

**1. Am J Physiol Renal Physiol. 2008 Jan;294(1):F110-9.  
Epub 2007 Nov 7.**

Anti-LOX-1 therapy in rats with diabetes and dyslipidemia:  
ablation of renal vascular and epithelial manifestations.

Dominguez JH, Mehta JL, Li D, Wu P, Kelly KJ, Packer CS, Temm C, Goss E, Cheng L, Zhang S, Patterson CE, Hawes JW, Peterson R.

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LOX-1 is a multifunctional membrane receptor that binds and internalizes oxidized LDL (oxLDL). We tested the hypothesis that blockade of LOX-1 with an anti-LOX-1 antibody limits nephropathy in male rats with diabetes and dyslipidemia (ZS rats; F(1) hybrid product of Zucker fatty diabetic rats and spontaneous hypertensive heart failure rats). Lean ZS rats were controls, while untreated obese ZS (OM), ZS obese rats injected with nonspecific rabbit IgG (OM-IgG; 2 microg intravenous injection given weekly), and obese ZS rats given anti-LOX-1 rabbit antibody (OM-Ab; 2 microg intravenous injection given weekly) were the experimental groups. The rats were treated from 6 to 21 wk of age. All obese groups had severe dyslipidemia and hyperglycemia. Kidneys of obese rats expressed LOX-1 in capillaries and tubules, were larger, accumulated lipid, had intense oxidative stress, leukocyte infiltration, depressed mitochondrial enzyme level and function, and peritubular fibrosis (all  $P < 0.05$  vs. lean ZS rats). Injections with LOX-1 antibody limited these abnormalities ( $P < 0.01$  vs. data in OM or OM-IgG rats). In vitro, renal epithelial LOX-1 expression was verified in a cultured proximal tubule cell line. Our study indicates that anti-LOX-1 (vascular and epithelial) therapy may effectively reverse critical pathogenic elements of nephropathy in diabetes and dyslipidemia.

PMID: 17989113

**2. Phytomedicine. 2007 Oct;14(10):681-9. Epub 2007 Aug 8.**

Ginseng modifies the diabetic phenotype and genes associated with diabetes in the male ZDF rat.

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Asian ginseng (*Panax ginseng*) and its close relative North American ginseng (*Panax quinquefolius*) are perennial aromatic herbs that are widely used in Oriental medicine and have been acclaimed to have various health benefits including diabetes treatment. In this study, we compared the effects of a diet containing rosiglitazone to a diet containing ginseng (*Panax quinquefolius*) in male Zucker diabetic fatty (ZDF) rats. Animals were assigned to one of three diets: control, rosiglitazone (0.1 g/1 kg diet), or ginseng (10 g/1 kg diet). During the 11-week study, body weight, food intake, organ weight, blood glucose, plasma cholesterol, and plasma triglyceride levels were evaluated. Animals treated with rosiglitazone or ginseng exhibited increased body weight ( $p < 0.05$ ) and decreased kidney weight ( $p < 0.05$ ) compared to control animals. The rosiglitazone group demonstrated decreased food intake and plasma triglyceride levels versus the other groups ( $p < 0.05$ ). The ginseng group revealed decreased cholesterol levels relative to the control group ( $p < 0.05$ ). Furthermore, ginseng and rosiglitazone had marked effects on the expression of genes involved in PPAR actions and triglyceride metabolism compared to controls. In conclusion, ginseng modified the diabetic phenotype and genes associated with diabetes in the male ZDF rat. These data are encouraging, and warrant further research to determine the therapeutic value of this medicinal herb in treating human diabetes.

PMID: 17689944

### **3. Ann Nutr Metab. 2007;51(1):42-52. Epub 2007 Mar 14.**

Soy protein and isoflavones influence adiposity and development of metabolic syndrome in the obese male ZDF rat.

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**BACKGROUND/AIMS:** Previously, we demonstrated that soy protein ameliorates the diabetic phenotype in several rodent models of obesity and metabolic syndrome (MS). This study was designed to further elucidate factors related to adiposity, glycemic control, and renal function in male Zucker Diabetic Fatty (ZDF/*Lepr*(fa)) rats. **METHODS:** Animals were randomly assigned to one of four diets: control, casein (C); low isoflavone (LIS) soy protein; high isoflavone (HIS) soy protein, or casein + rosiglitazone (CR) for 11 weeks. At sacrifice, physiological, biochemical, and molecular parameters were determined. **RESULTS:** Body weight and total adiposity were higher in LIS

and CR diet groups despite lower food intake. Additionally, these animals exhibited differential regulation of adipose-specific proteins (PPAR-gamma and GLUT4) and enzyme activity (FAS and GPDH). HIS-fed animals had reduced total and liver adiposity. Glycemic control was prolonged in both soy-based and rosiglitazone (RGZ) groups. Renal dysfunction was significantly reduced in soy-fed and RGZ-treated rodents as demonstrated by lower levels of proteinuria and dilated tubules with proteinaceous casts. **CONCLUSION:** Collectively, these data provide evidence that soy protein with low or high isoflavone content may have therapeutic significance in reducing severity of diabetes, MS, and renal disease as demonstrated in this preclinical model.

PMID: 17356265

#### 4. *Obes Res.* 2005 Nov;13(11):1915-24.

(+)-Z-Bisdehydrodoisynolic acid ameliorates obesity and the metabolic syndrome in female ZDF rats.

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**OBJECTIVE:** The putative selective estrogen receptor modulator (+)-Z-bisdehydrodoisynolic acid (Z-BDDA) has been found to improve cardiovascular risk in rodents. The objective of this study was to investigate the effectiveness of (+)-Z-BDDA compared with the antidiabetic drug, rosiglitazone, in treating obesity and risk factors associated with the metabolic syndrome. **RESEARCH METHODS AND PROCEDURES:** Female Zucker Diabetic Fatty rats were randomly assigned to three treatment groups for 29 weeks: control (C), 1.8 mg (+)-Z-BDDA/kg diet [control diet + (+)-Z-BDDA (CB)], or 100 mg rosiglitazone/kg diet [control diet + rosiglitazone (CR)]. At sacrifice, physiological, biochemical, and molecular parameters were examined. **RESULTS:** CB animals gained less weight and exhibited a decrease in total body lipids ( $p < 0.05$ ) as compared with C or CR rats. Body weight and total body lipids were the highest in CR rats ( $p < 0.05$ ). Liver weights in CB and CR rats were lower ( $p < 0.05$ ) than in C rats, whereas kidney weights were lower in CB ( $p < 0.05$ ) than in C and CR animals. Fasting plasma glucose was lower ( $p < 0.05$ ) in the CB and CR animals when compared with C animals. C rats exhibited the highest concentration of total plasma cholesterol, and CR-treated rats exhibited the lowest concentration. Plasma triglycerides followed the same pattern as plasma cholesterol. Histomorphometry of heart

vasculature revealed that CB and CR treatments produced a significant shift from small to large venules and arterioles compared with C ( $p < 0.05$ ). Liver expression profiles of peroxisome proliferator-activated receptor (PPAR) alpha, PPARgamma, and PPAR-regulated genes revealed encouraging CB-induced effects. **DISCUSSION:** These results suggest that (+)-Z-BDDA may have applications in treating obesity and complications associated with the metabolic syndrome.

PMID: 16339123

### **5. Obes Res. 2004 Dec;12(12):1907-13.**

Gene expression and adiposity are modified by soy protein in male Zucker diabetic fatty rats.

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It has earlier been demonstrated that soy protein diets ameliorate the diabetic phenotype in obese Zucker rats. In this study, we further investigated physiological changes related to adiposity in male Zucker diabetic fatty rats consuming soy-based diets and compared these diets with the insulin-sensitizing drug, rosiglitazone. Transcript abundance of known genes was assessed in the livers to identify potential molecular connections between soy diets and adiposity. Male Zucker diabetic fatty rats were assigned to casein (C) protein, low-isoflavone soy (LIS) protein, high-isoflavone soy (HIS) protein, or C + rosiglitazone (CR) diets. Compared with the C diet, the LIS diet decreased plasma lipids and increased body weight, but did not change liver weight or carcass adiposity. HIS decreased plasma lipids, liver weight, and body weight. CR decreased plasma lipids and increased carcass adiposity and body weight with no effect on liver weight. In LIS livers, 15 genes involved in signaling and lipid metabolism were up-regulated 2-fold or higher. In HIS livers, seven genes had a 2-fold or higher change in abundance. However, in CR livers, none of the genes was significantly changed compared with the C diet. There appears to be a distinct change in gene expression associated with soy diets as compared with C-based diets and rosiglitazone treatment.

PMID: 15687389

## 6. *Kidney Int.* 2000 Jan;57(1):92-104.

Studies of renal injury III: lipid-induced nephropathy in type II diabetes.

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Studies of renal injury III: Lipid-induced nephropathy in type II diabetes. **BACKGROUND:** Nephrotoxicity from elevated circulating lipids occurs in experimental and clinical situations. We tested the hypothesis that lipid-induced nephropathy causes advanced renal failure in rats with type II diabetes and dyslipidemia. **METHODS:** First generation (F1) hybrid rats derived from the spontaneous hypertensive heart failure rat (SHHF/Gmi-fa) and the LA/NIH-corpulent rat (LA/N-fa) were studied for 41 weeks while being on specific diets. Group 1 (14 rats) ingested 11.5% protein, 47.9% fat, and 40.6% carbohydrate. Group 2 (8 rats) ingested 26.9% protein, 16.7% animal fat, and 56.4% carbohydrate, and group 3 (20 rats) ingested 20.2% protein, 40.4% soy and coconut oil, and 39.4% carbohydrate. **RESULTS:** Hyperglycemia was more severe in rat groups 1 and 2 than in group 3. In contrast, circulating cholesterol and hydroperoxide levels were highest in group 3, intermediate in group 2, and lowest in group 1. Group 3 had severe renal failure secondary to glomerulosclerosis and tubulointerstitial disease, with striking deposition of the lipid peroxidation stress biomarker 4-hydroxynonenal in glomeruli and renal microvessels. Moreover, in group 3, increased arterial wall thickness also connoted vascular injury. In contrast, the glycoxidation stress biomarkers pentosidine and carboxymethyl-lysine were preferentially localized to renal tubules of hyperglycemic rats in groups 1 and 2 and did not segregate with the most severe renal injury. Glomerular and interstitial fibrosis was accompanied by proportional increases in renal transforming growth factor-beta1 levels, which were threefold higher in the hypercholesterolemic rats of group 3 than in the hyperglycemic rats of group 1. **CONCLUSIONS:** Acquisition of non-nodular glomerular sclerosis and tubulointerstitial disease is dependent on lipoxidation stress in rats with type II diabetes. On the other hand, in the absence of hypercholesterolemia, prolonged glycoxidation stress does not appear to be uniquely nephrotoxic.

PMID: 10620191

## **7. J Neurochem. 1985 Dec;45(6):1692-8.**

Effect of hyperglycemia and its prevention by insulin treatment on the incorporation of  $^{32}\text{P}$  into polyphosphoinositides and other phospholipids in peripheral nerve of the streptozotocin diabetic rat.

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The influence of varying doses of streptozotocin and preventive insulin treatment on phospholipid metabolism in sciatic nerve in vitro from diabetic rats was studied. Animals were given 30, 45, and 60 mg/kg injections of streptozotocin and 10 weeks later nerves were removed and incubated in the presence of [ $^{32}\text{P}$ ]-orthophosphate. The quantity of isotope incorporated into phosphatidylinositol-4,5-bisphosphate (PIP<sub>2</sub>) was progressively greater with increasing drug dosage, whereas uptake of label into other phospholipids was unchanged. Rats were made diabetic and within 72 h were implanted with long-acting, insulin-containing osmotic minipumps and the incorporation of [ $^{32}\text{P}$ ]orthophosphate into phospholipids of intact and epineurium-free nerves was examined 8 weeks later. For whole nerve, increased labeling in nerves from diabetic animals occurred only in PIP<sub>2</sub> and phosphatidylinositol-4-phosphate (PIP) and was completely prevented by insulin treatment. Isotope incorporation into polyphosphoinositides was also markedly elevated (greater than or equal to 100%) in desheathed diabetic nerves, but not in nerves from insulin-treated animals. Other phospholipids in epineurium-free nerves displayed some rise in isotope uptake, but the increases were not prevented by insulin treatment and appeared unrelated to hyperglycemia. Morphological examination of nerves extended previous findings that prolonged insulin treatment produces axonal degeneration. These observations indicate that abnormal nerve polyphosphoinositide metabolism is at least in part a consequence of hyperglycemia. The metabolic alterations may be intimately involved in reduced nerve conduction velocity, which is characteristic of diabetic neuropathy.

PMID: 2997392

## **8. Neurochem Res. 1985 Nov;10(11):1453-65.**

The fatty acid composition of glycerolipids in nerve, brain, and other tissues of the streptozotocin diabetic rat.

Lin CJ, Peterson R, Eichberg J.

The fatty acid composition of individual glycerolipids in

brain and sciatic nerve of rats made diabetic with streptozotocin and sacrificed 8 weeks later was determined and compared to the alterations that occurred in liver and kidney glycerolipids. A substantial decrease in the proportion of arachidonic acid and increases in the relative content of linoleic and docosahexenoic (22:6n3) acids occurred in the phosphoglycerides of visceral tissues from diabetic animals as reported by others. In contrast, except for a small rise in the percentage of linoleic acid, no consistent changes in fatty acid composition of phosphatidylcholine, phosphatidylethanolamine, ethanolamine plasmalogen, phosphatidylinositol or phosphatidylserine from brain or nerve were detected. The fatty acids of triacylglycerol associated with nerve exhibited alterations similar to those characteristic of liver. The differences which developed as a result of diabetes were completely prevented if animals were maintained continuously on insulin commencing shortly after administration of streptozotocin. It is concluded that the fatty acid composition of brain and nerve phosphoglycerides are unusually resistant to alteration in the diabetic animal and that consequently, changes in bulk membrane fluidity are unlikely to contribute to functional abnormalities displayed by diabetic peripheral nerve.

PMID: 2935746

### **1. Cardiovasc Diabetol. 2010 May 19;9:19.**

Rosiglitazone reverses endothelial dysfunction but not remodeling of femoral artery in Zucker diabetic fatty rats.

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**OBJECTIVES:** Endothelial dysfunction precedes atherogenesis and clinical complications in type 2 diabetes. The vascular dysfunction in Zucker diabetic fatty (ZDF) rats was evaluated at different ages along with the effect of treatment with rosiglitazone (Rosi) on endothelial function and mechanical remodeling. **METHODS:** The Rosi treatment was given to ZDF rats for 3 weeks. The endothelium-dependent vasodilation and alpha-adrenoceptor-dependent vasoconstriction of femoral arteries were studied using an ex-vivo isovolumic myograph. The biomechanical passive property of the arteries was studied in Ca<sup>2+</sup>-free condition. The expressions of endothelial nitric oxide synthase (eNOS), alpha-adrenoceptor, matrix metalloproteinase 9 (MMP9), and elastase were evaluated.

**RESULTS:** Endothelium-dependent vasorelaxation of the femoral artery was blunted at low doses in ZDF rats at 11 weeks of age and attenuated at all doses in ZDF rats at 19 weeks of age. The expression of eNOS was consistent with the endothelium-dependent vasorelaxation. The alpha-adrenoceptor was activated and the mechanical elastic modulus was increased in ZDF rats at 19 weeks of age. The expressions of alpha-adrenoceptor, MMP9, and elastase were up regulated in ZDF rats at 19 weeks of age. Rosi treatment for 3 weeks restored endothelium-dependent vasorelaxation and the expression of eNOS and the adrenoceptor activation at the doses below  $10^{-6}$  mole/L in ZDF rats at 19 weeks of age. Rosi treatment for 3 weeks did not, however, improve the mechanical properties of blood vessel, the expressions of alpha-adrenoceptor, MMP9, and elastase in ZDF rats.

**CONCLUSION:** The endothelial dysfunction and mechanical remodeling are observed as early as 19 weeks of age in ZDF rat. Rosi treatment for 3 weeks improves endothelial function but not mechanical properties.

PMCID: PMC2891691

PMID: 20482873

**2. Am J Physiol Endocrinol Metab. 2009 Apr;296(4):E765-74. Epub 2009 Jan 21.**

Skeletal changes associated with the onset of type 2 diabetes in the ZDF and ZDSD rodent models.

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The incidence and prevalence of type 2 diabetes (T2D) continue to escalate at an unprecedented rate in the United States, particularly among populations with high rates of obesity. The impact of T2D on bone mass, geometry, architecture, strength, and resistance to fracture has yet to be incontrovertibly characterized because of the complex and heterogeneous nature of this disease. This study utilized skeletally mature male diabetic rats of the commonly used Zucker diabetic fatty (ZDF) and Zucker diabetic Sprague-Dawley (ZDSD) strains as surrogate models to assess alterations in bone attributable to T2D-like states. After the animals were euthanized, bone data were collected using dual-energy X-ray absorptiometry, peripheral quantitative tomography, and micro-CT imaging modalities and via three-point bending or compression mechanical testing methods. ZDF and ZDSD diabetic rats

exhibited lower bone mineral densities, which coincided with declines in structural strength and increased fragility at the femoral midshaft and the L4 vertebral body in response to monotonic loading. Vertebral trabecular morphology was compromised in both diabetic rodent strains, and ZDSD diabetic rats exhibited additional phenotypic impairments to bone material properties at the spine. Because the metabolic origin of the T2D-like state that develops in the ZDSD rat strain is highly relevant to adult-onset diabetes, it is a particularly attractive novel model for future preclinical research.

PMCID: PMC2670632

PMID: 19158319

### **3. Horm Metab Res. 2005 May;37(5):316-25.**

Soy protein influences the development of the metabolic syndrome in male obese ZDFxSHHF rats.

Davis J, Iqbal MJ, Steinle J, Oitker J, Higginbotham DA, Peterson RG, Banz WJ.

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Previous investigations have demonstrated a marked effect of soy protein on the metabolic syndrome (MS). The purpose of this preliminary study was to identify the effects of soy-based diets on male obese ZDFxSHHF (fa/fa-cp/?) rats. Animals were randomly assigned to one of four diets: control, casein (C); low-isoflavone (LIS) soy protein; high-isoflavone (HIS) soy protein; or casein + rosiglitazone (CR). Physiological, biochemical, and molecular parameters were determined at sacrifice. Body weight ( $p < 0.01$ ) and food intake ( $p < 0.05$ ) were lower in LIS-fed rodents. Rosiglitazone-treated animals had higher body weight and adiposity ( $p < 0.05$ ). LIS and CR groups exhibited better glycemic control ( $p < 0.05$ ), but with a limited effect in rosiglitazone-treated animals. HIS fed rats had higher glucose and triacylglyceride levels ( $p < 0.01$ ), and lower plasma insulin ( $p < 0.01$ ). Renal function parameters with the exception of an increase in systolic blood pressure ( $p < 0.05$ ) were all suppressed in the LIS group ( $p < 0.01$ ). The CR group had twofold PPAR $\alpha$  and PPAR $\gamma$  mRNA abundance ( $p < 0.01$ ). LIS-fed animals also exhibited greater abundance of PPAR $\gamma$  mRNA ( $p < 0.001$ ), and nearly threefold FAS and CPT-1 mRNA levels ( $p < 0.05$ ). HIS-fed rats also had higher abundance of CPT-1 mRNA, as well as a lower abundance of ACC mRNA ( $p < 0.05$ ). Soy-based diets, influenced by isoflavone content and distinct from

rosiglitazone, improved several metabolic parameters in obese ZDFxSHHF rats.

PMID: 15971156

#### **4. Horm Metab Res. 2005 May;37(5):309-15.**

Soy protein influences insulin sensitivity and cardiovascular risk in male lean SHHF rats.

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Previous investigations have demonstrated a marked effect of soy protein on multiple physiological parameters associated with the metabolic syndrome (MS). This preliminary study investigated the physiological effects of soy-based diets on cardiovascular risk in a unique rodent model that reflects early stages of MS. Briefly, lean male SHHF (+/cp) rats were randomly assigned to the following treatment groups: casein (control, C); low-isoflavone (LIS) soy protein isolate; high-isoflavone (HIS) soy protein isolate; or C+ 0.01 % rosiglitazone (CR). Rats were fed for thirty-six weeks. Liver weight, heart weight, total plasma cholesterol, fasting blood glucose were lower in soy-fed animals compared to control ( $p < 0.01$ ). Body weight, kidney weight, alanine aminotransferase (ALT), fasting plasma insulin, and homeostasis model assessment (HOMA) score were also lower in LIS-fed rodents ( $p < 0.05$ ) compared to casein treatment. All diet groups exhibited lower urine protein ( $p < 0.01$ ) and small arteriole content ( $p < 0.05$ ) compared to controls. LIS feed had a slightly more profound influence on body weight, liver metabolism, and insulin sensitivity. However, both soy diets exhibited marked improvements over a casein-based diet.

PMID: 15971155

#### **5. Exp Neurol. 2005 Apr;192(2):407-19.**

A potent sorbitol dehydrogenase inhibitor exacerbates sympathetic autonomic neuropathy in rats with streptozotocin-induced diabetes.

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We have developed an animal model of diabetic sympathetic autonomic neuropathy which is characterized by neuroaxonal dystrophy (NAD), an ultrastructurally distinctive axonopathy, in chronic streptozotocin (STZ)-diabetic rats. Diabetes-induced alterations in the sorbitol pathway occur in sympathetic ganglia and therapeutic agents which inhibit aldose reductase or sorbitol dehydrogenase improve or exacerbate, respectively, diabetes-induced NAD. The sorbitol dehydrogenase inhibitor SDI-711 (CP-470711, Pfizer) is approximately 50-fold more potent than the structurally related compound SDI-158 (CP 166,572) used in our earlier studies. Treatment with SDI-711 (5 mg/kg/day) for 3 months increased ganglionic sorbitol (26-40 fold) and decreased fructose content (20-75%) in control and diabetic rats compared to untreated animals. SDI-711 treatment of diabetic rats produced a 2.5- and 4-5-fold increase in NAD in the SMG and ileal mesenteric nerves, respectively, in comparison to untreated diabetics. Although SDI-711 treatment of non-diabetic control rat ganglia increased ganglionic sorbitol 40-fold (a value 8-fold higher than untreated diabetics), the frequency of NAD remained at control levels. Levels of ganglionic sorbitol pathway intermediates in STZ-treated rats (a model of type 1 diabetes) and Zucker Diabetic Fatty rats (ZDF, a genetic model of type 2 diabetes) were comparable, although STZ-diabetic rats develop NAD and ZDF-diabetic rats do not. SDI failed to increase diabetes-related ganglionic NGF above levels seen in untreated diabetics. Initiation of Sorbinil treatment for the last 4 months of a 9 month course of diabetes, substantially reversed the frequency of established NAD in the diabetic rat SMG without affecting the metabolic severity of diabetes. These findings indicate that sorbitol pathway-linked metabolic alterations play an important role in the development of NAD, but sorbitol pathway activity, not absolute levels of sorbitol or fructose per se, may be most critical to its pathogenesis.

PMID: 15755558

**6. Anat Rec A Discov Mol Cell Evol Biol. 2004  
Apr;277(2):384-95.**

Development of multiorgan pathology in the wpk rat model of polycystic kidney disease.

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Rodent models of polycystic kidney disease (PKD) have provided valuable insight into the cellular changes associated with cystogenesis in humans. The present study characterizes the morphology of renal and extrarenal pathology of autosomal recessive PKD induced by the *wpk* gene in Wistar rats. In *wpk*(-/-) rats, proximal tubule and collecting duct cysts develop in utero and eventually consume the kidney. Increased apoptosis, mitosis, and extracellular tenascin deposition parallel cyst development. Extrarenal pathology occurs in the immune system (thymic and splenic hypoplasia) and central nervous system (CNS; hypoplasia to agenesis of the corpus callosum with severe hydrocephalus). Severity of hydrocephalus varied inversely with size of the corpus callosum. In *wpk*(-/-) rats, the corpus callosum exhibits relatively few axons that cross the midline. This CNS pathology is similar to that described in three human renal cystic syndromes: orofaciocardiac, genitopatellar, and cerebrorenal-digital syndromes. Collecting duct and ventricular ependymal cilia appear morphologically normal. To determine if rodent background strain and the presence of modifier genes affect severity of the disease, we crossed the Wistar-*wpk* rat with Brown Norway (BN) and Long Evan (LE) rats and found the degree of renal and cerebral pathology was diminished as evidenced by lower kidney weight as a percent of body weight and serum urea nitrogen concentration in cystic rats on LE or BN strains as well as less prominent cranial enlargement. Crosses with BN rats allowed us to localize the *wpk* gene on chromosome 5 very close to the D5Rat73 marker. The *wpk* gene lies within a chromosomal region known to harbor a PKD modifier locus. In summary, the types of renal and cerebral pathology seen in the Wistar *wpk* rat are a unique combination seen only in this rodent model.

PMID: 15052665

### **7. Am J Pathol. 2003 Jul;163(1):21-8.**

Analysis of the Zucker Diabetic Fatty (ZDF) type 2 diabetic rat model suggests a neurotrophic role for insulin/IGF-I in diabetic autonomic neuropathy.

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Dysfunction of the autonomic nervous system is a recognized complication of diabetes. Neuroaxonal dystrophy (NAD), a distinctive axonopathy involving distal axons and synapses, represents the neuropathologic hallmark of diabetic

sympathetic autonomic neuropathy in human and several insulinopenic experimental rodent models. Recent studies have suggested that loss of the neurotrophic effects of insulin and/or IGF-I on sympathetic neurons and not hyperglycemia per se, may underlie the development of sympathetic NAD. The streptozotocin (STZ)-diabetic and BB/W rat, the most commonly used experimental rodent models, develop marked hyperglycemia and concomitant deficiency in both circulating insulin and IGF-I. These animals reproducibly develop NAD in nerve terminals in the prevertebral sympathetic ganglia and the distal portions of noradrenergic ileal mesenteric nerves. The Zucker Diabetic Fatty (ZDF) rat, an animal model of type 2 diabetes, also develops severe hyperglycemia comparable to that in the STZ- and BB/W-diabetic rat models, although in the presence of hyperinsulinemia. In our study, ZDF rats maintained for 6 to 7 months in a severely diabetic state, as assessed by plasma glucose and glycated hemoglobin levels, maintained significant hyperinsulinemia and normal levels of plasma IGF-I at sacrifice. NAD did not develop in diabetic ZDF rat sympathetic ganglia and ileal mesenteric nerves as assessed by quantitative ultrastructural techniques, which is in dramatic contrast to neuropathologic findings in comparably hyperglycemic 6-month STZ-diabetic insulinopenic rats. These data combined with our previous results argue very strongly that hyperglycemia is not the critical and sufficient element in the pathogenesis of diabetes-induced NAD, rather that it is the loss of trophic support, most likely of IGF-I or insulin, that causes NAD.

PMCID: PMC1868158

PMID: 12819007

## **8. Acad Radiol. 2001 Jun;8(6):473-7.**

Suprarenal intraarterial infusion of alloxan and streptozotocin during balloon occlusion of the juxtarenal abdominal aorta: a simple technique for inducing diabetes mellitus in canines with reduced mortality.

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**RATIONALE AND OBJECTIVES:** The authors performed this study to evaluate the mortality and morbidity associated with a simple technique for inducing diabetes in dogs--suprarenal intraarterial infusion of alloxan and streptozotocin during balloon occlusion of the juxtarenal abdominal aorta.

**MATERIALS AND METHODS:** The authors attempted to induce diabetes in six purpose-bred dogs. After the dogs were fasted for 12 hours, the abdominal aorta at the level of the origin of the renal arteries was occluded with an angioplasty balloon introduced by means of a femoral approach. A 3-F microcatheter (n = 1) or infusion wire (n = 5) was introduced via the percutaneous transluminal angioplasty catheter and positioned at the level of the celiac axis, and a mixture of streptozotocin (20-25 mg/kg) and alloxan (20-25 mg/kg) was infused. Diabetes was considered to have been induced if the dogs experienced sustained hyperglycemia. **RESULTS:** There were no deaths during the follow-up period (range, 7 months to 2 1/2 years). A diabetes-like state was induced in five of the six dogs, and no nephrotoxicity was seen. Diabetes was not induced in one dog owing to caudal migration of an undersized balloon during the infusion; this also resulted in reversible renal damage. **CONCLUSION:** This simple technique is effective for inducing diabetes in dogs, and morbidity and mortality rates are lower than those reported in the literature with other described techniques.

PMID: 11394539

### 9. J Ocul Pharmacol Ther. 2000 Oct;16(5):471-9.

Acarbose partially inhibits microvascular retinopathy in the Zucker Diabetic Fatty rat (ZDF/Gmi-fa).

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We compared quantitative capillary retinopathic changes between non-insulin-dependent diabetic Zucker Diabetic Fatty (ZDF) rats and heterozygous nondiabetic Zucker controls and evaluated the effect of an orally administered glucosidase inhibitor, acarbose, on retinopathy in these animals. Four groups of eight rats were analyzed: treated and untreated ZDF and treated and untreated Zuckers. Retinal capillary basement membrane thickening and retinal capillary cell density were determined from transmission electron microscopy and trypsin digestion preparations. ZDF rats had thicker basement membranes ( $p < 0.0001$ ) and more cells per unit capillary length ( $p = 0.0003$ ) compared to Zuckers. Acarbose treatment significantly reduced basement membrane thickening in the treated ZDF rats ( $p = 0.001$ ), but the effects on cell density showed only a favorable trend. Acarbose treatment has an ameliorative effect on the development of microvascular retinopathy in the ZDF rat, probably due to lessening of hyperglycemia.

PMID: 11110039

### **10. Atherosclerosis. 2000 Feb;148(2):231-41.**

Effect of dietary fat on the development of non-insulin dependent diabetes mellitus in obese Zucker diabetic fatty male and female rats.

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The obese Zucker diabetic fatty male rat (ZDF/Gmi;trade mark omitted;-fa) has become a widely used animal model of NIDDM, in contrast to the obese ZDF females that rarely develop NIDDM. However, preliminary observations suggest that obese ZDF females may become diabetic on high-fat diets. Therefore, we studied the effect of dietary fat on development of NIDDM, dyslipidemia, and alterations in organ-specific serum panels in obese ZDF males and females. Results indicated different effects of dietary fat-content on development of diabetes in males and females. Males, even on low fat-content diets, developed diabetes but the process was accelerated as a function of dietary fat-content, whereas only the highest fat-content diet induced development of NIDDM in obese ZDF females. Additionally, triglyceride/apolipoprotein B ratios demonstrated gender-specific differences in the nature of circulating lipoprotein particles independent of diabetic state with values for females approximately twice those of males indicating more highly triglyceride-enriched lipoprotein particles in females. We conclude that the obese ZDF female rat has the potential to become an important animal model of NIDDM especially in women where few models currently exist.

PMID: 10657558

### **11. Prostaglandins Leukot Essent Fatty Acids. 1998 Sep;59(3):195-202.**

Evening primrose oil treatment corrects reduced conduction velocity but not depletion of arachidonic acid in nerve from streptozotocin-induced diabetic rats.

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The effects of evening primrose oil (EPO) treatment, a source of gamma-linolenic acid, on the proportions of arachidonoyl-containing molecular species (ACMS) in sciatic nerve phosphatidylcholine and phosphatidylethanolamine were determined in conjunction with alterations in nerve conduction velocity. Normal and diabetic rats were either untreated or fed a dietary supplement containing isocalorically equivalent amounts of either EPO or corn oil for the duration of the experiment. After 8 weeks of streptozotocin-induced diabetes, nerve conduction velocity was reduced 16% and this deficit was prevented by either EPO or corn oil treatment. Neither EPO nor corn oil supplementation significantly increased the depressed proportions of ACMS. The level of the linoleoyl-containing molecular species, 16:0/18:2, was elevated in the phospholipids from untreated diabetic rats and was further increased by EPO treatment. These results are consistent with decreased activity of the delta6 desaturase that is required for arachidonic acid synthesis in vivo, but suggests that an accompanying deficit in the subsequent delta5 desaturase-catalyzed reaction may be rate-limiting. These findings indicate that maintenance of normal ACMS levels is not required for prevention of diminished nerve conduction velocity and suggest that other factors influenced by an altered polyunsaturated fatty acid pattern, such as metabolites of linoleic acid or gamma-linolenic acid other than arachidonic acid, the energy state of the nerve or the degree of membrane fluidity may contribute to impaired nerve conduction velocity in diabetic neuropathy.

PMID: 9844993

## **12. Metabolism. 1998 Nov;47(11):1315-24.**

Lipoprotein alterations in 10- and 20-week-old Zucker diabetic fatty rats: hyperinsulinemic versus insulinopenic hyperglycemia.

Sparks JD, Phung TL, Bolognino M, Cianci J, Khurana R, Peterson RG, Sowden MP, Corsetti JP, Sparks CE.

Department of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry, NY 14642, USA.

Lipoprotein and apolipoprotein parameters were studied in the male Zucker diabetic fatty (ZDF) rat at 10 and 20 weeks of age, corresponding to hyperinsulinemic and insulinopenic type 2 diabetes mellitus, respectively. At both ages, ZDF rats had elevated serum triglycerides, free fatty acids, and corticosterone, whereas 20-week ZDF rats had reduced thyroid hormones. At 10 weeks, the hyperlipidemia was

confined to elevations in pre-beta triglyceride-rich ( $d < 1.006$  g/mL) lipoproteins. By 20 weeks, all lipoprotein density fractions were increased compared with lean rats, with substantial increases in both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. In ZDF rats, there was a progressive increase in apolipoprotein B (apo B) from 1.9 times control at 10 weeks to three times control at 20 weeks. The increase in apo B was accompanied by a shift of apo B, particularly B100, from very-low-density lipoprotein (VLDL) into denser lipoproteins corresponding to intermediate-density lipoproteins plus LDLs ( $1.006 < d < 1.063$  g/mL). In Zucker and 10-week ZDF rats, in the presence of hyperinsulinemia, the increase in serum apo B was predominantly apo B48 present in VLDL. By 20 weeks, when ZDF rats are insulinopenic, the mass ratio of B48:B100 shifted from 2.7 to 0.7. The shift was associated with a decrease in hepatic-edited apo B mRNA. Apo E increased in lean rats between 10 and 20 weeks of age. Although apo E also increased in ZDF rats, the increase by 20 weeks was less than that of lean rats. The molar ratio of apo E to B in VLDL was decreased in ZDF rats. In lean rats, greater than 50% of apo E was present in HDL, in contrast to ZDF rats, where less than 20% of apo E was present in HDL. VLDL apo E shifted to denser fractions by 20 weeks of age, similar to apo B. The apo C level was more than double compared with the level in lean rats and was redistributed from the HDL fraction to lipoprotein fractions containing apo B. Both apo A-I and apo A-IV levels more than doubled between 10 and 20 weeks in ZDF rats. The ZDF rat model may be useful in comparative studies of lipoproteins during diabetic progression from hyperinsulinemia to insulinopenia.

PMID: 9826206

### **13. Metabolism. 1998 Sep;47(9):1042-7.**

The effect of glucose and glucagon-like peptide-1 stimulation on insulin release in the perfused pancreas in a non-insulin-dependent diabetes mellitus animal model.

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This study was designed to investigate the effect of glucagon-like peptide-1 (GLP-1) on pancreatic beta-cell function in normal, Zucker diabetic fatty (ZDF) rats, a model for non-insulin-dependent diabetes mellitus (NIDDM or type II diabetes) and their heterozygous siblings. Pancreas perfusion and enzyme-linked immunosorbent assay (ELISA) were used to detect the changes in insulin release under

fasting and hyperglycemic conditions and following stimulation with GLP-1. Animals from the ZDF/Gmi-fa rats (ZDF) were grouped according to age, sex, and phenotype (obese or lean), and compared with LA lean rats. Glucose stimulation (10 mmol/L) in obese rats showed repressed response in insulin release. Glucose plus GLP-1 stimulation caused increased insulin release in all groups. The degree of this response differed between groups: lean > obese; young > adult; female > male. The LA lean control group was most sensitive, while the ZDF overtly diabetic group had the lowest response. In addition, the pulsatile pattern of insulin secretion was suppressed in ZDF rats, especially in obese groups. These results support the hypothesis that GLP-1 can effectively stimulate insulin secretion. Insulin release was defective in ZDF obese rats and could be partially restored with GLP-1. ZDF lean rats also showed suppression of beta-cell function and there was a difference in beta-cell function related to sex in ZDF strain. This study documents the efficacy of GLP-1 to stimulate insulin release and contributes to our understanding of the pathophysiological mechanisms underlying NIDDM.

PMID: 9751230

#### **14. J Am Soc Nephrol. 1997 Jun;8(6):943-8.**

Overexpression of GLUT2 gene in renal proximal tubules of diabetic Zucker rats.

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Renal tubular reabsorption of glucose is substantially increased in humans and rats with diabetes mellitus. The influx of luminal glucose is mediated by Na<sup>+</sup>/glucose cotransporter system and glucose efflux from tubules to interstitium by facilitative glucose transporters (GLUT). In Zucker diabetic rats, GLUT2 protein levels of renal proximal tubules were higher than in control litter mates: 9.67 +/- 1.95 versus 4.72 +/- 1.55 (P = 0.0073). In the same proximal tubules, diabetes was associated with minor decreases in GLUT1 protein levels: 1.96 +/- 0.37 for diabetics and 2.37 +/- 0.34 for controls (P = 0.12). Na<sup>+</sup>/glucose cotransporter system protein levels were similar in both groups, whereas Na<sup>+</sup>/K<sup>+</sup> ATPase levels were slightly decreased in diabetic rats, but the difference was not statistically significant. In this report, it is suggested that in long-term uncontrolled diabetes, GLUT2 transporters are overexpressed in renal tubules. This

adaptation promotes low-affinity, high-capacity glucose efflux. The higher number of high K(m) GLUT2 ensures that glucose reabsorption is increased by promoting glucose efflux, which could be rate-limiting in the face of hyperglycemia.

PMID: 9189862

### **15. Metabolism. 1997 Mar;46(3):261-7.**

Incretin hormone expression in the gut of diabetic mice and rats.

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To elucidate the question of whether production of the insulinotropic gut hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) is altered by a diabetic metabolic state, their intestinal expression pattern was evaluated. Two rodent models for diabetes mellitus were used, non-obese diabetic (NOD) mice as a model for insulin-dependent diabetes and Zucker diabetic fatty (ZDF) rats for non-insulin-dependent diabetes mellitus (NIDDM). Expression of both incretin hormones followed typical patterns, which were similar in both animals and unaltered by the diabetic state. The GIP gene was greatly expressed in the duodenum, jejunum, and ileum, with a continuous decrease from the upper to lower intestines. This pattern was observed in both NOD mice and ZDF rats regardless of the diabetic state. This expression data was corroborated by radioimmunoassay (RIA) analysis of the gene product GIP. Expression of the proglucagon gene encoding GLP-1 had an opposite appearance. The highest expression was seen in the large bowel and the ileum. RIA analysis of the gene product GLP-1 mirrored these data. Although the distribution pattern was similar in both animal models, in contrast to diabetic NOD mice, a regulated expression was found in diabetic ZDF rats. Compared with lean nondiabetic controls, fatty hyperglycemic animals showed an increased expression of the proglucagon gene in the colon and a concomitant reduction in the small intestine. This was mirrored by the GLP-1 content of the colon and ileum. Overall, basal GLP-1 plasma levels were increased in ZDF rats (17.0 +/- 2.8 pmol) compared with lean Zucker rats (12.4 +/- 1.8 pmol). In conclusion, incretin hormone expression (GIP and GLP-1) follows specific patterns throughout the gut and is unaltered by the diabetic state. In ZDF rats, regulation of proglucagon expression occurs mainly in the large intestine.

**16. J Peripher Nerv Syst. 1997;2(2):155-63.**

Effects of hypoxia and severity of diabetes on Na,K-ATPase activity and arachidonoyl-containing glycerophospholipid molecular species in nerve from streptozotocin diabetic rats.

Doss DJ, Kuruvilla R, Bianchi R, Peterson RG, Eichberg J.

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The pathogenesis of experimental diabetic neuropathy is associated with the development of endoneurial hypoxia. Exposure of normal rats to hypoxic conditions has previously been shown to reduce nerve conduction velocity. To study the biochemical effects of hypoxia further, streptozotocin-induced diabetic and age-matched nondiabetic rats were maintained in air containing 10% oxygen for nine weeks. As compared to nondiabetic rats kept in room air, sciatic nerve Na,K-ATPase activity was decreased 38% in nondiabetic, hypoxic rats and tended to be lower in diabetic animals maintained in a normoxic environment. However, the enzyme activity was unchanged in diabetic, hypoxic rats, suggesting the existence of an undefined compensatory interaction between these two conditions. Arachidonoyl-containing molecular species (ACMS) of phosphatidylcholine and phosphatidylethanolamine were substantially depleted in nerves from diabetic rats. Hypoxia alone also caused a lesser depletion of some but not all of these ACMS. However, the two conditions together did not produce a further decrease, consistent with the concept that the same mechanism is responsible for loss of ACMS in hypoxia and diabetes. To examine the effects of severity of diabetes on these parameters, groups of rats were injected with either 50 mg/kg or 100 mg/kg streptozotocin. The latter group was maintained by administration of minimal insulin doses and the experiment was terminated after 3 weeks. Serum glucose in rats that received the high dose of drug averaged 12% higher than in the low dose group. As compared to nondiabetic rats, Na,K-ATPase activity was reduced 32-36%, but there was no difference in activity between the two diabetic groups. However, there was a greater loss of ACMS in the more severely hyperglycemic rats. In rats that received comparable streptozotocin doses, measurement of ACMS depletion after 3, 9 and 32 weeks of diabetes revealed the loss is progressive with time. Thus, glycerophospholipid ACMS is a sensitive index of the severity and duration of experimental

diabetic neuropathy.

PMID: 10959229

**17. Metabolism. 1996 Mar;45(3):320-7.**

An aldose reductase inhibitor but not myo-inositol blocks enhanced polyphosphoinositide turnover in peripheral nerve from diabetic rats.

Berti-Mattera L, Day N, Peterson RG, Eichberg J.

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Experimental diabetic neuropathy, whether chemically induced or present in several spontaneously diabetic animal models, is characterized by sorbitol accumulation and myo-inositol depletion and usually also by enhanced turnover of the monoesterified moieties of polyphosphoinositides, particularly phosphatidylinositol-4,5-bisphosphate (PIP<sub>2</sub>). This study examined the relationship of these alterations by assessing the effects of myo-inositol and the aldose reductase inhibitor, sorbinil, supplied as dietary supplements, on sorbitol and myo-inositol concentrations and incorporation of <sup>32</sup>P into polyphosphoinositides in sciatic nerve from rats killed 8 weeks after induction of diabetes with streptozotocin. Nerves from diabetic rats killed after 8 weeks of disease exhibited 52% to 76% greater PIP<sub>2</sub> labeling, markedly elevated sorbitol levels, and 30% less myo-inositol when compared with age-matched normal rats. Incorporation of isotope into PIP<sub>2</sub> in nerves from animals fed a myo-inositol supplement, added to either a high-sucrose diet or standard rat chow beginning immediately after induction of diabetes, remained substantially elevated, whereas myo-inositol levels were corrected to normal. Essentially the same results were obtained when rats were fed the myo-inositol-containing diet beginning 4 weeks after streptozotocin injection. In contrast, PIP<sub>2</sub> labeling in nerves from diabetic rats that received the sorbinil-supplemented diet for either 4 or 8 weeks was not different from that in controls. myo-Inositol levels in these animals were also restored to normal, whereas sorbitol levels remained elevated, albeit reduced by approximately 30%. These results indicate that myo-inositol administration is unable to completely counteract the impact of diabetes on the turnover of monoesterified phosphate groups in PIP<sub>2</sub>. In contrast, sorbinil can correct this abnormality, but this beneficial effect is not dependent on the presence of normal sorbitol concentrations.

PMID: 8606638

**18. Eur J Clin Invest. 1994 Aug;24 Suppl 3:11-8.**

alpha-Glucosidase inhibitors in diabetes: lessons from animal studies.

Peterson RG.

Department of Anatomy, Indiana University School of Medicine, Indianapolis 46202-5120.

Two rat models for non-insulin-dependent diabetes mellitus (NIDDM) have been used in our laboratory to study the effects of alpha-glucosidase inhibitors. These models become hyperglycaemic and have other characteristics which make them good models for NIDDM, and both prevention and reversal studies have been carried out; the prevention experiments were started before the animal became diabetic while the reversal groups were treated after diabetes had fully developed. In both models blood glucose was significantly lowered toward control levels using a dose of 40 mg per 100 g of diet while there was a less dramatic, but still significant, correction with half that dose. Treatment increased the weight gain of the more diabetic model (ZDF) while there was no effect of treatment on the weight of the Wistar diabetic fatty (WDF) rat. Other parameters such as glycated haemoglobins, nerve conduction velocity and nerve sugar content are also reversed with effective treatment of the hyperglycaemic condition.

PMID: 8001621

**19. Biochim Biophys Acta. 1994 May 25;1226(2):145-50.**

Inhibition of glycolytic enzymes by endogenous aldehydes: a possible relation to diabetic neuropathies.

Novotny MV, Yancey MF, Stuart R, Wiesler D, Peterson RG.

Department of Chemistry, Indiana University, Bloomington 47405.

Endogenous saturated and unsaturated aldehydes were found in significant elevations in serum of diabetic humans and rats. These compounds, originating from the lipid peroxidation processes, are shown here to be potent inhibitors of the glycolytic enzymes, phosphofructokinase and glyceraldehyde-3-phosphate dehydrogenase. The inhibition process is non-competitive and progressive. The aldehyde mixture, when supplemented to the standard rat diet at 1/100 ratio, caused nerve damage that is reminiscent of diabetic polyneuropathies.

PMID: 8204661

**20. Diabet Med. 1993;10 Suppl 2:16S-20S.**

Inositol and phospholipid metabolism in diabetic nerve.

Eichberg J, Abe S, Berti-Mattera LN, Day NS, Lowery JM, Zhu X, Peterson RG.

Department of Biochemical and Biophysical Sciences, University of Houston, TX 77204.

PMID: 8392922

**21. Am J Physiol. 1991 Dec;261(6 Pt 1):E782-8.**

Altered expression of muscle glucose transporter GLUT-4 in diabetic fatty Zucker rats (ZDF/Drt-fa).

Friedman JE, de Venté JE, Peterson RG, Dohm GL.

Department of Biochemistry, School of Medicine, East Carolina University, Greenville, North Carolina 27858.

We examined GLUT-4 glucose transporter protein and mRNA in muscle tissue from a new rodent model of non-insulin-dependent diabetes mellitus (NIDDM), the male obese Zucker diabetic fatty (ZDF) rat [ZDF/Drt-fa(F10)]. We also determined whether prevention of hyperglycemia might affect GLUT-4 expression by feeding the intestinal alpha-glucosidase inhibitor acarbose (40 mg/100 g diet) in the diet of male ZDF rats for 19 wk, starting at least 1 wk before the onset of diabetes. Fasting glucose was four- to sixfold greater in diabetic ZDF rats (24.1 +/- 6.7 mM) compared with lean or obese nondiabetic rats. Fasting insulin in diabetic ZDF rats (0.5 +/- 0.1 ng/ml) was similar to lean rats (0.4 +/- 0.1) but greatly reduced compared with obese nondiabetic rats (18.7 +/- 4.0 ng/ml). Acarbose treatment significantly reduced fasting glucose levels to 13.4 +/- 1.4 mM, while insulin levels increased to 1.6 +/- 0.3 ng/ml. GLUT-4 protein levels in diabetic ZDF rats were reduced approximately 40% in red quadriceps and mixed gastrocnemius muscles but were unchanged in white quadriceps muscle. Acarbose treatment was associated with a twofold increase in GLUT-4 protein and mRNA in mixed gastrocnemius muscle. These data indicate that, in this obese model of NIDDM without hyperinsulinemia, there is reduced muscle GLUT-4 protein in red but not white muscle fiber types. The decrease in muscle GLUT-4 expression in this model of NIDDM can be prevented by acarbose treatment, which reduces hyperglycemia and increases beta-cell

responsiveness.

PMID: 1767839

**22. J Neurol Sci. 1991 Feb;101(2):204-7.**

Oxygen affinity of hemoglobin and peripheral nerve degeneration in experimental diabetes.

Farber SD, Farber MO, Brewer G, Magnes CJ, Peterson RG.

Indiana University School of Medicine, Indianapolis.

Peripheral neuropathy remains a major complication of diabetes. Numerous etiological theories of metabolic and/or vascular disturbances have been suggested including decreased endoneurial oxygen tension with presumed tissue hypoxia. Increases in the affinity of hemoglobin for oxygen (Hb-O<sub>2</sub> affinity) may also produce tissue hypoxia and such Hb-O<sub>2</sub> affinity changes have been implicated in the pathogenesis of diabetic microangiopathy. In order to test whether affinity hypoxia might contribute to the development of diabetic peripheral neuropathy, we have utilized a rat model of high and normal Hb-O<sub>2</sub> affinity produced by backcrossing animals with increased and decreased levels of 2,3-diphosphoglycerate (DPG). Diabetes was induced in ten high and ten low DPG animals with a tail vein injection of 55 mg/kg streptozotocin (STZ). Five animals in each group were treated with 2.4 U protamine zinc insulin (PZI)/day while the remaining animals were untreated. All rats were killed after 30 days, sections of tibial and sural nerve were rapidly removed and processed for teased fiber analysis. A minimum of 125 axons were assessed per nerve for E degeneration (myelin ovoids) using the classification developed by Dyck et al. Untreated animals, regardless of DPG levels, demonstrated 0% neuropathy. In contrast, all insulin-treated animals showed degeneration (0.4-17%) that inversely correlated with the DPG level ( $r = -0.59$ ,  $P$  less than 0.04). The results of this study suggest that the level of RBC DPG (and presumably the Hb-O<sub>2</sub> affinity) with its attendant effect on tissue oxygen release may play a role in the development of peripheral neuropathy in STZ-induced diabetic rats treated with insulin.

PMID: 2033405

**23. Proc Natl Acad Sci U S A. 1990 Dec;87(24):9953-7.**

Evidence that down-regulation of beta-cell glucose transporters in non-insulin-dependent diabetes may be the cause of diabetic

hyperglycemia.

Orci L, Ravazzola M, Baetens D, Inman L, Amherdt M, Peterson RG, Newgard CB, Johnson JH, Unger RH.

Department of Morphology, University of Geneva Medical School, Switzerland.

Non-insulin-dependent diabetes mellitus (NIDDM) is attributed to a failure of pancreatic beta cells to maintain insulin secretion at a level sufficient to compensate for underlying insulin resistance. In the ZDF rat, a model of NIDDM that closely resembles the human syndrome, we have previously reported profound underexpression of GLUT-2, the high-Km facilitative glucose transporter expressed by beta cells of normal animals. Here we report that islets of diabetic rats exhibit a marked decrease in the volume of GLUT-2-positive beta cells and a reduction at the electron-microscopic level in the number of GLUT-2-immunoreactive sites per unit of beta-cell plasma membrane. The deficiency of GLUT-2 cannot be induced in normal beta cells by in vivo or in vitro exposure to high levels of glucose nor can it be prevented in beta cells of prediabetic ZDF rats by elimination of hyperglycemia. We conclude that this dearth of immunodetectable GLUT-2 in NIDDM is not secondary to hyperglycemia and therefore that it may well play a causal role in the development of hyperglycemia.

PMCID: PMC55292

PMID: 2263645

#### **24. Diabetes. 1989 Mar;38(3):373-8.**

Alteration of phosphoinositide metabolism, protein phosphorylation, and carbohydrate levels in sciatic nerve from Wistar fatty diabetic rats.

Berti-Mattera LN, Lowery J, Day SF, Peterson RG, Eichberg J.

Department of Biochemical and Biophysical Sciences, University of Houston 77004.

Sciatic nerve from the Wistar fatty diabetic (FD) rat, a prospective model for non-insulin-dependent diabetes mellitus, was investigated to determine the content of carbohydrates and to measure the incorporation of <sup>32</sup>P into phosphoinositides and proteins. This strain has been shown to develop structural abnormalities in nerves and to exhibit reduced conduction velocity. Males became diabetic between the ages of 8 and 10 wk and were maintained

together with lean sibling controls until the animals were either 22 or 44 wk old. Throughout this period, FD rats displayed moderate hyperglycemia. The carbohydrate profile of FD rat sciatic nerve exhibited modest increases in glucose, fructose, and sorbitol levels and significantly reduced myo-inositol concentrations, which were comparable at both ages. When nerves from 22-wk-old animals were incubated with [32P]orthophosphate and incorporation of radioactivity into phospholipids was measured, an increase in isotope uptake into phosphatidylinositol-4,5-bisphosphate and phosphatidylinositol-4-phosphate in the distal portions of tissue from the FD rat was observed. This effect was more pronounced in nerves from 44-wk-old rats. Phosphorylation of the major myelin protein P0 was 70% higher in the most distal portion of FD sciatic nerve from 22-wk-old animals. A comparable rise in phosphorylation of P0 as well as the large (P1) and small (Pr) myelin basic proteins occurred in nerves from 44-wk-old rats. In these animals, an approximately 50% decrease in the uptake of 32P into P0 and P1 in the most proximal region of FD nerve was also apparent. (ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 2537246

**25. J Neurol Sci. 1988 Dec;88(1-3):293-301.**

Hypoglycemic neuropathy in experimental diabetes.

Potter CG, Sharma AK, Farber MO, Peterson RG.

Program in Medical Neurobiology, Indiana University School of Medicine, Indianapolis 46223.

Morphological and electrophysiological observations were made over 4 weeks on 5 groups of 8-week-old male Sprague-Dawley rats. These were comprised of controls, untreated diabetics, and diabetic animals in which sustained hypoglycemia, moderate hypoglycemia, or normoglycemia was induced by continuous subcutaneous insulin infusion (CSII) therapy. Teased fiber studies showed a marked increase in the number of myelinated fibers undergoing axonal degeneration and regeneration in the tibial nerve of severe hypoglycemic and also in moderate hypoglycemic animals but not in controls, untreated diabetic and normoglycemic groups. There was also a significant correlation between episodes of hypoglycemia (less than or equal to 2.0 mmol/l) and the prevalence of axonal degeneration and regeneration in CSII-treated diabetics. Motor nerve conduction velocity was significantly reduced in the moderate and severe hypoglycemic groups and also in untreated diabetic animals when compared with controls. However, it was significantly improved in the normoglycemic group over the untreated

diabetic and severe hypoglycemic groups. In conclusion, this study has demonstrated that severe or even mild hypoglycemia produced a detrimental effect on peripheral nerve structure and function in experimental diabetes. Therefore, it may be desirable to avoid even asymptomatic hypoglycemia in the management of diabetes.

PMID: 3225627

## **26. J Neurol Sci. 1988 Jun;85(2):131-47.**

Ultrastructural observations on myelinated fibres in experimental diabetes: effect of the aldose reductase inhibitor ponalrestat given alone or in conjunction with insulin therapy.

Bhojrul S, Sharma AK, Stribling D, Mirrlees DD, Peterson RG, Farber MO, Thomas PK.

Department of Anatomy, Marischal College, University of Aberdeen, U.K.

Six groups of rats were studied over a 12-week period: onset and end controls, untreated diabetics, ponalrestat-treated diabetics, insulin-treated diabetics, and diabetics treated with ponalrestat and insulin. The concentrations of glucose, sorbitol and fructose significantly increased and that of myo-inositol significantly decreased in the sciatic nerve of untreated diabetic animals. Ponalrestat administration completely normalized sorbitol levels and partially corrected fructose and myo-inositol concentrations without altering nerve glucose levels. The biochemical abnormalities were also corrected in both the insulin-treated and insulin and ponalrestat-treated diabetic animals. Myelinated fibre cross-sectional areas and axonal areas were significantly less in the tibial nerve of diabetic animals as compared with age-matched controls. Insulin treatment partially corrected the reduction in fibre and axonal area but teased fibre preparations showed an excess of axonal degeneration as compared with controls, untreated diabetics and ponalrestat-treated diabetics. Ponalrestat given alone or in conjunction with insulin therapy did not correct the reduction in fibre or axonal area and single isolated fibres from diabetic animals treated with ponalrestat and insulin showed a marked excess of axonal degeneration, probably related to hypoglycaemia. The study fails to reveal any significant beneficial effect of aldose reductase inhibition on the structural abnormalities in peripheral nerve in experimental diabetes.

PMID: 2968441

**27. Anat Rec. 1983 Dec;207(4):563-71.**

Electron microscopic study of intramembranous changes in protein-extracted peripheral nervous system myelin.

Cullen MJ, Peterson RG, Webster HD.

Sciatic nerves from young mice were incubated for 2-8 hours in 0.5% Triton X-100 in 0.5 M ammonium acetate, a solution which solubilizes the large and small basic proteins of the myelin sheath. As previously noted (Peterson and Gruener, 1978), myelin sheaths from treated nerves extensively split and unravelled along major dense lines. Small focal areas of compact myelin remained. In freeze-fracture replicas, areas of myelin with lamellar splitting contained few intramembranous particles, while membrane areas with greater than normal densities of particles were associated with the patches of compact myelin membrane. Fixation for as short a time as 15 minutes stabilized the myelin membrane enough to prevent the Triton X-100 effects, even when incubations were extended to 20 hours. Controls, both untreated and 0.5 M ammonium acetate-treated nerves, had predominantly compact myelin sheaths; their leaflets were covered with numerous intramembranous particles. The data suggest that Triton X-100 alters the compact structure of peripheral nervous system myelin. In areas where lamellae are split and separated, there is a loss of intramembranous particles. It appears that the loss of intramembranous particles is related to the removal of the basic proteins which are located in major dense line regions of compact myelin sheaths.

PMID: 6670754

**28. J Neurol Sci. 1983 Sep;61(1):93-107.**

Degenerative neuropathy in insulin-treated diabetic rats.

Westfall SG, Felten DL, Mandelbaum JA, Moore SA, Peterson RG.

Peripheral neuropathic alterations associated with diabetes and its treatment with insulin were studied in alloxan-induced diabetic rats. Treatment regimens included daily injections of Protamine Zinc Insulin (PZ), daily injections of Ultralente Insulin and subcutaneously implanted osmotic minipump delivered insulin. Non-diabetic and untreated diabetic groups served as controls. Two separate but similar studies were run, one lasting 4 weeks and the other 8 weeks. Conduction velocities performed on both sensory and motor nerves revealed no statistically significant differences among groups. Anatomical analysis of teased fibers from tibial nerves showed a significant number of

fibers with ovoids, consistent with Wallerian-type axonal degeneration, only in the treated diabetic groups. Degeneration was especially severe in the PZI-treated group. Metabolic studies were performed using incorporation of radioactive isotopes ([<sup>3</sup>H]fucose, [<sup>14</sup>C]leucine) into myelin proteins of sciatic nerves. The ratio of [<sup>3</sup>H]fucose/[<sup>14</sup>C]leucine for the PZI-treated group was significantly decreased when compared to the control groups in both the 4 and 8 week study whereas the minipump-treated group showed no statistically significant difference from the control group in either study. Similar decreases in this ratio have been seen in conditions of peripheral nerve degeneration. It is concluded that daily injections of PZI insulin result in significant nerve degeneration in the alloxan diabetic rat, while continuous levels of insulin delivered by osmotic minipumps result in less degeneration.

PMID: 6355399

### **29. Neurochem Res. 1983 Apr;8(4):465-72.**

Altered metabolic incorporation of fucose and leucine into PNS myelin of 25-week-old diabetic (C57BL/Ks [db/db]) mice: effects of untreated diabetes on nerve metabolism.

Chez MG, Peterson RG.

Sciatic nerves of 25-week-old genetically diabetic (C57BL/Ks [db/db]) mice and their litter-mate controls were removed, and their metabolic incorporation of [<sup>3</sup>H]fucose and [<sup>14</sup>C]leucine into myelin was studied in vitro. Untreated diabetic animals showed significant increases (p less than 0.05) in the fucose/leucine incorporation into myelin when compared to values found for their litter-mates. These results correlated well with previous experiments performed on alloxan or streptozotocin-diabetic rats and thus show the in vitro incubation procedure to be a good indicator of altered metabolic conditions in peripheral nerves due to diabetes mellitus. The resulting ratio increases seen in diabetic animals is at variance with the decrease in ratios found in animals undergoing typical Wallerian degeneration. These results suggest that different metabolic processes operate in untreated diabetics than in normals or in those undergoing other degenerative nerve processes.

PMID: 6888648

### **30. Brain Res Bull. 1983 Mar;10(3):377-84.**

Neuropathic changes associated with insulin treatment of diabetic rats: electron microscopic and morphometric analysis.

Mandelbaum JA, Felten DL, Westfall SG, Newlin GE, Peterson RG.

Tibial nerves from control, untreated alloxan diabetic, and 4-week insulin treated alloxan diabetic rats were examined with light microscopy and computerized morphometric analysis of axons. Teased fiber preparations and electron microscopy were utilized to evaluate nerve degeneration. The insulin treatment regimens included daily injections of protamine zinc insulin (PZI), daily injections of ultralente insulin, and continuously delivered insulin through osmotic minipumps. Evaluation of axon:myelin ratios, teased fiber profiles, and electron microscopic cross sections of nerves demonstrated different degrees of neuropathic changes within the treated groups. The control group and untreated diabetic group showed little or no degeneration, while all insulin-treated groups showed evidence of Wallerian degeneration. Among these insulin treated groups, the PZI-treated group showed the greatest number of degenerating profiles while the minipump group showed the least. These data suggest that insulin treatment of alloxan diabetes results in axonal degeneration which closely resembles findings in human diabetic neuropathies. The substantially diminished number of degenerating axons seen in the osmotic minipump insulin-treated rats suggests that continuous delivery of insulin may decrease the neuropathic changes seen with single injection insulin therapy. Since virtually all insulin-dependent diabetic patients receive daily administration of insulin, the possibility that peripheral neuropathies may in part result from the insulin treatment requires more extensive investigation in a variety of animal models to separate the neuropathic effects of diabetes from the neuropathic effects of insulin therapy.

PMID: 6850362

### **31. J Pharmacol Exp Ther. 1982 Aug;222(2):501-8.**

Comparison of the metabolic and toxic effects of 2-chloropropionate and dichloroacetate.

Yount EA, Felten SY, O'Connor BL, Peterson RG, Powell RS, Yum MN, Harris RA.

The metabolic and toxic effects of 2-chloropropionate and dichloroacetate, activators of the pyruvate dehydrogenase complex, were compared. In 4-hr fasted mice, the oral LD50 values for 2-chloropropionate and dichloroacetate were 15.4 +/- 0.1 and 32.1 +/- 1.1 mmol/kg, respectively. In suckling rats, both compounds effectively lowered blood lactate and glucose levels and increased blood ketone bodies. Although

comparable effects were brought about by both compounds on other metabolites, dichloroacetate caused a greater increase in blood ketone bodies. In a prolonged oral toxicity study using male rats, both compounds decreased growth rate and food consumption and caused neurotoxic effects. Both compounds brought about hind limb weakness, slower nerve conduction velocities and decreased diameter of tibial nerves. 2-Chloropropionate treatment caused testicular abnormalities manifested by testicular maturation arrest and degeneration of germ cells. 2-Chloropropionate-treated rats had significantly lower plasma triacylglycerol levels than control or dichloroacetate-treated rats. In mature rats, total serum ketone bodies were increased by dichloroacetate but not significantly elevated by 2-chloropropionate. Although 2-chloropropionate may lack sufficient safety to warrant chronic use in humans, it is a useful research tool for studying the metabolic effects of activation of the pyruvate dehydrogenase complex. Since 2-chloropropionate is not converted to oxalate and is not as ketogenic as dichloroacetate, 2-chloropropionate may be useful clinically in situations requiring only short-term therapy.

PMID: 7097569

### **32. J Neurochem. 1982 Jul;39(1):192-200.**

Metabolism of phospholipids in peripheral nerve from rats with chronic streptozotocin-induced diabetes: increased turnover of phosphatidylinositol-4,5-bisphosphate.

Bell ME, Peterson RG, Eichberg J.

The effect of chronic streptozotocin-induced diabetes on phospholipid metabolism in rat sciatic nerve in vitro was investigated. In normal nerve incubated for 2 h in Krebs-Ringer-bicarbonate buffer containing [<sup>32</sup>P]orthophosphate, radioactivity was primarily incorporated into phosphatidylinositol-4,5-bisphosphate and phosphatidylcholine. Smaller amounts were present in phosphatidylinositol-4-phosphate, phosphatidylinositol, and phosphatidic acid. As compared to controls, phosphatidylinositol-4,5-bisphosphate in nerves from animals made diabetic 2, 10, and 20 weeks earlier accounted for 30-46% more of the isotope, expressed as a percentage, incorporated into all phospholipids. In contrast, the proportion of radioactivity in phosphatidylcholine decreased by 10-25%. When the results were expressed as the quantity of phosphorus incorporated into phospholipid, only phosphatidylinositol-4,5-bisphosphate displayed a change. The amount of isotope which entered this lipid increased

60% and 67% for 2- and 10-week diabetic animals, respectively. Increased phosphatidylinositol-4,5-bisphosphate labeling was observed when epineurial-free preparations were used or when the composition of the incubation medium was varied. Sciatic and caudal nerve conduction velocities were decreased after 10 and 20 weeks but were unchanged after 2 weeks. We conclude that an increase in the turnover of phosphatidylinositol-4,5-bisphosphate in sciatic nerve from streptozotocin-diabetic rats appears relatively early and persists throughout the course of the disease. This metabolic alteration may be related to a primary defect responsible for the accompanying deficient peripheral nerve function.

PMID: 6283017

### **33. Brain Res Bull. 1982 Jun;8(6):593-607.**

Effects of streptozotocin diabetes on the noradrenergic innervation of the rat heart: a longitudinal histofluorescence and neurochemical study.

Felten SY, Peterson RG, Shea PA, Besch HR Jr, Felten DL.

The effects of the age of induction and total duration of streptozotocin diabetes on the sympathetic noradrenergic innervation of the rat heart was examined with glyoxylic acid induced histofluorescence to demonstrate the distribution of noradrenergic fibers within the heart, and with high performance liquid chromatography with electrochemical detection to measure tissue levels of the neurotransmitter norepinephrine. Diabetes was induced in male Sprague-Dawley rats at 1, 2, and 4 months of age. Within each of these groups, diabetic rats survived for periods of 1, 2, and 4 months. Additional groups of diabetic rats survived to a chronological age of 8 months. Norepinephrine levels in the hearts of diabetic rats were increased over those of control rats in all groups at 1 month duration of diabetes. Ventricles were generally affected to a greater extent than atria. At 2 months duration of diabetes, ventricular levels remained elevated while atrial norepinephrine levels were at or below control levels. At 4 months duration of diabetes, and in all groups at 8 months of age, the norepinephrine levels were at or below control levels, except in the ventricles of rats induced at 4 months of age, which remained elevated. Histofluorescence studies demonstrated the presence of axon bundles and varicose noradrenergic profiles in the diabetic rat hearts, distributed in a pattern similar to that seen in controls. However, at 1 month duration of diabetes in all groups, the density of noradrenergic varicosities in diabetic rat hearts appeared increased with abundant

branched profiles. These results are surprising, since studies on genetic models of diabetes have suggested decreased norepinephrine levels in the heart. The present study suggests that during the early phases of streptozotocin induced diabetes, noradrenergic nerves are still intact and may be susceptible to pharmacologic manipulation. The later fall of norepinephrine levels back to or below control levels may indicate actual neuronal damage, suggesting that early intervention may be necessary to protect these nerves from degeneration. This issue is potentially important in view of the reported toxic effects of high NE levels on the heart, and the high incidence of death from myocardial infarct in diabetic humans with autonomic neuropathy.

PMID: 6754009

#### **34. J Chromatogr. 1982 Mar 12;228:33-42.**

Excretion of urinary volatile metabolites in response to alloxan induced diabetes of short duration in rats.

Rhodes G, Holland ML, Wiesler D, Novotn•• M, Moore SA, Peterson RG, Felten DL.

Alterations in urine volatile metabolites due to the induction of alloxan diabetes in the rat were examined by capillary gas chromatography and gas chromatography--mass spectrometry for the five days immediately following the onset of chronic hyperglycemia. Elevations of a number of metabolites were observed including several short chain ketones, acetophenone, 2-acetylfuran and indole. The value of urine volatile metabolic profiles as characteristic indicators of the diabetic condition is demonstrated through profiles obtained from a diabetic animal which spontaneously reverted to normal.

PMID: 7076757

#### **35. Brain Res Bull. 1982 Mar;8(3):317-23.**

Ultrastructural axonal pathology in experimentally diabetic and aging control rats.

Moore SA, Peterson RG, Felten DL, O'Connor BL.

Electron microscopic examination of tibial nerves from streptozotocin-diabetic, alloxan-diabetic and age-matched control rats was undertaken at two weeks and two, four, eight, and twelve months following the induction of diabetes. Many myelinated axons of both diabetic and control rats contained glycogen-like granules, axon-Schwann

cell networks and fingerlike intrusions of myelin. These axonal changes were observed more frequently with advancing age and duration of diabetes, suggesting that they are related to aging or repeated injury. A larger proportion of diabetic axons than control axons were affected at early time periods, but by eight and twelve months the control axons were as frequently (or more frequently) involved as diabetic axons. Thus, experimental diabetes may confer upon peripheral myelinated axons an increased susceptibility to aging or repeated injury. Specific morphologic abnormalities in peripheral myelinated axons associated uniquely with streptozotocin or alloxan diabetes in the rat were not noted.

PMID: 7093738

### **36. Experientia. 1982 Jan 15;38(1):75-7.**

Structural relationships between the endogenous volatile urinary metabolites of experimentally diabetic rats and certain neurotoxins (1).

Rhodes G, Holland ML, Wiesler D, Novotny M, Moore SA, Peterson RG, Felten DL.

High resolution glass capillary gas chromatography and GC/MS were utilized to examine qualitative and quantitative variations from normal of urinary volatile metabolites of long-term alloxan and streptozotocin diabetic rats. Volatile metabolites were structurally compared with known neurotoxins to examine any possible relationship between these metabolites and the development of the diabetic polyneuropathy.

PMID: 7056362

### **37. Neurochem Res. 1982 Jan;7(1):99-114.**

Synthesis of myelin, particulate, and soluble protein subfractions of rat sciatic nerve during the early stage of Wallerian degeneration: a comparison of metabolic studies using double and single isotope methods and recovery.

Bell ME, Peterson RG, Wiggins RC.

The recovery, electrophoretic composition and synthesis of the myelin, particulate protein and soluble protein subfractions of rat sciatic nerve were compared in normal, sham-operated, and degenerating rat sciatic nerve at one, three and five days after neurotomy. Both single and double isotope methods were used to measure changes in synthesis in vitro and double isotope methods were used in vivo. The

wet weights of nerves undergoing Wallerian degeneration for 5 days increased by 40 percent compared to normal and sham-operated nerves. The recovery, specific radioactivity, and synthesis of the myelin was reduced. The effect on myelin protein synthesis was similar in vitro and in vivo. The myelin loss was relatively constant in amount (30-40 microgram) regardless of differences in nerve sizes of young and old rats, consequently the percentage of myelin loss was inversely proportional to nerve size. The recovery of particulate protein increased, its rate of synthesis remained unchanged, and accordingly the specific radioactivity was decreased. The recovery, specific radioactivity, and the rate of synthesis of the soluble protein fraction were all elevated. The protein composition of the three fractions, as analyzed qualitatively by polyacrylamide disc gel electrophoresis, remained essentially unchanged through five days of degeneration. With regard to comparisons of the single and double isotope methods, results shows that the latter are more ideally suited to measuring changes in synthesis during the non-steady state conditions that are characteristics of rapid degeneration.

PMID: 7040996

### **38. J Neurol Sci. 1981 Nov-Dec;52(2-3):289-303.**

Glycogen accumulation in tibial nerves of experimentally diabetic and aging control rats.

Moore SA, Peterson RG, Felten DL, O'Connor BL.

Tibial nerves of streptozotocin-diabetic, alloxan-diabetic, and age-matched control rats were examined at 2 weeks and 2, 4, 8, and 12 months following the induction of diabetes. Glycogen-like granules accumulated within perineurial and Schwann cells of only the diabetic animals. This accumulation may reflect a metabolic abnormality in these cells which could account for the reduced conduction velocities seen in the peripheral nerves of these same diabetic rats (Moore et al. 1980a). Glycogen-like granules were also present and increased with age in myelinated axons of both diabetic and control rats. Quantitative data suggest that axonal accumulation of glycogen-like granules is related to aging or injury related phenomena to which diabetic axons may be more susceptible.

PMID: 7310436

**39. Horm Metab Res. 1981 Jun;13(6):331-5.**

The effect of diabetes on leucine and fucose incorporation into PNS myelin proteins.

Baughman S, Felten SY, Lee W, Moore SA, O'Connor BL, Peterson RG.

Peripheral neuropathy is a common complication associated with diabetes mellitus. Segmental demyelination and other pathological changes frequently accompany loss of sensory and motor nerve function. Morphological changes seen in diabetic nerve myelin may be a result of altered Schwann cell metabolism under hyperglycemic conditions. Using both alloxan and streptozotocin - induced diabetic rats of 2, 4 and 8 months duration of diabetes, metabolic changes in isolated sciatic nerve myelin were assessed using a double-label in vitro incubation system. Incorporation of <sup>3</sup>H-fucose and <sup>14</sup>C-leucine into myelin was determined per microgram protein. Specific activities of incorporated protein precursors were compared as a ratio of fucose to leucine. Using the Newman-Kuels test for multiple comparisons, statistically significant increases were found in the incorporation ratios of diabetic rats at 2 and 4 months of diabetes when tested against age-matched controls.

PMID: 7262834

**40. J Neurobiol. 1981 Mar;12(2):193-7.**

Alteration of fucose/leucine incorporation into PNS myelin by isoniazid neuropathy.

Colip MP, Baughman S, Peterson RG.

PMID: 6260895

**41. Neurochem Res. 1981 Feb;6(2):213-23.**

Incorporation of fucose and leucine into PNS myelin proteins in nerves undergoing early Wallerian degeneration.

Peterson RG, Baughman S, Scheidler DM.

The simultaneous incorporation of [<sup>3</sup>H]fucose and [<sup>14</sup>C]leucine into normal rat sciatic nerve was examined using an in vitro incubation model. A linear rate of protein precursor uptake was found in purified myelin protein over 1/2-6 hr of incubation utilizing a supplemented medium containing amino acids. This model was then used to examine myelin protein synthesis in nerves undergoing degeneration at 1-4 days following a crush

injury. Data showed a statistically significant decrease in the ratio of fucose to leucine at 2, 3, and 4 days of degeneration, which was the consequence of a significant increase in leucine uptake. These results, plus substantial protein recovery in axotomized nerves, are indicative of active synthesis of proteins that purify with myelin during early Wallerian degeneration.

PMID: 7242779

**42. Brain Res Bull. 1981 Jan;6(1):83-94.**

Sympathetic innervation of murine thymus and spleen: evidence for a functional link between the nervous and immune systems.

Williams JM, Peterson RG, Shea PA, Schmedtje JF, Bauer DC, Felten DL.

Sympathetic innervation was demonstrated in both perivascular and parenchymal regions of murine thymus and spleen. Catecholamine varicosities were associated with mast cells in these areas. The antibody response to sheep red blood cells of 7 week old mice that had been sympathectomized with six-hydroxydopamine (6OHDA) at birth was significantly elevated compared with saline treated controls. Alpha-methyl tyrosine (alpha-MT) and 6OHDA treatment of mice, producing a more complete sympathectomy, showed a significantly enhanced anti-SRBC response with respect to mice treated with alpha-MT or 6OHDA alone. Catecholamine levels in thymus, spleen, and adrenals of both experimental and control mice were measured using liquid chromatography with electrochemical detection (LCEC). The present study suggests that the sympathetic nervous system has a functional role in modulating the humoral immune response in vivo.

PMID: 7193506

**43. Exp Neurol. 1980 Dec;70(3):548-55.**

Reduced sensory and motor conduction velocity in 25-week-old diabetic [C57BL/Ks (db/db)] mice.

Moore SA, Peterson RG, Felten DL, Cartwright TR, O'Connor BL.

PMID: 7439292

**44. J Neurol Sci. 1980 Oct;48(1):133-52.**

A quantitative comparison of motor and sensory conduction velocities in short- and long-term streptozotocin- and alloxan-diabetic rats.

Moore SA, Peterson RG, Felten DL, O'Connor BL.

Motor and sensory conduction velocities were measured in the sural and tibial nerves of streptozotocin (stz)-diabetic, alloxan-diabetic, and age-matched control rats. Conduction velocity (CV) determinations were made 2 weeks and 2, 4, 8, and 12 months following the induction of diabetes. CVs of control, stz-diabetic, and alloxan-diabetic rats were compared at each time period by one way analysis of variance and when appropriate by the Newman-Keuls multiple range test for multiple comparisons. Reductions of 10-20% in CV of diabetic rats were observed in several classes of sensory and motor nerve fibers. Larger reductions (31 and 38%) were seen in 2 classes of sensory nerve fibers in 12 month stz-diabetic rats. Sensory CV was slowed earlier and more frequently than motor CV. Differential involvement was also seen among the several classes of sensory nerve fibers examined. Slower conducting sensory fibers appeared to be affected earlier and more frequently than faster conducting sensory fibers. Comparing alloxan-diabetic with stz-diabetic rats revealed significant differences in CV 8 months after the induction of diabetes. Motor and sensory CVs of the tibial nerve were slower in stz-diabetic rats than in alloxan-diabetic rats. In general, the neuropathy appeared to be less severe and to develop later in the alloxan-diabetic rats. These data suggest that the neuropathy of stz- and alloxan-diabetes is primarily sensory in nature, and that the neuropathy in these 2 widely used models of diabetes may not be entirely equivalent.

PMID: 6448276

#### **45. Brain Res. 1978 Aug 18;152(1):17-29.**

Morphological localization of PNS myelin proteins.

Peterson RG, Gruener RW.

The localization of PNS myelin protein was studied using two methods: (1) lactoperoxidase catalysed iodination of intraperiod band material, (2) solubilization of basic proteins with ammonium acetate--Triton X-100 solutions. When myelin was swollen in the presence of lactoperoxidase and subsequently submitted to lactoperoxidase catalysed iodination P0 and what appeared to be the X protein labeled with <sup>125</sup>I. In specimens which were disrupted in 50% ethyl alcohol, the basic proteins P1 and P2 were also iodinated. When the lactoperoxidase was omitted, there was no labeling of proteins. Ammonium acetate--Triton X-100 solutions solubilized basic proteins from both whole nerve and purified myelin preparations. Electron microscopic changes

which accompanied this modification included swelling and splitting of the main period band. These data indicate that the P0 and X proteins are available for iodination in the intraperiod band of swollen PNS myelin and that basic proteins are localized in the main period band.

PMID: 679022

**46. Life Sci. 1976 Apr 15;18(8):845-9.**

Myelin protein changes with digestion of whole sciatic nerve in trypsin.

Peterson RG.

PMID: 1271955

**47. Exp Neurol. 1975 Aug;48(2):252-60.**

Ultrastructure and biochemistry of myelin after isoniazid-induced nerve degeneration in rats.

Sea CP, Peterson RG.

PMID: 1149855