

PANCREAS ALERTS

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Kallikrein inhibitors limit kinin B₂ antagonist-induced progression of oedematous to haemorrhagic pancreatitis in rats.

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Exocrine hyperstimulation with caerulein is an established model for oedematous acute pancreatitis. Prevention of oedema formation by bradykinin B₂ receptor antagonists induces a progression to a haemorrhagic course in this model. The authors have investigated whether increased kallikrein activity in the pancreas is responsible for vascular damage and whether this could be prevented by selective kallikrein inhibitors. Experimental approach: caerulein was infused i.v. and vascular damage was assessed by histological evaluation and determination of haemoglobin accumulation in the tissue. In addition, oedema formation, tissue and plasma kallikrein (PK) activities and the endogenous kallikrein inhibitors alpha₁-antitrypsin (alpha₁-AT) and alpha₂-macroglobulin (alpha₂-M) were measured. Haemorrhagic lesions induced by icatibant in caerulein-induced pancreatitis were associated with a reduction in alpha₁-AT and alpha₂-M in the pancreas and a concomitant augmentation of tissue kallikrein (TK) activity. The TK inhibitor VA999024 (previously FE999024), or its combination with the PK inhibitor VA999026 (previously FE999026), inhibited oedema formation to the same extent but did not induce vascular damage. Furthermore, VA999024 inhibited TK activity. When icatibant was combined with VA999024 and VA999026, progression from oedematous to haemorrhagic pancreatitis was abolished. Reduced oedema formation by B₂ antagonists prevented influx of endogenous kallikrein inhibitors and led to

an excessive activity of kallikrein in the pancreas leading to vascular damage. This can be prevented by a combined inhibition of both tissue-type and plasma-type kallikrein. Kallikrein inhibitors thus should be further evaluated for their therapeutic potential in preventing haemorrhagic lesions in acute pancreatitis.

Proteomics 2008 Aug 6.
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Proteomic profiling in an animal model of acute pancreatitis.

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Acute pancreatitis (AP) is an inflammatory disease of the pancreas, which evolves in approximately 20% of the patients to a severe illness associated with a high mortality rate. In this study, the authors performed a comparative proteomic analysis of pancreatic tissue extracts from rats with AP and healthy rodent controls in order to identify changes in protein expression related to the pathobiological processes of this disease. Pancreatic extracts from diseased and control rats were analyzed by 2-DE and MS/MS. A total of 125 proteins were identified from both samples. Comparative analysis allowed the detection of 42 proteins or protein fragments differentially expressed between diseased and control pancreas, some of them being newly described in AP. Interestingly, these changes were representative of the main pathobiological pathways involved in this disease. The authors observed activation of digestive proteases and increased expression of various inflammatory markers, including several members of the alpha-macroglobulin family. They also detected changes related to oxidative and cell stress responses. Finally,

the authors highlighted modifications of 14-3-3 proteins that could be related to apoptosis regulation. These results showed the interest of proteomic analysis to identify changes characterizing pancreatic tissue damage and, therefore, to highlight new potential biomarkers of AP.

Immunopharmacol Immunotoxicol. 2008(1):1-15.
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Hydrogen sulfide: A novel mediator of leukocyte activation.

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Accumulating evidence has suggested that hydrogen sulfide (H₂S) is endogenously generated in many types of mammalian cells. Since H₂S plays an important role in cardiovascular, central nervous and gastrointestinal systems, it is currently considered to be the third gaseous mediator. Recently, more and more attention has been paid to the biological functions of H₂S in inflammation. In various animal models of inflammatory diseases (such as acute pancreatitis, sepsis and endotoxemia), endogenous H₂S has been shown to be overproduced and participate in regulating the severity of inflammatory response and associated organ injury. Inhibition of H₂S formation is likely to protect animals against these inflammatory diseases. H₂S may exert its effect on inflammation via regulating the function of leukocytes, leukocyte trafficking and immune cell survival. Furthermore, H₂S has been suggested to induce the release or production of neuropeptides (substance P and calcitonin gene-related peptide), which are considered to be pro-inflammatory mediators, and therefore contribute to inflammatory response. In addition, some studies reported that low doses of sodium hydrosulfide (NaHS, an H₂S donor) exhibited some anti-inflammatory effect on local inflammation (such as non-steroidal anti-inflammatory drug-induced gastric

injury). Taken together, all these findings demonstrate that in addition to the vasodilation and neuromodulation activity of H₂S, it may contribute to the pathogenesis of inflammatory diseases via regulating the activation of leukocytes.

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Feasibility of tissue elastography using transcutaneous ultrasonography for the diagnosis of pancreatic diseases.

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The authors investigated the feasibility of using real-time tissue elastography (EG) with transcutaneous ultrasonography (EG-US) for pancreatic diseases. A preliminary study (phase I) and a prospective (phase II) study were conducted. Phase I: subjects were 10 volunteers, 5 with cancer, 2 with endocrine tumor, 5 with chronic pancreatitis, 14 with intraductal papillary-mucinous neoplasm. To determine the characteristic EG images (diagnostic criteria for phase II), B-mode images were compared with EG images and histopathologic findings. Phase II: 53 consecutive patients were enrolled. The visualization rate by EG-US in lesions visualized by B mode was assessed, and the correct diagnosis rate by B mode alone (B diagnosis) or in combination with EG-US was evaluated. Phase I: normal parenchyma was a homogeneous color. In cancer, EG-US showed a markedly hard area with soft spots inside. Endocrine tumor was uniform and soft comparable to parenchyma. Chronic pancreatitis showed a mixture of various colors. Phase II: the authors identified 77.4% (41/53) of the lesions and observed 60.0% (15/25) of the cancers, 100% (3/3) of the endocrine tumor, 92.0% (23/25) of the cases of chronic pancreatitis cases on EG-US. The B-diagnosis rates ranged from about 70% to

80%. The diagnosis rates of the combination were more than 90% of lesions of each type. In conclusions, the EG-US is feasible in the diagnosis of pancreatic diseases.

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Validation of high-resolution DNA melting analysis for mutation scanning of the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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High-resolution melting analysis of polymerase chain reaction products for mutation scanning, which began in the early 2000s, is based on monitoring of the fluorescence released during the melting of double-stranded DNA labeled with specifically developed saturation dye, such as LC-Green. The authors report the validation of this method to scan 98% of the coding sequence of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. They designed 32 pairs of primers to amplify and analyze the 27 exons of the gene. Thanks to the addition of a small GC-clamp at the 5' ends of the primers, one single melting domain and one identical annealing temperature were obtained to co-amplify all of the fragments. A total of 307 DNA samples, extracted by the salt precipitation method, carrying 221 mutations and 21 polymorphisms, plus 20 control samples free from variations (confirmed by denaturing high-performance liquid chromatography analysis), was used. With the conditions described in this study, 100% of samples that carry heterozygous mutations and 60% of those with homozygous mutations were identified. The study of a cohort of 136 idiopathic chronic pancreatitis patients enabled the authors to prospectively evaluate this technique. Thus, high-resolution melting analysis is a robust and sensitive single-tube technique for screening mutations in a gene

and promises to become the gold standard over denaturing high-performance liquid chromatography, particularly for highly mutated genes such as CFTR, and appears suitable for use in reference diagnostic laboratories.

World J Gastroenterol 2008; 14(28):4486-91.
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Association between calcium sensing receptor gene polymorphisms and chronic pancreatitis in a US population: Role of serine protease inhibitor Kazal 1-type and alcohol.

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The authors aimed to test the hypothesis that calcium sensing receptor (CASR) polymorphisms are associated with chronic pancreatitis (CP), and to determine whether serine protease inhibitor Kazal 1-type (SPINK1) N34S or alcohol are necessary co-factors in its etiology. Initially, 115 subjects with pancreatitis and 66 controls were evaluated, of whom 57 patients and 21 controls were predetermined to carry the high-risk SPINK1 N34S polymorphism. The authors sequenced CASR gene exons 2, 3, 4, 5 and 7, areas containing the majority of reported polymorphisms and novel mutations. Based on the initial results, the authors added 223 patients and 239 controls to analyze three common nonsynonymous single nucleotide polymorphisms (SNPs) in exon 7 (A986S, R990G, and Q1011E). The CASR exon 7 R990G polymorphism was significantly associated with CP (OR, 2.01; 95% CI, 1.12-3.59; P=0.015). The association between CASR R990G and CP was stronger in subjects who reported moderate or heavy alcohol consumption (OR, 3.12; 95% CI, 1.14-9.13; P=0.018). There was no association between the various CASR

genotypes and SPINK1 N34S in pancreatitis. None of the novel CASR polymorphisms reported from Germany and India was detected. In conclusion, this United States-based study confirmed an association of CASR and CP and for the first time demonstrated that CASR R990G is a significant risk factor for CP. The authors also conclude that the risk of CP with CASR R990G is increased in subjects with moderate to heavy alcohol consumption.

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Progressive metaplastic and dysplastic changes in mouse pancreas induced by cyclooxygenase-2 overexpression.

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Cyclooxygenase-2 (COX-2) overexpression is an established factor linking chronic inflammation with metaplastic and neoplastic change in various tissues. The authors generated transgenic mice (BK5.COX-2) in which elevation of COX-2 and its effectors trigger a metaplasia-dysplasia sequence in exocrine pancreas. Histologic evaluation revealed a chronic pancreatitis-like state characterized by acinar-to-ductal metaplasia and a well-vascularized fibroinflammatory stroma that develops by 3 months. By 6 to 8 months, strongly dysplastic features suggestive of pancreatic ductal adenocarcinoma emerge in the metaplastic ducts. Increased proliferation, cellular atypia, and loss of normal cell/tissue organization are typical features in transgenic pancreata. Alterations in biomarkers associated with human inflammatory and neoplastic pancreatic disease were detected using immunohistochemistry. The abnormal pancreatic phenotype can be completely prevented by maintaining mice on a diet containing celecoxib, a well-characterized

COX-2 inhibitor. Despite the high degree of atypia, only limited evidence of invasion to adjacent tissues was observed, with no evidence of distant metastases. However, cell lines derived from spontaneous lesions are aggressively tumorigenic when injected into syngeneic or nude mice. The progressive nature of the metaplastic/dysplastic changes observed in this model make it a valuable tool for examining the transition from chronic inflammation to neoplasia.

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Suppression of inhibitor of differentiation 2, a target of mutant p53, is required for gain-of-function mutations.

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Overexpression of mutant p53 is a common theme in human tumors, suggesting a tumor-promoting gain-of-function for mutant p53. To elucidate whether and how mutant p53 acquires its gain-of-function, mutant p53 is inducibly knocked down in the SW480 colon cancer cell line, which contains mutant p53(R273H/P309S), and the MIA PaCa-2 pancreatic cancer cell line, which contains mutant p53(R248W). The authors found that knockdown of mutant p53 markedly inhibits cell proliferation. In addition, knockdown of mutant p53 sensitizes tumor cells to growth suppression by various chemotherapeutic drugs. To determine whether a gene involved in cell growth and survival is regulated by mutant p53, gene expression profiling analysis was performed and showed that the expression level of Id2, a member of the inhibitor of differentiation (Id) family, was markedly increased upon knockdown of mutant p53. To confirm this, Northern blot analysis was performed and showed that the expression level of Id2 was regulated by various mutant p53s in multiple cell lines. In addition, the authors found that the Id2

promoter is responsive to mutant but not wild-type p53, and mutant p53 binds to the Id2 promoter. Consistent with these observations, expression of endogenous Id2 was found to be inhibited by exogenous mutant p53 in p53-null HCT116 cells. Finally, the authors showed that knockdown of Id2 can restore the proliferative potential of tumor cells inhibited by withdrawal of mutant p53. Together, these findings suggest that one mechanism by which mutant p53 acquires its gain-of-function is through the inhibition of Id2 expression.

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The combination of epidermal growth factor receptor inhibitors with gemcitabine and radiation in pancreatic cancer.

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Gemcitabine-radiotherapy is a standard treatment for locally advanced pancreatic cancer. Clinical data have shown that gemcitabine plus erlotinib is superior to gemcitabine alone for advanced pancreatic cancer. Therefore, the authors investigated the effects of the combination of epidermal growth factor receptor inhibitors with gemcitabine and radiation on a pancreatic cancer model. EGFR signaling was analyzed by measuring phosphorylated EGFR (pEGFR((Y845), (Y1173))) and AKT (pAKT((S473))) protein levels in pancreatic cancer cell lines and tumors. The effects of scheduling on gemcitabine-mediated cytotoxicity and radiosensitization combined with erlotinib were determined by clonogenic survival. *In vivo*, the effects of cetuximab or erlotinib in combination with gemcitabine-radiation on the growth of BxPC-3 tumor xenografts were measured. The authors found *in vitro* that gemcitabine induced

phosphorylation of EGFR at Y845 and Y1173 that was blocked by erlotinib. Treatment of BxPC-3 cells with gemcitabine before erlotinib enhanced gemcitabine-mediated cytotoxicity without abrogating radiosensitization. *In vivo*, cetuximab or erlotinib in combination with gemcitabine-radiation inhibited growth compared with gemcitabine-radiation (time to tumor doubling: gemcitabine + radiation, 19±3 days; cetuximab + gemcitabine + radiation, 30±3 days; P<0.05, erlotinib + gemcitabine + radiation 28±3 days; P<0.1). Cetuximab or erlotinib in combination with gemcitabine-radiation resulted in significant inhibition of pEGFR((Y1173)) and pAKT((S473)) early in treatment, and pEGFR((Y845)), pEGFR((Y1173)), and pAKT((S473)) by the end of treatment. This study shows a novel difference pEGFR((Y845)) and pEGFR((Y1173)) in response to EGFR inhibition.

CONCLUSIONS: These results show that the EGFR inhibitors cetuximab and erlotinib increase the efficacy of gemcitabine-radiation. This work supports the integration of EGFR inhibitors with gemcitabine-radiation in clinical trials for pancreatic cancer.

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Proteasome inhibition activates epidermal growth factor receptor (EGFR) and EGFR-independent mitogenic kinase signaling pathways in pancreatic cancer cells.

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The authors investigate the activation of antiapoptotic signaling pathways in response to proteasome inhibitor treatment in pancreatic cancer and evaluate the use of concomitant inhibition of these pathways to augment proteasome inhibitor treatment

responses. Pancreatic cancer cell lines and mouse flank xenografts were treated with proteasome inhibitor alone or in combination with chemotherapeutic compounds (gemcitabine, erlotinib, and bevacizumab), induction of apoptosis and effects on tumor growth were assessed. The effect of bortezomib (a first-generation proteasome inhibitor) and NPI-0052 (a second-generation proteasome inhibitor) treatment on key pancreatic mitogenic and antiapoptotic pathways (epidermal growth factor receptor, extracellular signal-regulated kinase, and phosphoinositide-3-kinase (PI3K)/AKT) was determined and the ability of inhibitors of these pathways to enhance the effects of proteasome inhibition was assessed *in vitro* and *in vivo*. The data showed that proteasome inhibitor treatment activates antiapoptotic and mitogenic signaling pathways (epidermal growth factor receptor, extracellular signal-regulated kinase, c-Jun-NH₂-kinase, and PI3K/AKT) in pancreatic cancer. Additionally, the authors found that activation of these pathways impairs tumor response to proteasome inhibitor treatment and inhibition of the c-Jun-NH₂-kinase and PI3K/AKT pathways increases the antitumor effects of proteasome inhibitor treatment. These preclinical studies suggest that targeting proteasome inhibitor-induced antiapoptotic signaling pathways in combination with proteasome inhibition may augment treatment response in highly resistant solid organ malignancies. Further evaluation of these novel treatment combinations in clinical trials is warranted.

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Inhibition of mitogen-activated protein kinase phosphatase 3 activity by interdomain binding.

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Mitogen-activated protein kinase phosphatase 3 is a cytoplasmic dual specificity phosphatase that functions to attenuate signalling via dephosphorylation and subsequent deactivation of its substrate and allosteric regulator, extracellular signal-regulated protein kinase 2. Expression of mitogen-activated protein kinase phosphatase 3 has been shown to be under the control of extracellular signal-regulated protein kinase 2, thus providing an elegant feedback mechanism for regulating the rate and duration of proliferative signals. Previously published studies suggest that mitogen-activated protein kinase phosphatase 3 might serve as a tumour suppressor; however, significantly elevated, rather than reduced, levels of this protein have been reported in early lesions. Since overexpression of this phosphatase is counter intuitive to a proposed tumour suppressor function, the observed cellular tolerance suggests a self-inactivation mechanism. Using surface plasmon resonance, the authors provide direct evidence of physical interaction between the N- and C-terminal domains. Kinetic analysis using dimethyl sulfoxide to activate the C-terminal fragment in the absence of extracellular signal-regulated protein kinase 2 showed that the isolated C-terminal domain had higher catalytic efficiency than the similarly activated full-length protein. Furthermore, when isolated N-terminal domain was added to activated C-terminal domain, a dose-dependant inhibition of catalytic activity was observed. The similarity between the KI and KD values obtained indicate that interdomain binding stabilizes the inactive conformation of the catalytic site and implies that the N-terminal domain functions as an allosteric inhibitor of phosphatase activity. Finally, the authors provide evidence for oligomerization of mitogen-activated protein kinase phosphatase 3 in pancreatic cancer cells expressing elevated levels of this phosphatase.

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Polymorphisms of p21 and p27 jointly contribute to an earlier age at diagnosis of pancreatic cancer.

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p21 and p27, members of the kinase inhibitor protein (KIP) family, bind to cyclin-CDK complexes to inhibit their catalytic activity and induce cell cycle arrest. The purpose of this study was to identify whether the p21 (C-to-A), and p27 (T-to-G) polymorphisms were associated with age at diagnosis of pancreatic cancer, either independently or jointly. Two hundred and five patients with a diagnosis of pancreatic cancer were genotyped for the p21 and p27 polymorphisms. The authors found patients with the p21 variant genotype (CA/AA) had an earlier age at diagnosis than those with the wild-type genotype (CC) (log-rank, $P=0.001$; HR=1.89; 95% CI, 1.28-2.78). The p21 and p27 polymorphisms combined had a joint effect on age-associated risk for early diagnosis of pancreatic cancer (log-rank, $P=0.004$; HR=2.91; 95% CI, 1.49-5.67). These findings suggest that the p21 polymorphism independently and p21 and p27 polymorphisms jointly contribute to a significantly earlier age at diagnosis of pancreatic cancer.

Diabetologia 2008 Aug 12.
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Insulin protein and proliferation in ductal cells in the transplanted pancreas of patients with type 1 diabetes and recurrence of autoimmunity.

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The authors investigated whether beta cell neof ormation occurs in the transplanted pancreas in patients with type 1 diabetes who had received a simultaneous pancreas-kidney

transplant (SPK) and later developed recurrence of autoimmunity. The authors examined pancreas transplant biopsies from nine SPK patients with or without recurrent autoimmunity or recurrent diabetes and from 16 non-diabetic organ donors. Tissues were analysed by immunohistochemistry and immunofluorescence. Numerous cytokeratin-19 (CK-19)⁺ pancreatic ductal cells stained for insulin in six SPK recipients with recurrent autoimmunity, in five of whom diabetes requiring insulin therapy recurred. These cells also stained for the transcription factor pancreatic-duodenal homeobox-1 (Pdx-1), which is implicated in pancreatic development and beta cell differentiation. The number of insulin⁺ ductal cells varied, being highest in the patient with the most severe beta cell loss and lowest in the normoglycaemic patient. In the patient with the most severe beta cell loss, the authors detected insulin⁺CK-19⁺Pdx-1⁺ cells staining for the proliferation-related Ki-67 antigen (Ki-67), indicating proliferation. The authors were unable to detect Ki-67⁺ beta cells within the islets in any SPK patient. Some insulin⁺CK-19⁻ ductal cells contained chromogranin A, suggesting further endocrine differentiation. Insulin⁺ cells were rarely noted in the pancreas transplant ducts in three SPK patients without islet autoimmunity and in six of 16 non-diabetic organ donors; these insulin⁺ cells were never CK-19⁺. Insulin⁺ pancreatic ductal cells, some apparently proliferating, were found in the transplanted pancreas with recurrent islet autoimmunity/diabetes. Replicating beta cells were not detected within islets. The observed changes may represent attempts at tissue remodelling and beta cell regeneration involving ductal cells in the human transplanted pancreas, possibly stimulated by hyperglycaemia and chronic inflammation.

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Novel role of curcumin in the prevention of cytokine-induced islet death *in vitro* and diabetogenesis *in vivo*.

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Oxidative stress caused by cytokine exposure is a major cause of pancreatic islet death *in vitro* and of diabetogenesis. Antioxidant compounds may prevent cytokine-induced damage to islet cells. Hence, the authors studied the potential of curcumin, an antioxidant and anti-inflammatory compound, *in vitro* to protect islets against pro-inflammatory cytokines and *in vivo* to prevent the progression of diabetes induced by multiple low doses of streptozotocin (MLD-STZ). Pancreatic islets from C57/BL6J mice were pretreated with curcumin (10 μ M) and then exposed to a combination of cytokines. Islet viability, reactive oxygen species (ROS), NO, inducible NO synthase and NF-kappaB translocation were studied. Curcumin pretreated (7.5 mg kg⁻¹ day⁻¹) C57/BL6J mice were given MLD-STZ (40 mg kg⁻¹), and various parameters of diabetes induction and progression were monitored. Curcumin protected islets from cytokine-induced islet death *in vitro* by scavenging ROS and normalized cytokine-induced NF-kappaB translocation by inhibiting phosphorylation of inhibitor of kappa B alpha (IkappaBalpha). *In vivo*, curcumin also prevented MLD-STZ, as revealed by sustained normoglycaemia, normal glucose clearance and maintained pancreatic GLUT2 levels. Pro-inflammatory cytokine concentrations in the serum and pancreas were raised in STZ-treated animals, but not in animals pretreated with curcumin before STZ. The authors have demonstrated for the first time that curcumin *in vitro* protects pancreatic islets against cytokine-induced death and dysfunction and *in vivo* prevents STZ-induced diabetes.

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Prenatal nicotine exposure alters early pancreatic islet and adipose tissue development with consequences on the

control of body weight and glucose metabolism later in life

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Despite medical advice, 20% to 30% of female smokers continue to smoke during pregnancy. Epidemiological studies have associated maternal smoking with increased risk of obesity and type-2 diabetes in the offspring. The authors investigated the impact of prenatal nicotine exposure (3 mg/kg in Sprague-Dawley rats via osmotic Alzet minipumps) on the early endocrine pancreas and adipose tissue development in rat pups before weaning. Body weight, fat deposition, food intake and food efficiency, cold tolerance, spontaneous physical activity, glucose utilization and insulin sensitivity were also examined at adulthood. Prenatal nicotine exposure led to a decrease in endocrine pancreatic islet size and number at 7 days of life (PND7) which corroborates with a decrease in gene expression of specific transcription factors such as Pdx-1, Pax-6, Nkx6.1 and of hormones such as insulin and glucagon. The prenatal nicotine exposure also led to an increase in epididymal white adipose tissue (eWAT) weight at weaning (PND21), and marked hypertrophy of adipocytes, with increased gene expression of proadipogenic transcription factors such as C/EBP-alpha, PPAR-gamma and SREBP-1C. These early tissue alterations led to significant metabolic consequences, as shown by increased body weight and fat deposition, increased food efficiency on high fat diet, cold intolerance, reduced physical activity, glucose intolerance combined with insulin resistance observed at adulthood. These results prove a direct association between fetal nicotine exposure and offspring metabolic syndrome with early signs of dysregulations of adipose tissue and pancreatic development.

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