria in the pathogenesis of diabetes: a proteomic view**

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Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia due to absolute or relative lack of insulin. Though great efforts have been made to investigate the pathogenesis of diabetes, the underlying mechanism behind the development of diabetes and its complications remains unexplored. Cumulative evidence has linked mitochondrial modification to the pathogenesis of diabetes and its complications and they are also observed in various tissues affected by diabetes. Proteomics is an attractive tool for the study of diabetes since it allows researchers to compare normal and diabetic samples by identifying and quantifying the differentially expressed proteins in tissues, cells or organelles. Great progress has already been made in mitochondrial proteomics to elucidate the role of mitochondria in the pathogenesis of diabetes and its complications. Further studies on the changes of mitochondrial protein specifically post-translational modifications during the diabetic state using proteomic tools, would provide more information to better understand diabetes.