

Ray Peat's Newsletter

"On waxen tablets you cannot write anything new until you rub out the old. With the mind it is not so; there you cannot rub out the old until you have written the new." Frances Bacon

Copyright 2014

Raymond Peat P.O. Box 5764 Eugene OR 97405

Not for republication without written permission.

March 2014

Protecting and restoring nerves

In the 1950s, the food and drug industries were promoting polyunsaturated "essential" fatty acids as protectors against heart disease, because they lowered cholesterol. Estrogen was being promoted as the cure for infertility, menopause, and numerous other problems, and the fact that it lowered cholesterol was seen as another marketing opportunity. The development of new diuretics to treat high blood pressure led to the demonizing of salt, and new drugs to treat diabetes led to indoctrinating the public with the idea that sugar was harmful.

For the television audience, these things became part of "mainstream medical science," and they are still influential ideas, visible in medical journals, affecting the ways physiological events are interpreted. To understand any problem, such as malfunction of nerves, all of these stereotypes have to be reconsidered--the ways sugars, fats, cholesterol and hormones interact are involved in the normal and abnormal functions of any kind of cell.

For example, there is still a general neglect of the difference between cholesterol itself, and cholesterol that has been altered by the attachment of a fatty acid. These are two distinct molecules, with extremely different functions in cells. (I'll refer to these as free cholesterol and the ester form of cholesterol.) In a newborn child, the large amount of cholesterol in the brain is almost entirely the simple free molecule, which has been synthesized from sugar during gestation, while in the senile Alzheimer's disease brain, cholesterol is mostly in the ester form, attached to a fatty acid. This kind of change in balance occurs in other

failing tissues, and is affected by the diet and by environmental stresses.

The incidence of "diabetes" has been increasing rapidly in most parts of the world. The original understanding of diabetes was that it was a wasting disease, involving excessive urination and the loss of a lot of glucose in the urine, with most of the glucose derived from the breakdown of the body's protein. It involved a deficiency of insulin, and came to be treated by regular injections of insulin. Later, it was discovered that many obese people had very high blood glucose, and also had a normal amount of insulin. The first, somewhat rare condition, was named "type I, insulin dependent" diabetes, the second, more common condition, was named "type II, insulin resistant" diabetes. Both of these conditions have been increasing rapidly around the world.

Despite the ability to regulate blood sugar with insulin, about half of the people who have been diagnosed as "diabetic" will develop problems with the degeneration of nerves, including autonomic nerves that regulate the circulatory and digestive systems and other functions, the motor nerves that control movement, the sensory nerves, especially for the hands and feet, and the optic nerves and retinas.

The carpal tunnel syndrome, in which the fingers become numb or develop a tingling or burning sensation (resulting from compression caused by swollen connective tissue in the wrist), is fairly common in the general population, including people who experience hypoglycemia, but it's sometimes an early symptom of diabetes. People diagnosed as diabetic are about 40% more likely to experience it. This syndrome is about three times more common in women than in men. Usually, the carpal tunnel syndrome disappears quickly when hypothyroidism is corrected.

Nerve malfunctions clearly caused by hypothyroidism overlap with the degenerative neuropathies of diabetes. If a person with diabetes is unable to oxidize glucose (and instead, wastes it), the liver's stores of glycogen are depleted, and the ability to activate thyroxin by deiodination, forming T3, will be decreased. Deficiency of the active T3 hormone decreases the ability to oxidize glucose and to store glycogen, in a vicious circle. The medical habit of thinking in terms of discrete diseases has caused many physiological principles to be overlooked.

Because an obvious swelling and constriction of the connective tissue in the carpal tunnel is the immediate cause of the nerve malfunction, carpal tunnel syndrome isn't usually considered as one of the diabetic neuropathies. The medical profession is committed to the idea that the essence of diabetes is the presence of high blood sugar, and that the cause of the nervous degeneration must be found in the hyperglycemia.

Another condition that isn't usually included in the "diabetic neuropathies" is optic neuritis. Although optic neuritis, which can cause sudden loss of vision, and affects mostly young people, especially women, is considered to be an autoimmune inflammatory problem, it's often associated with the development of diagnosed diabetes. (Warren and Warren, 1983.)

The distinction between diabetic neuropathy and other nerve problems is hindering the understanding of diabetes itself, as well as helping to mystify the nature of nerve function and malfunction.

There is a narrow and well defined medical orthodoxy on the subject of diabetic neuropathy. The nerve malfunctions are explained primarily in terms of (1) microvascular disease, (2) glycation of proteins by sugars and their oxidation products, (3) the activation of protein kinase C (PKC), (4) activation of the polyol or sorbitol pathway leading to cell swelling and depletion of NADPH and NAD⁺, with reduction of nitric oxide and glutathione and loss of protection against oxidative damage, and, more recently (5) endoplasmic reticulum stress and (6) the unfolded protein response.

The problem with these hypotheses is that each of the processes can be more easily explained in terms of biological stress with an excess of free fatty acids, than in terms of excess glucose. Increased glucose is associated with the changes occurring in stress, because the hormones that respond to stress, adrenaline and cortisol, increase glucose. To distinguish causes and effects it's necessary to look beyond mere associations.

For example, the diabetogenic action of excessive growth hormone, which increases free fatty acids, involves the production of abnormalities in blood vessels (Rymaszewski, et al., 1991), inflammation (Liu, et al., 2002), and it is an activator of PKC (Nivet, et al, 1993). Growth hormone increases free fatty acids and VEGF, and fatty acids and VEGF activate aldose reductase in the polyol pathway. (Growth hormone is secreted in response to hypoglycemia, providing fatty acids as an alternative source of energy.)

Most of these processes, especially 5 and 6, are reactions that protect against stress. They are increased by the stress of glucose deprivation (Zhang and Kauffman, 2006; Shinohara, et al., 2006), and are adaptive neuroprotective reactions (Yan, et al., 2014; Matus, et al., 2008) rather than being agents of neurodegeneration.

In the medical mechanisms of diabetic neuropathy, excess glucose is the cause, but the reason for its excess is essentially unexplained: It is either because of a lack of insulin, or because of an inability to respond to insulin. The lack of insulin is typically explained by "glucotoxicity" which kills the pancreatic beta cells, and the insensitivity to insulin is typically explained by an excess of sugar in the diet. This complex of hypothetical "explanations" is kind of a landmark in science, representing as much useless work as the Ptolemaic epicycles did 1000 years ago.

Simply getting outside the world of compartmentalized diseases, there is an abundance of evidence showing the variety of ways in which cells can fail. Energy is needed for cell maintenance and adaptation, and the type of fuel used to provide the energy is crucial. Fatty acids interfere with the oxidation of glucose, and this effect can be seen in heart failure, immunodeficiency, and

dementia, as well as in simple stress, diabetes, and many other situations (dementia: Montine and Morrow, 2005. Yaqoob, et al 1994.)

This competition between fatty acids and glucose, which has been called the "Randle cycle" for about 50 years, can be applied to the treatment of diabetes and other degenerative/stress problems by adjusting the diet, or by using supplements such as niacinamide and aspirin, which improve glucose oxidation by lowering the free fatty acids in the serum.

Stress, even emotional stress, decreases the barrier function of the intestine, allowing bacterial endotoxin to be absorbed. Endotoxin activates a variety of enzymes, including those that liberate free fatty acids from the tissues. This is associated with systemic inflammation, and conditions including liver cirrhosis, Parkinson's disease, and nerve inflammation (Garate, et al, 2013). This immediate direct effect of endotoxin, the lipolytic increase of free fatty acids in the circulation, blocks insulin-stimulated glucose uptake (Buhl, et al., 2013; Wellhoener 2011). Despite this now well established role of stress and endotoxin in the production of hyperglycemia, the medical diagnosis of "diabetes" is universally made without measuring either cortisol or endotoxin.

Increased serum lactate, which is a feature of diabetes, occurs quickly after the exposure to endotoxin, even in the presence of adequate oxygen ("aerobic glycolysis"), showing that the oxidative apparatus of the cell has been impaired (Bundgaard, et al., 2003). Several factors are involved in this effect on the mitochondria. Besides the direct effects of endotoxin and fatty acids, endotoxin's activation of the synthesis of prostaglandins and nitric oxide contribute to the metabolic shift toward inflammation and away from efficient oxidation of glucose.

The importance of free fatty acids in the development of diabetes has been simply demonstrated in the experiment of Wright and Lacy (1988) in which either endotoxin or fasting (both of which increase free fatty acids) increased the speed of onset and the intensity of the diabetes stimulated by low doses of streptozocin, destroying beta cells. The so-called "essential fatty acids" seem to

be essential for that toxin to produce diabetes (Wright, et al., 1988; Wright, et al., 1995).

The glycation of proteins, which is increased in diabetes, is produced by various reactive substances, including methylglyoxal.

It has been traditional to think of glucose-derived lactic acid as the source of methylglyoxal, because some of it can be produced by the enzymic modification of glucose. However, in stress, when fat is being released into the blood stream, glycerol is also liberated from the stored fat. Serum glycerol is increased in diabetics, as in other lipolytic states, and it stimulates the synthesis of glucose. D-lactate, which is formed from methylglyoxal, is also increased in the serum of diabetics. In the lipolytic states, glycerol, rather than glucose, is a major source of this highly reactive material (Kondoh, et al., 1994).

The enzyme aldose reductase, which controls the polyol pathway, reacts more readily with methylglyoxal, detoxifying it, than it does with glucose. Its activity is greatly increased by the presence of methylglyoxal. It also detoxifies other reactive fragments produced by fatty acid breakdown during stress, protecting against protein carbonylation. In the lens, this enzyme protects against cataracts (Pladzyk, et al., 2006), suggesting that the medical inhibition of it would have harmful effects. By its effect on the peroxisome system (PPAR; Qiu, et al., 2008) it affects the balance (Beyer, et al., 2008) between the useful free form of cholesterol, precursor to protective steroids, and the ester form, which is associated with degenerative diseases including atherosclerosis and dementia.

When free fatty acids are increased by stress, they amplify other inflammatory signals, by being converted to prostaglandins. One of the actions of prolonged prostaglandin formation is the activation of aromatase, the enzyme that forms estrogen, at the expense of testosterone. In normal aging, most tissues, including fat, begin to produce some estrogen, but in diabetes its levels are increased. In experimental animals, 3 months of diabetes produced by streptozotocin increases aromatase in sciatic nerves and in the hippocampus (Burul-Bozkurt, et al., 2010). In the kidney, the diabetic increase in aromatase is associated with decreased

function; aromatase increases in the eye and other tissues (Prabhu, et al., 2010). Blocking aromatase and supplementing DHT, the form of testosterone that can't be converted to estrogen, reduces kidney injury in diabetic rats (Manigrasso, et al., 2012).

The increase of estrogen synthesis in many tissues such as fat cells and blood vessels, in itself promotes the changes associated with type 2 diabetes, including abdominal obesity, vascular malfunction, and loss of muscle (Williams, 2010, 2012; Baghaei, et al., 2003). In brain injury, astrocytes, the supportive glial cells that normally don't produce estrogen, begin producing estrogen and multiplying.

Depriving the brain of glucose (Estrada, et al., 2009) or oxygen stimulates the proliferation of astrocytes. In age-related dementia, there is an increase in astrocytes, and astrocytosis is a characteristic of the diabetic brain. The prion diseases, the "spongiform encephalopathies," involve an extreme overgrowth of the astrocytes.

In peripheral nerves, large nerve cells are associated with Schwann cells that synthesize pregnenolone, progesterone, and other steroids, and with satellite glia, that react to injury with some of the features of astrocytes, producing increased sensitivity of the nerves; in chronic injury, these satellite glia can activate the production of estrogen in the nerves (Schaeffer, et al., 2010), while their deterioration results in a reduced production of progesterone and its metabolites. Similar processes exist in the brain as well as in peripheral nerves.

A source of brain injury that is often neglected is bacterial endotoxin, and the nitric oxide and prostaglandin that it produces (Sheng., et al., 2011), especially when insulin is deficient (Li, et al., 2013). Continued exposure to endotoxin produces astrogliosis in animals (Wang, et al., 2010). The oligodendrocytes, which produce progesterone in the brain, are killed by the glial cells activated by endotoxin, and their replacement from stem cells is blocked (Pang, et al., 2009). Similar processes can occur in the peripheral nerves.

In good health, the formation of estrogen in nerve cells in response to moderate stress would stimulate the glial cells to produce more

progesterone, to counteract the stress; progesterone, besides counteracting the stress, normally turns off estrogen production by inactivating the aromatase enzyme (Yilmaz, et al., 2011; Schmidt, et al., 1998).

Aldosterone is involved in many inflammatory and degenerative, fibrotic processes, including heart failure and kidney failure, by promoting production of nitric oxide and prostaglandins, and it can cause nerve damage by its actions on astrocytes (Min, et al., 2011). Estrogen stimulates the production of aldosterone (Kau, et al., 1999; Bekker and Svechnikova, 1981). Progesterone antagonizes both aldosterone and estrogen.

Cells synthesize steroids from the free form of cholesterol, and it is this form of cholesterol which is depleted in the Alzheimer's disease brain, and in atherosclerotic plaques, while the cholesterol esters are increased (Boettcher, et al., 1964; Ando, et al., 1984; Wallin, et al., 1989; Roher, et al., 2002). The ester form is required for the proliferation of at least some cancers. Cholesterol in the free form protects brain cells against cytotoxins (Sponne, et al., 2004). Things that inhibit cholesterol synthesis in the brain cause neurodegeneration (Ledesma and Dotti, 2005; Abad-Rodriguez, et al., 2004). The formation of myelin is associated with formation of the free form of cholesterol (Ghosh and Grogan, 1990.)

Besides the failure to synthesize enough cholesterol, the loss of free cholesterol by its combination with fatty acids is recognized in the neurodegenerative diseases and in autism (Anchisi, et al., 2012). The oral supplementation of purified cholesterol has been used to treat autism (Bukelis, 2007).

There is evidence that estrogen inhibits the liberation of cholesterol from the ester form, and that progesterone increases the activity of the enzyme that removes the fatty acid (Gandarias, et al., 1984; Peiretti, et al., 2007; Mulas, et al., 2011). Hypothyroidism, which increases the ratio of estrogen to progesterone, reduces the synthesis of cholesterol. Thyroid hormone activity corresponds to a shift of cholesterol toward the free form (Field, et al., 1986; Severson, et al., 1984; Severson and Fletcher, 1981), which would be expected, since thyroid hormone increases the

production of pregnenolone and progesterone from cholesterol. Since the 1980s, the multiple dangers of low cholesterol have been documented, but the cholesterol-lowering industry has diligently obscured the evidence.

By the 1970s, there was clear evidence of progesterone's brain-protective effects, and of the neurotoxic effects of unopposed estrogen, mostly from animal studies. A few people were using progesterone supplements to treat neurological diseases. It was known that the brain's concentration of progesterone and DHEA was much higher than their concentration in the blood, but it was only in the 1980s that it was shown that they are synthesized in the brain, and a few years later, they were shown to be synthesized in the peripheral nerves. The concentration of these neurosteroids decreases with age, but diabetes causes an exaggerated and premature decrease of them in the brain and peripheral nerves (Caruso, et al., 2008; Pesaresi, et al., 2010).

Stimulating their increase with a synthetic drug (Cermenati, et al., 2010), or directly supplementing progesterone is protective against the neuropathic effects of diabetes (Leonelli, et al., 2007; Roglio, et al., 2008; Sameni, et al., 2008).

The effects of progesterone on nerve cells are comprehensive. In the developing brain, it controls the availability of intracellular cholesterol for synthesizing neurosteroids, and regulates the provision of sugar which is required by mitochondria for the energy needed to synthesize the steroids, and in mature cells it regulates the two-way flow of substance in the axons, which transports cholesterol, mitochondria, proteins, and other substances from the distant cell bodies. It stabilizes the metabolic apparatus of the mitochondria, and inhibits the production of nitric oxide by mitochondria, which in the absence of progesterone would block the use of oxygen. In myelin-forming cells, it has multiple functions, maintaining or restoring their ability to produce myelin, and their ability to provide steroids to the axons they surround. It reduces the inflammatory substances that would make the nerves overexcitable, and it accelerates the transmission of nerve impulses, which is slowed in diabetes. It inhibits the release of fatty acids, reducing

inflammation and protecting against their multiple harmful effects.

The drug industry recognizes its tremendous importance, and they are looking for synthetic chemicals that will increase its production in the brain and peripheral nerves without the serious side effects the present stimulants have, such as the SSRI antidepressants, and the industry is also interested in metabolites of progesterone, such as allopregnanolone, which is therapeutic for dementia, but which (being near the end of a metabolic sequence) might not have the radically restorative functions of progesterone, making it a better product for their business.

Cholesterol and the neurosteroids have a protective role in conditions that have been considered to be very different: Amyotrophic lateral sclerosis, epilepsy, Alzheimer's disease, schizophrenia, autism, diabetic neuropathy, depression, mania, hyperactivity, multiple sclerosis, for example.

Many simple therapies and foods synergize with progesterone--aspirin, caffeine, niacinamide, sugar, thyroid, pregnenolone, vitamins D, E, and K, stress reduction. Regular exposure to bright light, and avoiding hypothermia, are important.

REFERENCES

- J Cell Biol. 2004 Dec 6;167(5):953-60. **Neuronal membrane cholesterol loss enhances amyloid peptide generation.** Abad-Rodriguez J, Ledesma MD, Craessaerts K, Perga S, Medina M, Delacourte A, Dingwall C, De Strooper B, Dotti CG.
- Front Physiol. 2012; 3: 486. **Cholesterol homeostasis: a key to prevent or slow down neurodegeneration** Anchisi L, Dessì S, Pani A, Mandas A.
- Jpn J Exp Med. 1984 Dec;54(6):229-34. **Alterations in brain gangliosides and other lipids of patients with Creutzfeldt-Jakob disease and subacute sclerosing panencephalitis (SSPE).** Ando S, Toyoda Y, Nagai Y, Ikuta F.
- Obes Res. 2003 Apr;11(4):578-85. **The CYP19 gene and associations with androgens and abdominal obesity in premenopausal women.** Baghaei FI, Rosmond R, Westberg L, Hellstrand M, Eriksson E, Holm G, Björntorp P.
- Probl Endokrinol (Mosk). 1981 Sep-Oct;27(5):42-5. [Sex and age differences in the peripheral blood aldosterone levels]. [Article in Russian] Bekker VI, Svechnikova NV.
- Lipids. 2008 Jul;43(7):611-8. **Peroxisome proliferator-activated receptor alpha agonists regulate cholesterol ester transfer protein.** Beyer TP(1), Chen Y, Porter RK, Lu D, Schmidt RJ, Mantlo NB, Konrad RJ, Cao G.
- Proc R Soc Med. Sep 1964; 57(9): 792-795. **Chemical Constituents of Human Atherosclerotic Lesions.** Boettcher, CJF.
- J Clin Endocrinol Metab. 2013 May;98(5):2090-9. **Direct effects of locally administered lipopolysaccharide on glucose, lipid, and protein metabolism in the placebo-controlled, bilaterally infused human leg.** Buhl MI, Bosnjak E, Vendelbo MH, Gjedsted J, Nielsen RR, K-Hafstrom T, Vestergaard ET, Jessen N, Tonnesen E, Moller AB, Pedersen SB, Pilegaard H, Bieno, RS, Jorgensen JO, Moller N.

Am J Psychiatry November 2007; 164:11, 1655. Clinical Case Conference: Smith-Lemli-Optiz Syndrome and Autism Spectrum Disorder. Bukelis I, Porter FD, Zimmerman AW, Tierney E.

Am J Physiol Heart Circ Physiol. 2003 Mar;284(3):H1028-34. **Endotoxemia stimulates skeletal muscle Na⁺-K⁺-ATPase and raises blood lactate under aerobic conditions in humans.** Bundgaard H, Kjeldsen K, Suarez Krabbe K, van Hall G, Simonsen L, Qvist J, Hansen CM, Moller K, Fonsmark L, Lav Madsen P, Klaklund Pedersen B.

Cell Mol Neurobiol. 2010 Apr;30(3):445-51. **Diabetes alters aromatase enzyme levels in sciatic nerve and hippocampus tissues of rats.** Burul-Bozkurt N(1), Pekiner C, Kelicen P.

Neurochem Int. 2008 Mar-Apr;52(4-5):560-8. **Evaluation of neuroactive steroid levels by liquid chromatography-tandem mass spectrometry in central and peripheral nervous system: effect of diabetes.** Caruso D, Scurati S, Maschi O, De Angelis L, Roglio I, Giatti S, Garcia-Segura LM, Melcangi RC.

J Neurosci. 2010 Sep 8;30(36):11896-901. **Activation of the liver X receptor increases neuroactive steroid levels and protects from diabetes-induced peripheral neuropathy.** Cermenati G, Giatti S, Cavalletti G, Bianchi R, Maschi O, Pesaresi M, Abbaioli F, Volonterio A, Saez E, Caruso D, Melcangi RC, Mitro N.

Neurosci Lett. 2009 Aug 14;459(3):109-14. **Astrogliosis is temporally correlated with enhanced neurogenesis in adult rat hippocampus following a glucoprivive insult.** Estrada FS(1), Hernandez VS, Medina MP, Corona-Morales AA, Gonzalez-Perez O, Vega-Gonzalez A, Zhang L.

Metabolism. 1986 Dec;35(12):1085-9. **The effect of hypothyroidism and thyroxine replacement on hepatic and intestinal HMG-CoA reductase and ACAT activities and biliary lipids in the rat.** Field FI, Albright E, Mathur SN.

Lipids. 1984 Dec;19(12):916-22. **Cholesterol ester hydrolysis in rat liver cytosol. Modulation by female sex hormones.** Gandarias JM, Lacort M, Ochoa B.

Biol Psychiatry. 2013 Jan 1;73(1):32-43. **Stress-induced neuroinflammation: role of the Toll-like receptor-4 pathway.** Garate II, Garcia-Bueno B, Madrigal JL, Caso JR, Alou L, Gomez-Lus ML, Micá A, Leza JC.

Brain Res Dev Brain Res. 1990 Jun 1;54(1):147-9. **Activation of myelin-associated cholestryler ester hydrolase in developing rat brain.** Ghosh S, Grogan WM.

J Cell Biochem. 1999 Apr 1;73(1):137-44. **Effects of estradiol on aldosterone secretion in ovariectomized rats.** Kau MM(1), Lo MJ, Tsai SC, Chen JJ, Lu CC, Lin H, Wang SW, Wang PS.

J Biochem. 1994 Mar;115(3):590-5. **Carbon sources for D-lactate formation in rat liver.** Kondoh Y(1), Kawase M, Hirata M, Ohmori S.

Biochem Soc Symp. 2005;(72):129-38. **The conflicting role of brain cholesterol in Alzheimer's disease: lessons from the brain plasminogen system.** Ledesma MD, Dotti CG.

Neuroscience. 2007 Feb 23;144(4):1293-304. **Progesterone and its derivatives are neuroprotective agents in experimental diabetic neuropathy: a multimodal analysis.** Leonelli E, Bianchi R, Cavalletti G, Caruso D, Crippa D, Garcia-Segura LM, Lauria G, Magnaghi V, Roglio I, Melcangi RC.

Brain Res. 2013 Apr 19;1506:1-11. **Insulin inhibits lipopolysaccharide-induced nitric oxide synthase expression in rat primary astrocytes.** Li H(1), Liu B, Huang J, Chen H, Guo X, Yuan Z.

Ann Clin Lab Sci. 2002 Spring;32(2):164-70. **Growth hormone increases lung NF-kappaB activation and lung microvascular injury induced by lipopolysaccharide in rats.** Liu ZL, Yu Y, Jiang Y, Li J.

Am J Physiol Renal Physiol. 2012 May 1;302(9):F1203-9. **Combined inhibition of aromatase activity and dihydrotestosterone supplementation attenuates renal injury in male streptozotocin (STZ)-induced diabetic rats.** Manigrasso MB, Sawyer RT, Hutchens ZM Jr, Flynn ER, Maric-Bilkan C.

Curr Mol Med. 2008 May;8(3):157-72. **The stress rheostat: an interplay between the unfolded protein response (UPR) and autophagy in neurodegeneration.** Matus S(1), Lisbona F, Torres M, Leão C, Thielen P, Hetz C.

Hypertens Res. 2011 Jun;34(6):773-8. **Angiotensin II and aldosterone-induced neuronal damage in neurons through an astrocyte-dependent mechanism.** Min LJ(1), Mogi M, Iwanami J, Sakata A, Jing F, Tsukuda K, Ohshima K, Horiochi M.

Am J Pathol. 2005 May;166(5):1283-9. **Fatty acid oxidation in the pathogenesis of Alzheimer's disease.** Montine TJ, Morrow JD.

Cell Prolif. 2011 Aug;44(4):360-71. **Cholesterol esters as growth regulators of lymphocytic leukaemia cells.** Mulas MF, Abete C, Pulisci D, Pani A, Massidda B, Dessa S, Mandas A.

Metabolism. 1993 Oct;42(10):1291-5. **Evidence that growth hormone stimulates protein kinase C activity in isolated rat hepatocytes.** Nivet VI, Clot JP, Do XT, Barraut V, Prelot M, Durand D.

Science. 2009 Dec 24. **Lipopolysaccharide-activated microglia induce death of oligodendrocyte progenitor cells and impede their development.** Pang Y, Campbell L, Zheng B, Fan L, Cai Z, Rhodes P.

Invest Ophthalmol Vis Sci. 2007 Aug;48(8):3450-8. **Modulation of cholesterol homeostasis by antiproliferative drugs in human pterygium fibroblasts.** Peiretti E, Dessé S, Mulas C, Abete C, Norfo C, Putzolu M, Fossarelli M.

Horm Behav. 2010 Jan;57(1):46-55. **Sex differences in neuroactive steroid levels in the nervous system of diabetic and non-diabetic rats.** Pesaresi M, Maschi O, Giatti S, Garcia-Segura LM, Caruso D, Melcangi RC.

Exp Eye Res. 2006 Aug;83(2):408-16. **Aldose reductase prevents aldehyde toxicity in cultured human lens epithelial cells.** Pladzyk A(1), Ramana KV, Ansari NH, Srivastava SK.

Steroids. 2010 Nov;75(11):779-87. **Expression of aromatase, androgen and estrogen receptors in peripheral target tissues in diabetes.** Prabhu A(1), Xu Q, Manigrasso MB, Biswas M, Flynn E, Iliescu R, Lephart ED, Maric C.

J Biol Chem. 2008 Jun 20;283(25):17175-83. **Aldose reductase regulates hepatic peroxisome proliferator-activated receptor alpha phosphorylation and activity to impact lipid homeostasis.** Qiu L(1), Wu X, Chau JF, Szeto IY, Tam WY, Guo Z, Chung SK, Oates PJ, Chung SS, Yang JY.

Brain Res Rev. 2008 Mar;57(2):460-9. **Neuroactive steroids and peripheral neuropathy.** Roglio I, Giatti S, Pesaresi M, Bianchi R, Cavalletti G, Lauria G, Garcia-Segura LM, Melcangi RC.

Biochemistry. 2002 Sep 17;41(37):11080-90. **Increased A beta peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's disease.** Roher AE, Weiss N, Kokjohn TA, Kuo YM, Kalback W, Anthony J, Watson D, Luehrs DC, Sue L, Walker D, Emmerling M, Goux W, Beach T.

Proc Natl Acad Sci U S A. 1991 Jan 15; 88(2): 617-621. **Human growth hormone stimulates proliferation of human retinal microvascular endothelial cells in vitro.** Rymaszewski Z, Cohen RM, Chomczynski P.

Cell J. 2011 Spring;13(1):31-8. **The Effect of Co-administration of 4-Methylcatechol and Progesterone on Sciatic Nerve Function and Neurohistological Alterations in Streptozotocin-Induced Diabetic Neuropathy in Rats.** Sameni H, Panahi M.

Pak J Biol Sci. 2008 Aug 15;11(16):1994-2000. **The neuroprotective effects of progesterone on experimental diabetic neuropathy in rats.** Sameni HR, Panahi M, Sarkaki A, Saki GH, Makvandi M.

Glia. 2010 Jan 15;58(2):169-80. **Sciatic nerve injury induces apoptosis of dorsal root ganglion satellite glial cells and selectively modifies neurosteroidogenesis in sensory neurons.** Schaeffer V(1), Meyer L, Patte-Mensah C, Eckert A, Mensah-Nyagan AG.

Prog Neurobiol. 2010 Sep;92(1):33-41. **Progress in dorsal root ganglion neurosteroidogenic activity: basic evidence and pathophysiological correlation.** Schaeffer V(1), Meyer L, Patte-Mensah C, Mensah-Nyagan AG.

J Endocrinol. 1998 Sep;158(3):401-7. **Progesterone inhibits glucocorticoid-dependent aromatase induction in human adipose fibroblasts.** Schmidt M, Renner C, Loffler G.

Biochim Biophys Acta. 1981 Jul;675(2):256-64. **Effect of thyroid hormones on acid cholesterol ester hydrolase activity in rat liver, heart and epididymal fat pads.** Severson DL, Fletcher T.

Can J Physiol Pharmacol. 1984 Feb;62(2):244-7. **Hormonal regulation of acid cholesterol ester hydrolase activity: effects of triiodothyronine and 17 alpha-ethynodiol.** Severson DL, Hayden LJ, Fletcher T.

J Neuroinflammation. 2011 Sep 24;8:121. **Pro-inflammatory cytokines and lipopolysaccharide induce changes in cell morphology, and upregulation of ERK1/2, iNOS and sPLA₂-IIA expression in astrocytes and microglia.** Sheng W, Zong Y, Mohammad A, Ajit D, Cui J, Han D, Hamilton JL, Simonyi A, Sun AY, Gu Z, Hong JS, Weisman GA, Sun GY.

Med Hypotheses. 2006;66(2):365-70. **Cataracts: role of the unfolded protein response.** Shinohara T(1), Ikesugi K, Mulhern ML.

FASEB J. 2004 May;18(7):836-8. **Membrane cholesterol interferes with neuronal apoptosis induced by soluble oligomers but not fibrils of amyloid-beta peptide.** Sponne I, Fifre A, Koziel V, Oster T, Olivier JL, Pillot T.

Acta Neurol Scand. 1989 Oct;80(4):319-23. **Decreased myelin lipids in Alzheimer's disease and vascular dementia.** Wallin A, Gottfries CG, Karlsson I, Svennerholm L.

Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2012 May;28(3):253-4, 262. **[Progesterone exerts neuroprotective effect on hypoxic-ischemic encephalopathy-induced brain damage via inhibition expression of inducible nitric oxide synthase and nitric oxide production].** [Article in Chinese] Wang XY, Li XJ, Li DL, Wang CR, Guo XP.

Can J Ophthalmol. 1983 Aug;18(5):228-32. **Optic neuritis, diabetes mellitus and multiple sclerosis: a three-way association.** Warren SA, Warren KG.

Horm Metab Res. 2011 Oct;43(11):754-9. **Metabolic alterations in adipose tissue during the early phase of experimental endotoxemia in humans.** Wellhoener PI, Vitheer A, Sayk F, Schaaf B, Lehnert H, Dott C.

Mol Cell Endocrinol. 2012 Apr 4;351(2):269-78. **Aromatase up-regulation, insulin and raised intracellular oestrogens in men, induce adiposity, metabolic syndrome and prostate disease, via aberrant ER-β± and GPER signalling.** Williams G.

Eur J Cancer Prev. 2010 Jul;19(4):256-71. **The role of oestrogen in the pathogenesis of obesity, type 2 diabetes, breast cancer and prostate disease.** Williams GP.

Proc Natl Acad Sci U S A. 1988 Aug;85(16):6137-41. **Essential fatty acid deficiency prevents multiple low-dose streptozotocin-induced diabetes in CD-1 mice.** Wright JR Jr, Lefkowitz JB, Schreiner G, Lacy PE.

Acta Diabetol. 1995 Jun;32(2):125-30. **Essential fatty acid deficiency prevents multiple low-dose streptozotocin-induced diabetes in naive and cyclosporin-treated low-responder murine strains.** Wright JR Jr, Fraser RB, Kapoor S, Cook HW.

Diabetes. 1988 Jan;37(1):112-8. **Synergistic effects of adjuvants, endotoxin, and fasting on induction of diabetes with multiple low doses of streptozocin in rats.** Wright JR Jr, Lacy PE.

Neurosci Lett. 2014 Feb 7. pii: S0304-3940(14)00093-7. **Endoplasmic reticulum stress is associated with neuroprotection against apoptosis via autophagy activation in a rat model of subarachnoid hemorrhage.** Yan F, Li J, Chen J, Hu Q, Gu C, Lin W, Chen G.

Immunol Lett. 1994 Jul;41(2-3):241-7. **Inhibition of natural killer cell activity by dietary lipids.** Yaqoob PI, Newsholme EA, Calder PC.

J Mol Endocrinol. 2011 Jul 18;47(1):69-80. **Aromatase promoter I-f is regulated by progesterone receptor in mouse hypothalamic neuronal cell lines.** Yilmaz MB, Wolfe A, Zhao H, Brooks DC, Bulun SE.

Neurology. 2006 Jan 24;66(2 Suppl 1):S102-9. **The unfolded protein response: a stress signaling pathway critical for health and disease.** Zhang K(1), Kaufman RJ.