The dark side of stress (learned helplessness)

From the original article in 2016. Author: Ray Peat.

Acetylcholine is the "neurotransmitter" of cholinergic nerves, including the parasympathetic system. Cholinesterase (or acetylcholinesterase) is an enzyme that destroys acetylcholine, limiting the action of the cholinergic nerves. Attaching a phosphate group to the cholinesterase enzyme inactivates it, prolonging and intensifying the action of cholinergic stimulation.

The autonomic nervous system has traditionally been divided into the sympathetic-adrenergic system, and the parasympathetic-cholinergic system, with approximately opposing functions, intensifying energy expenditure and limiting energy expenditure, respectively. The hormonal system and the behavioral system interact with these systems, and each is capable of disrupting the others. Disruptive factors in the environment have increased in recent decades.

Living is development; the choices we make create our individuality. If genetically identical mice grow up in a large and varied environment, small differences in their experience will affect cell growth in their brains, leading to large differences in their exploratory behavior as they age (Freund, et al., 2013). Geneticists used to say that "genes determine our limits," but this experiment shows that an environment can provide both limitations and opportunities for expanding the inherited potential. If our environment restricts our choices, our becoming human is thwarted, the way rats' potentials weren't discovered when they were kept in the standard little laboratory boxes. An opportunity to be complexly involved in a complex environment lets us become more of what we are, more humanly differentiated.

A series of experiments that started at the University of California in 1960 found that rats that lived in larger spaces with various things to explore were better at learning and solving problems than rats that were raised in the standard little laboratory cages (Krech, et al., 1960). Studying their brains, they found that the enzyme cholinesterase, which destroys the neurotransmitter, acetylcholine, was increased. They later found that the offspring of these rats were better learners than their parents, and their brains contained more cholinesterase. Their brains were also larger, with a considerable thickening of the cortex, which is considered to be the part mainly responsible for complex behavior, learning and intelligence.

These processes aren't limited to childhood. For example, London taxi drivers who learn all the streets in the city develop a larger hippocampus, an area of the brain involved with memory.

The 1960s research into environmental enrichment coincided with political changes in the US, but it went against the dominant scientific ideas of the time. Starting in 1945, the US government had begun a series of projects to develop techniques of behavior modification or mind control, using drugs, isolation, deprivation, and torture. In the 1950s, psychiatry often used lobotomies (about 80,000, before they were generally discontinued in the 1980s) and electroconvulsive "therapy," and university psychologists tortured animals, often as part of developing techniques for controlling behavior.

The CIA officially phased out their MKultra program in 1967, but that was the year that Martin Seligman, at the University of Pennsylvania, popularized the idea of "learned helplessness." He found that when an animal was unable to escape from torture, even for a very short time, it would often fail to even try to escape the next time it was tortured. Seligman's lectures have been attended by psychologists who worked at Guantanamo, and he recently received a no-bid Pentagon grant of $31,000,000, to develop a program of "comprehensive soldier fitness," to train marines to avoid learned helplessness.

Curt Richter already in 1957 had described the "hopelessness" phenomenon in rats ("a reaction of hopelessness is shown by some wild rats very soon after being grasped in the hand and prevented from moving. They seem literally to give up,") and even how to cure their hopelessness, by allowing them to have an experience of escaping once (Richter, 1957, 1958). Rats which would normally be able to keep swimming in a tank for two or three days, would often give up and drown in just a few minutes, after having an experience of "inescapable stress." Richter made the important discovery that the hearts of the hopeless rats slowed down before they died, remaining relaxed and filled with blood, revealing the dominant activity of the vagal nerve, secreting acetylcholine.

The sympathetic nervous system (secreting noradrenaline) accelerates the heart, and is usually activated in stress, in the "fight or flight" reaction, but this radically different (parasympathetic) nervous activity hadn't previously been seen to occur in stressful situations. The parasympathetic, cholinergic, nervous system had been thought of as inactive during stress, and activated to regulate processes of digestion, sleep, and repair. Besides the cholinergic nerves of the parasympathetic system, many nerves of the central nervous system also secrete acetylcholine, which activates smooth muscles, skeletal muscles, glands, and other nerves, and also has some inhibitory effects. The parasympathetic nerves also secrete the enzyme, cholinesterase, which destroys acetylcholine. However, many other types of cell (red blood cells, fibroblasts, sympathetic nerves, marrow cells), maybe all cells, can secrete cholinesterase.

Because cholinergic nerves have been opposed to the sympathetic, adrenergic, nerves, there has been a tendency to neglect their nerve exciting roles, when looking at causes of excitotoxicity, or the stress-induced loss of brain cells. Excessive cholinergic stimulation, however, can contribute to excitotoxic cell death, for example when it's combined with high cortisol and/or hypoglycemia.

Drugs that block the stimulating effects of acetylcholine (the anticholinergics) as well as chemicals that mimic the effects of acetylcholine, such as the organophosphate insecticides, can impair the ability to think and learn. This suggested to some people that age-related dementia was the result of the deterioration of the cholinergic nerves in the brain. Drugs to increase the stimulating effects of acetylcholine in the brain (by inactivating cholinesterase) were promoted as treatment for Alzheimer's disease.

Although herbal inhibitors were well known, profitable new drugs, starting with Tacrine, were put into use. It was soon evident that Tacrine was causing serious liver damage, but wasn't slowing the rate of mental deterioration.

As the failure of the cholinergic drug Tacrine was becoming commonly known, another drug, amantadine (later, the similar memantine) was proposed for combined treatment. In the 1950s, the anticholinergic drug atropine was proposed a few times for treating dementia, and amantadine, which was also considered anticholinergic, was proposed for some mental conditions, including Creutzfeldt-Jacob Disease (Sanders and Dunn, 1973). It must have seemed odd to propose that an anticholinergic drug be used to treat a condition that was being so profitably treated with a pro-cholinergic drug, but memantine came to be classified as an anti-excitatory "NMDA blocker," to protect the remaining cholinergic nerves, so that both drugs could logically be prescribed simultaneously. The added drug seems to have a small beneficial effect, but there has been no suggestion that this could be the result of its previously-known anticholinergic effects.

Over the years, some people have suspected that Alzheimer's disease might be caused partly by a lack of purpose and stimulation in their life, and have found that meaningful, interesting activity could improve their mental functioning. Because the idea of a "genetically determined hard-wired" brain is no longer taught so dogmatically, there is increasing interest in this therapy for all kinds of brain impairment. The analogy to the Berkeley enrichment experience is clear, so the association of increasing cholinesterase activity with improving brain function should be of interest.

The after-effect of poisoning by nerve gas or insecticide has been compared to the dementia of old age. The anticholinergic drugs are generally recognized for protecting against those toxins. Traumatic brain injury, even with improvement in the short term, often starts a long-term degenerative process, greatly increasing the likelihood of dementia at a later age. A cholinergic excitotoxic process is known to be involved in the traumatic degeneration of nerves (Lyeth and Hayes, 1992), and the use of anticholinergic drugs has been recommended for many years to treat traumatic brain injuries (e.g., Ward, 1950: Ruge, 1954; Hayes, et al., 1986).

In 1976 there was an experiment (Rosellini, et al.) that made an important link between the enrichment experiments and the learned helplessness experiments. The control animals in the enrichment experiments were singly housed, while the others shared a larger enclosure. In the later experiment, it was found that the rats "who were reared in isolation died suddenly when placed in a stressful swimming situation," while the group-housed animals were resistant, effective swimmers. Enrichment and deprivation have very clear biological meaning, and one is the negation of the other.

The increase of cholinesterase, the enzyme that destroys acetylcholine, during enrichment, serves to inactivate cholinergic processes. If deprivation does its harm by increasing the activity of the cholinergic system, we should expect that a cholinergic drug might substitute for inescapable stress, as a cause of learned helplessness, and that an anticholinergic drug could cure learned helplessness. Those tests have been done: "Treatment with the anticholinesterase, physostigmine, successfully mimicked the effects of inescapable shock." "The centrally acting anticholinergic scopolamine hydrobromide antagonized the effects of physostigmine, and when administered prior to escape testing antagonized the disruptive effects of previously administered inescapable shock." (Anisman, et al., 1981.)

This kind of experiment would suggest that the anticholinesterase drugs still being used for Alzheimer's disease treatment aren't biologically helpful. In an earlier newsletter I discussed the changes of growth hormone, and its antagonist somatostatin, in association with dementia: Growth hormone increases, somatostatin decreases. The cholinergic nerves are a major factor in shifting those hormones in the direction of dementia, and the anticholinergic drugs tend to increase the ratio of somatostatin to growth hormone. Somatostatin and cholinesterase have been found to co-exist in single nerve cells (Delfs, et al., 1984).

Estrogen, which was promoted so intensively as prevention or treatment for Alzheimer's disease, was finally shown to contribute to its development. One of the characteristic effects of estrogen is to increase the level of growth hormone in the blood. This is just one of many ways that estrogen is associated with cholinergic activation. During pregnancy, it's important for the uterus not to contract. Cholinergic stimulation causes it to contract; too much estrogen activates that system, and causes miscarriage if it's excessive. An important function of progesterone is to keep the uterus relaxed during pregnancy. In the uterus, and in many other systems, progesterone increases the activity of cholinesterase, removing the acetylcholine which, under the influence of estrogen, would cause the uterus to contract.

Progesterone is being used to treat brain injuries, very successfully. It protects against inflammation, and in an early study, compared to placebo, lowered mortality by more than half. It's instructive to consider its anticholinergic role in the uterus, in relation to its brain protective effects. When the brain is poisoned by an organophosphate insecticide, which lowers the activity of cholinesterase, seizures are likely to occur, and treatment with progesterone can prevent those seizures, reversing the inhibition of the enzyme (and increasing the activity of cholinesterase in rats that weren't poisoned) (Joshi, et al., 2010). Similar effects of progesterone on cholinesterase occur in menstrually cycling women (Fairbrother, et al., 1989), implying that this is a general function of progesterone, not just something to protect pregnancy. Estrogen, with similar generality, decreases the activity of cholinesterase. DHEA, like progesterone, increases the activity of cholinesterase, and is brain protective (Aly, et al., 2011).

Brain trauma consistently leads to decreased activity of this enzyme (Östberg, et al., 2011; Donat, et al., 2007), causing the acetylcholine produced in the brain to accumulate, with many interesting consequences. In 1997, a group (Pike, et al.) created brain injuries in rats to test the idea that a cholinesterase inhibitor would improve their recovery and ability to move through a maze. They found instead that it reduced the cognitive ability of both the injured and normal rats. An anticholinergic drug, selegeline (deprenyl) that is used to treat Parkinson's disease and, informally, as a mood altering antiaging drug, was found by a different group (Zhu, et al., 2000) to improve cognitive recovery from brain injuries.

One of acetylcholine's important functions, in the brain as elsewhere, is the relaxation of blood vessels, and this is done by activating the synthesis of NO, nitric oxide. (Without NO, acetylcholine constricts blood vessels; Librizzi, et al., 2000.) The basic control of blood flow in the brain is the result of the relaxation of the wall of blood vessels in the presence of carbon dioxide, which is produced in proportion to the rate at which oxygen and glucose are being metabolically combined by active cells. In the inability of cells to produce CO_2 at a normal rate, nitric oxide synthesis in blood vessels can cause them to dilate. The mechanism of relaxation by NO is very different, however, involving the inhibition of mitochondrial energy production (Barron, et al., 2001). Situations that favor the production and retention of a larger amount of carbon dioxide in the tissues are likely to reduce the basic "tone" of the parasympathetic nervous system, as there is less need for additional vasodilation.

Nitric oxide can diffuse away from the blood vessels, affecting the energy metabolism of nerve cells (Steinert, et al., 2010). Normally, astrocytes protect nerve cells from nitric oxide (Chen, et al., 2001), but that function can be altered, for example by bacterial endotoxin absorbed from the intestine (Solà, et al., 2002) or by amyloid-beta (Tran, 2001), causing them to produce nitric oxide themselves.

Nitric oxide is increasingly seen as an important factor in nerve degeneration (Doherty, 2011). Nitric oxide activates processes (Obukuro, et al., 2013) that can lead to cell death. Inhibiting the production of nitric oxide protects against various kinds of dementia (Sharma & Sharma, 2013; Sharma & Singh, 2013). Brain trauma causes a large increase in nitric oxide formation, and blocking its synthesis improves recovery (Hüttemann, et al., 2008; Gahm, et al., 2006). Organophosphates increase nitric oxide formation, and the protective anticholinergic drugs such as atropine reduce it (Chang, et al., 2001; Kim, et al., 1997). Stress, including fear (Campos, et al., 2013) and isolation (ZlatkoviÄ‡ & FilipoviÄ‡, 2013) can activate the formation of nitric oxide, and various mediators of inflammation also activate it. The nitric oxide in a person's exhaled breath can be used to diagnose some diseases, and it probably also reflects the level of their emotional well-being.

The increase of cholinesterase by enriched living serves to protect tissues against an accumulation of acetylcholine. The activation of nitric oxide synthesis by acetylcholine tends to block energy production, and to activate autolytic or catabolic processes, which are probably involved in the development of a thinner cerebral cortex in isolated or stressed animals. Breaking down acetylcholine rapidly, the tissue renewal processes are able to predominate in the enriched animals.

Environmental conditions that are favorable for respiratory energy production are protective against learned helplessness and neurodegeneration, and other biological problems that involve the same mechanisms. Adaptation to high altitude, which stimulates the formation of new mitochondria and increased thyroid (T3) activity, has been used for many years to treat neurological problems, and the effect has been demonstrated in animal experiments (Manukhina, et al., 2010). Bright light can reverse the cholinergic effects of inescapable stress (Flemmer, et al., 1990).

During the development of learned helplessness, the T3 level in the blood decreases (Helmreich, et al., 2006), and removal of the thyroid gland creates the "escape deficit," while supplementing with thyroid hormone before exposing the animal to inescapable shock prevents its development (Levine, et al., 1990). After learned helplessness has been created in rats, supplementing with T3 reverses it (Massol, et al., 1987, 1988).

Hypothyroidism and excess cholinergic tone have many similarities, including increased formation of nitric oxide, so that similar symptoms, such as muscle inflammation, can be produced by cholinesterase inhibitors such as Tacrine, by increased nitric oxide, or by simple hypothyroidism (Jeyarasasingam, et al., 2000; Franco, et al., 2006).

Insecticide exposure has been suspected to be a factor in the increased incidence of Alzheimer's disease (Zaganas, et al., 2013), but it could be contributing to many other problems, involving inflammation, edema, and degeneration. Another important source of organophosphate poisoning is the air used to pressurize airliners, which can be contaminated with organophosphate fumes coming from the engine used to compress it.

Possibly the most toxic component of our environment is the way the society has been designed, to eliminate meaningful choices for most people. In the experiment of Freund, et al., some mice became more exploratory because of the choices they made, while others' lives became more routinized and limited. Our culture reinforces routinized living. In the absence of opportunities to vary the way you work and live to accord with new knowledge that you gain, the nutritional, hormonal and physical factors have special importance.

Supplements of thyroid and progesterone are proven to be generally protective against the cholinergic threats, but there are many other factors that can be adjusted according to particular needs. Niacinamide, like progesterone, inhibits the production of nitric oxide, and also like progesterone, it improves recovery from brain injury (Hoane, et al., 2008). In genetically altered mice with an Alzheimer's trait, niacinamide corrects the defect (Green, et al., 2008). Drugs such as atropine and antihistamines can be used in crisis situations. Bright light, without excess ultraviolet, should be available every day.

The cholinergic system is much more than a part of the nervous system, and is involved in cell metabolism and tissue renewal. Most people can benefit from reducing intake of phosphate, iron, and polyunsaturated fats (which can inhibit cholinesterase; Willis, et al., 2009), and from choosing foods that reduce production and absorption of endotoxin. And, obviously, drugs that are intended to increase the effects of nitric oxide (asparagine, zildenafil/Viagra, minoxidil/Rogaine) and acetylcholine (bethanechol, benzpyrinium, etc.) should be avoided.

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Toxicol Appl Pharmacol. 2013 Aug 3. pii: S0041-008X(13)00326-8.**Arsenic toxicity induced endothelial dysfunction and dementia: Pharmacological interdiction by histone deacetylase and inducible nitric oxide synthase inhibitors.**Sharma B, Sharma PM.

2. Pharmacol Biochem Behav. 2013 Feb;103(4):821-30.**Pharmacological inhibition of inducible nitric oxide synthase (iNOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, convalesce behavior and biochemistry of hypertension induced vascular dementia in rats.**Sharma B, Singh N. CNS and CVS Research Lab., Pharmacology Division, Department of Pharmaceutical Sciences and Drug Research, Faculty of Medicine, Punjabi University, Patiala 147002, Punjab, India.bhupeshresearch@gmail.com Cognitive disorders are likely to increase over the coming years (5-10). Vascular dementia (VaD) has heterogeneous pathology and is a challenge for clinicians. Current Alzheimer's disease drugs have had limited clinical efficacy in treating VaD and none have been approved by major regulatory authorities specifically for this disease. Role of iNOS and NADPH-oxidase has been reported in various pathological conditions but there role in hypertension (Hypt) induced VaD is still unclear. This research work investigates the salutiferous effect of aminoguanidine (AG), an iNOS inhibitor and 4'-hydroxy-3'-methoxyacetophenone (HMAP), a NADPH oxidase inhibitor in Hypt induced VaD in rats. Deoxycorticosterone acetate-salt (DOCA-S) hypertension has been used for development of VaD in rats. Morris water-maze was used for testing learning and memory. Vascular system assessment was done by testing endothelial function. Mean arterial blood pressure (MABP), oxidative stress [aortic superoxide anion, serum and brain thiobarbituric acid reactive species (TBARS) and brain glutathione (GSH)], nitric oxide levels (serum nitrite/nitrate) and cholinergic activity (brain acetyl cholinesterase activity-AChE) were also measured. DOCA-S treated rats have shown increased MABP with impairment of endothelial function, learning and memory, reduction in serum nitrite/nitrate & brain GSH levels along with increase in serum & brain TBARS, and brain AChE activity. AG as well as HMAP significantly convalesce Hypt induced impairment of learning, memory, endothelial function, and alterations in various biochemical parameters. It may be concluded that AG, an iNOS inhibitor and HMAP, a NADPH-oxidase inhibitor may be considered as potential agents for the management of Hypt induced VaD. Copyright © 2012 Elsevier Inc. All rights reserved.

[Curr Pharm Des. 2010;16(25):2837-50. Nitric oxide: target for therapeutic strategies in Alzheimer's disease. Fernandez AP, Pozo-Rodrigalvarez A, Serrano J, Martinez-Murillo R. "**data implicating nitric oxide (NO) in the progression of the disease. The three isoforms of the NO-synthesizing enzyme (NOS) operate as central mediators of amyloid beta-peptide (Aβ) action, giving rise to elevated levels of NO that contributes to the maintenance, self-perpetuation and progression of the disease.**"]

J Neuropathol Exp Neurol. 2007 Apr;66(4):272-83. Nitric oxide synthase 3-mediated neurodegeneration after intracerebral gene delivery. de la Monte SM, Jhaveri A, Maron BA, Wands JR. "**increased nitric oxide synthase 3 (NOS3) expression correlates with apoptosis in cortical neurons and colocalizes with amyloid precursor protein (APP)-amyloid beta (Abeta) deposits in the brain."**

Neuroscience. 2000;101(2):283-7.**Nitric oxide synthase inhibitors unmask acetylcholine-mediated constriction of cerebral vessels in the in vitro isolated guinea-pig brain.**Librizzi L, Folco G, de Curtis M.

Pharmacology. 2000 Feb;60(2):82-9. Choline is a full agonist in inducing activation of neuronal nitric oxide synthase via the muscarinic M1 receptor. Carriere JL, El-Fakahany EE.

Glia. 2003 Jan 15;41(2):207-11. Alzheimer's disease is associated with a selective increase in alpha7 nicotinic acetylcholine receptor immunoreactivity in astrocytes. Teaktong T, Graham A, Court J, Perry R, Jaros E, Johnson M, Hall R, Perry E.

16. Neuroscientist. 2010 Aug;16(4):435-52. **Nitric oxide signaling in brain function, dysfunction, and dementia.** Steinert JR, Chernova T, Forsythe ID. Neurotoxicity at the Synaptic Interface, MRC Toxicology Unit, University of Leicester, Leicester, UK. Nitric oxide (NO) is an important signaling molecule that is widely used in the nervous system. With recognition of its roles in synaptic plasticity (long-term potentiation, LTP; long-term depression, LTD) and elucidation of calcium-dependent, NMDAR-mediated activation of neuronal nitric oxide synthase (nNOS), numerous molecular and pharmacological tools have been used to explore the physiology and pathological consequences for nitrergic signaling. In this review, the authors summarize the current understanding of this subtle signaling pathway, discuss the evidence for nitrergic modulation of ion channels and homeostatic modulation of intrinsic excitability, and speculate about the pathological consequences of spillover between different nitrergic compartments in contributing to aberrant signaling in neurodegenerative disorders. Accumulating evidence points to various ion channels and particularly voltage-gated potassium channels as signaling targets, whereby NO mediates activity-dependent control of intrinsic neuronal excitability; such changes could underlie broader mechanisms of synaptic plasticity across neuronal networks. In addition,**the inability to constrain NO diffusion suggests that spillover from endothelium (eNOS) and/or immune compartments (iNOS) into the nervous system provides potential pathological sources of NO and where control failure in these other systems could have broader neurological implications.**Abnormal NO signaling could therefore contribute to a variety of neurodegenerative pathologies such as stroke/excitotoxicity, Alzheimer's disease, multiple sclerosis, and Parkinson's disease.

Neurosci Bull. 2011 Dec;27(6):366-82. Nitric oxide in neurodegeneration: potential benefits of non-steroidal anti-inflammatories. Doherty GH.18.

Neuroscience. 2010 Dec 15;171(3):859-68. Low energy laser light (632.8 nm) suppresses amyloid-β peptide-induced oxidative and inflammatory responses in astrocytes. Yang X, Askarova S, Sheng W, Chen JK, Sun AY, Sun GY, Yao G, Lee JC.

Neurosci Behav Physiol. 2010 Sep;40(7):737-43.**Prevention of neurodegenerative damage to the brain in rats in experimental**

Alzheimer's disease by adaptation to hypoxia. Manukhina EB, Goryacheva AV, Barskov IV, Viktorov IV, Guseva AA, Pshennikova MG, Khomenko IP, Mashina SY, Pokidyshev DA, Malyshev IY.

Physiol Behav. 1990 Jul;48(1):165-7. **Thyroparathyroidectomy produces a progressive escape deficit in rats.** Levine JD, Strauss LR, Muenz LR, Dratman MB, Stewart KT, Adler NT. Department of Anatomy, University of Pennsylvania, Philadelphia. Abnormal thyroid status and affective disorders have been associated in the human clinical literature. It has recently been shown **that pretreatment with thyroid hormone can prevent escape deficits produced by inescapable shock in an animal analogue of depression.** In this report we provide evidence that **hypothyroid status can produce an escape deficit in rats.** While sham-operated rats improved their performance on a simple escape task over three days of testing, thyroparathyroidectomized rats showed a pronounced decrease in their responses. Markov transition analysis was used to obtain conditional probabilities of escaping given a prior escape or failure to escape for the two groups. This analysis shows that the structure of the data set may be similar for the two groups. These results suggest that if intact rats learn to escape, then hypothyroid rats may learn not to escape.

1. Pharmacol Biochem Behav. 1990 Aug;36(4):775-8. **Bright light blocks the capacity of inescapable swim stress to supersensitize a central muscarinic mechanism.** Flemmer DD, Dilsaver SC, Peck JA. Department of Psychiatry, Ohio State University. Clinical and basic researchers have proposed that muscarinic cholinergic mechanisms mediate some effects of chronic stress. Chronic inescapable (forced) swim stress depletes brain biogenic amines and is used to produce learned helplessness in rats. Behavioral and biochemical characteristics of animals in the state of learned helplessness lead some investigators to believe this condition provides a useful animal model of depression. **Inescapable swim stress also produces supersensitivity to the hypothermic effect of the muscarinic agonist oxotremorine in the rat.** The authors previously demonstrated that bright light potently induces subsensitivity of a central muscarinic mechanism involved in the regulation of core temperature under a variety of circumstances. They now report using a repeated measures design that inescapable swim stress of five days duration produces supersensitivity to oxotremorine (increase in thermic response of 405%). This **supersensitivity is reversed within five days by treatment with bright light, despite continuation of daily swim stress. Daily inescapable swim stress was continued beyond cessation of treatment with bright light.** Five days later, supersensitivity to the hypothermic effect of oxotremorine was once again evident.

Pharmacol Biochem Behav. 1986 Aug;25(2):415-21. Neurochemical and behavioral consequences of mild, uncontrollable shock: effects of PCPA. Edwards E, Johnson J, Anderson D, Turano P, Henn FA. The present experiments examined the role of the serotonergic system in the behavioral deficit produced by uncontrollable shock. In Experiment 1: Establishment of model, the behavioral potential of the Sprague-Dawley rat was defined. When exposed to mild uncontrollable stress such as a 0.8 mA electric footshock, a significant percentage of rats developed a shock escape deficit which was evident when subsequently placed in a shock escape paradigm. Serotonin depletion was produced by chronic treatment with p-chlorophenylalanine. Biogenic amine levels and 5-HT levels were monitored in various brain areas using HPLC. Following chronic treatment with PCPA, the shock escape capability of the Sprague-Dawley rat was assessed. **The severe depletion of 5-HT in various brain regions was highly correlated with a dramatic improvement in the shock escape scores. Thus, the detrimental effects of exposure to a mild course of inescapable shock can be prevented by chronic treatment with PCPA**. These experiments implicate the serotonergic system as a possible mediator of the "learned helplessness" phenomenon.

Biol Psychiatry. 1985 Sep;20(9):1023-5. Triiodothyronine-induced reversal of learned helplessness in rats. Martin P, Brochet D, Soubrie P, Simon P.

Pharmacol Biochem Behav. 1982 Nov;17(5):877-83. Evidence for a serotonergic mechanism of the learned helplessness phenomenon. Brown L, Rosellini RA, Samuels OB, Riley EP. The present experiments examined the role of the serotonergic system in the learned helplessness phenomenon. In Experiment 1, a 200 mg/kg dose of 1-tryptophan injected 30 min prior to testing disrupted acquisition of Fixed Ratio 2 shuttle escape behavior. In Experiment 2, a 100 mg/kg dose of 5-HTP produced interference with the acquisition of the escape response. Furthermore, this interference was prevented by treatment with the serotonergic antagonist methysergide. In Experiment 3, animals were pretreated with a subeffective dose of 1-tryptophan in combination with subeffective exposure to inescapable shock. These animals showed a deficit in the acquisition of FR-2 shuttle escape. In Experiment 4, combined exposure to a subeffective dose of 5-HTP and inescapable shock (40 trials) resulted in an acquisition deficit. This deficit was reversed by methysergide. Experiment 5 showed that the detrimental effects of exposure to prolonged (80 trials) of inescapable shock can be prevented by treatment with methysergide. These studies implicate the serotonergic system as a possible mediator of the learned helplessness phenomenon.

45. Med Hypotheses. 2004;63(2):308-21. Brain cholinesterases: II. The molecular and cellular basis of Alzheimer's disease. Shen ZX. 2436 Rhode Island Avenue #3, Golden valley, MN 55427-5011, USA. zhengxshen@yahoo.com Currently available evidence demonstrates that cholinesterases (ChEs), owing to their powerful enzymatic and non-catalytic actions, unusually strong electrostatics, and **exceptionally ubiquitous presence and redundancy in their capacity as the connector, the organizer and the safeguard of the brain,** play fundamental role(s) in the well-being of cells, tissues, animal and human lives, while they present themselves adequately in quality and quantity. The widespread intracellular and extracellular membrane networks of ChEs in the brain are also subject to various insults, such as aging, gene anomalies, environmental hazards, head trauma, excessive oxidative stress, imbalances and/or deficits of organic constituents. The loss and the alteration of ChEs on the outer surface membranous network may initiate the formation of extracellular senile plaques and induce an outside-in cascade of Alzheimer's disease (AD). The alteration in ChEs on the intracellular compartments membranous network may give rise to the development of intracellular neurofibrillary tangles and induce an inside-out cascade of AD. The abnormal patterns of glycosylation and configuration changes in ChEs may be reflecting their impaired metabolism at the molecular and cellular level and causing the enzymatic and pharmacodynamical modifications and neurotoxicity detected in brain tissue and/or CSF of patients with AD and in specimens in laboratory experiments. The inflammatory reactions mainly arising from ChEs-containing neuroglial cells may facilitate the pathophysiologic process of AD. It is proposed that brain ChEs may serve as a central point rallying various hypotheses regarding the etio-pathogenesis of AD.

3. Neurology. 2011 Mar 22;76(12):1046-50. doi: 10.1212/WNL.0b013e318211c1c4. Cholinergic dysfunction after traumatic brain injury: preliminary findings from a PET study. Östberg A, Virta J, Rinne JO, Oikonen V, Luoto P, Någren K, Arponen E, Tenovuo O. Department of Neurology, University of Turku and Turku University Central Hospital, Turku, Finland. OBJECTIVE: There is evidence that the cholinergic system is frequently involved in the cognitive consequences of traumatic brain injury (TBI). We studied whether the brain cholinergic function is altered after TBI in vivo using PET. METHODS: Cholinergic function was assessed with [methyl-(11)C]N-methylpiperidyl-4-acetate, which reflects the acetylcholinesterase (AChE) activity, in 17 subjects more than 1 year after a TBI and in 12 healthy controls. All subjects had been without any centrally acting drugs for at least 4 weeks. RESULTS: The AChE activity was significantly lower in subjects with TBI compared to controls in several areas of the neocortex (-5.9% to -10.8%, $p=0.053$ to 0.004). CONCLUSIONS: Patients with chronic cognitive symptoms after TBI show widely lowered AChE activity across the neocortex. © 2011 by AAN Enterprises, Inc.

9. Brain Inj. 2007 Sep;21(10):1031-7. Alterations of acetylcholinesterase activity after traumatic brain injury in rats. Donat CK, Schuhmann MU, Voigt C, Nieber K, Schliebs R, Brust P. Institute of Interdisciplinary Isotope Research, Permoserstasse 15, 04318 Leipzig, Germany. donat@iif-leipzig.de OBJECTIVE: The cholinergic system is highly vulnerable to traumatic brain injury (TBI). However, limited information is available to what extent the degrading enzyme acetylcholinesterase (AChE) is involved. The present study addresses this question. METHOD: Thirty-six anaesthetized Sprague-Dawley rats were subjected to sham operation or to TBI using controlled cortical impact (CCI). The AChE activity was histochemically determined in frozen brain slices at 2, 24 and 72 hours after TBI. RESULTS: High enzyme activity

was observed in regions rich in cholinergic innervation such as the olfactory tubercle, basal forebrain, putamen and superior colliculi.**Low activity was found in the cortex, cerebellum and particularly in the white matter. A decrease of AchE activity (20-35%) was found in the hippocampus and hypothalamus already at 2 hours after TBI.**An increase of approximately 30% was found in the basal forebrain at 2 and 24 hours. No changes occurred at 72 hours. CONCLUSION: The findings are consistent with impairment of the cholinergic neurotransmission after TBI and suggest the involvement of the AChE in short-term regulatory mechanisms.

35. Res Commun Chem Pathol Pharmacol. 1990 Jun;68(3):391-4. Increase of muscarinic receptor following kainic acid lesions of the nucleus basalis magnocellularis in rat brain: an autoradiographic study. Katayama S, Kito S, Yamamura Y. Third Department of Internal Medicine, Hiroshima University School of Medicine, Japan. We observed changes in cholinergic markers in rat brain seven days after lesioning the nucleus basalis magnocellularis (nbm) with kainic acid. In histochemical preparations stained for acetylcholinesterase (AChE),**there was a marked loss of large AChE reactive neurons within and beneath the nbm on the injected side, and the AChE positive fibers were greatly decreased particularly in the IV-VI layers of the frontal and parietal cortices ipsilateral to the** kainate lesion. Using in vitro receptor autoradiography, we found a significant increase (about 25%) in 3H-QNB binding sites in the I-IV layers of the ipsilateral frontal and parietal cortices (p 0.05, Student's t-test).**The area with decreased AChE activity**and increased density in 3H-QNB binding sites corresponded to the innervation of the cholinergic system arising from the nbm. The increase of density in 3H-QNB binding sites was considered to reflect the postsynaptic denervation supersensitivity.

36. Hum Exp Toxicol. 1992 Nov;11(6):517-23. Long-term study of brain lesions following soman, in comparison to DFP and metrazol poisoning. Kadar T, Cohen G, Sahar R, Alkalai D, Shapira S. Department of Pharmacology, Israel Institute for Biological Research, Ness-Ziona, Israel. The long-term histopathological effects of acute lethal (95 micrograms kg-1) and sublethal (56 micrograms kg-1) doses of soman were studied in rats and were compared to lesions caused by equipotent doses of either another cholinesterase (ChE) inhibitor, DFP (1.8 mg kg-1), or a non-organophosphorus convulsant, metrazol (100 mg kg-1). Severe toxic signs were noted following one LD50 dose administration of all the compounds, yet only soman induced brain lesions. Moreover, even when administered at a sublethal dose (0.5 LD50), soman induced some histological changes without any clinical signs of intoxication. Soman-induced brain lesions were assessed quantitatively using a computerized image analyser. The analysis was carried out for up to 3 months following administration, and a dynamic pattern of pathology was shown. The cortical thickness and area of CA1 and CA3 cells declined significantly as early as 1 week post-exposure. No pathological findings were detected following DFP and metrazol administration. It is therefore suggested that brain lesions are not common for all ChE inhibitors and that convulsions per se are not the only factor leading to brain damage following the administration of soman. The degenerative process (found also with the sublethal dose of soman) might be due to a secondary effect, unrelated to soman's clinical toxicity, but leading to long-term brain injuries.

42. J Neurotrauma. 1997 Dec;14(12):897-905.**Effect of tetrahydroaminoacridine, a cholinesterase inhibitor, on cognitive performance following experimental brain injury.**Pike BR, Hamm RJ, Temple MD, Buck DL, Lyeth BG. Department of Psychology, Virginia Commonwealth University, Medical College of Virginia, Richmond 23284-2018, USA. An emerging literature exists in support of deficits in cholinergic neurotransmission days to weeks following experimental traumatic brain injury (TBI). In addition, novel cholinomimetic therapeutics have been demonstrated to improve cognitive outcome following TBI in rats. We examined the effects of repeated postinjury administration of a cholinesterase inhibitor, tetrahydroaminoacridine (THA), on cognitive performance following experimental TBI. Rats were either injured at a moderate level of central fluid percussion TBI (2.1+/-0.1 atm) or were surgically prepared but not delivered a fluid pulse (sham injury). Beginning 24 h after TBI or sham injury, rats were injected (IP) daily for 15 days with an equal volume (1.0 ml/kg) of either 0.0, 1.0, 3.0, or 9.0 mg/kg THA (TBI: n = 8, 8, 10, and 7, respectively, and Sham: n = 5, 7, 8, 7, respectively). Cognitive performance was assessed on Days 11-15 after injury in a Morris water maze (MWM).**Analysis of maze latencies over days indicated that chronic administration of THA produced a dose-related impairment in MWM performance in both the injured and sham groups, with the 9.0 mg/kg dose producing the largest deficit. T**he 1.0 and 3.0 mg/kg doses of THA impaired MWM performance without affecting swimming speeds. Thus, the results of this investigation do not support the use of THA as a cholinomimetic therapeutic for the treatment of cognitive deficits following TBI.

43. Toxicol Lett. 1998 Dec 28;102-103:527-33. Chronic effects of low level exposure to anticholinesterases--a mechanistic review. Ray DE. Medical Research Council Toxicology Unit, Leicester, UK.der2@le.ac.uk High dose exposure to anticholinesterases which results in symptomatic poisoning can have lasting consequences due to the trauma of intoxication, excitotoxicity, secondary hypoxic damage, and (for some agents) a delayed onset polyneuropathy (OPIDN). The potential effects of low level exposure are less well defined. The most reliable data comes from controlled clinical trials with specific agents. A single dose of sarin or repeated doses of metrifonate or mevinphos, have produced only transient adverse effects at doses causing substantial acetylcholinesterase inhibition. Other data comes from epidemiological surveys. These have often used more sensitive indices than the clinical studies, but are less reliable due to the difficulty of defining exposure and matching control and exposed populations. Subtle, mainly cognitive, differences between exposed and non-exposed populations are sometimes seen. Low level exposure can cause a reversible down-regulation of cholinergic systems, and a range of non-cholinesterase effects that are structure-specific, and do not always parallel acute toxicity. Novel protein targets sensitive to low level exposure to some organophosphates are known to exist in the brain, but their functional significance is not yet understood.

44. Exp Neurol. 2000 Nov;166(1):136-52. Postinjury administration of L-deprenyl improves cognitive function and enhances neuroplasticity after traumatic brain injury. Zhu J, Hamm RJ, Reeves TM, Povlishock JT, Phillips LL. Department of Anatomy, Medical College of Virginia, Richmond, Virginia 23298-0709, USA. The rat model of combined central fluid percussion traumatic brain injury (TBI) and bilateral entorhinal cortical lesion (BEC) produces profound, persistent cognitive deficits, sequelae associated with human TBI. In contrast to percussive TBI alone, this combined injury induces maladaptive hippocampal plasticity. Recent reports suggest a potential role for dopamine in CNS plasticity after trauma. We have examined the effect of the dopamine enhancer l-deprenyl on cognitive function and neuroplasticity following TBI. Rats received fluid percussion TBI, BEC alone, or combined TBI + BEC lesion and were treated once daily for 7 days with l-deprenyl, beginning 24 h after TBI alone and 15 min after BEC or TBI + BEC. Postinjury motor assessment showed no effect of l-deprenyl treatment. Cognitive performance was assessed on days 11-15 postinjury and brains from the same cases examined for dopamine beta-hydroxylase immunoreactivity (DBH-IR) and acetylcholinesterase (AChE) histochemistry. Significant cognitive improvement relative to untreated injured cases was observed in both TBI groups following l-deprenyl treatment; however, no drug effects were seen with BEC alone. l-Deprenyl attenuated injury-induced loss in DBH-IR over CA1 and CA3 after TBI alone. However, after combined TBI + BEC, l-deprenyl was only effective in protecting CA1 DBH-IR. AChE histostaining in CA3 was significantly elevated with l-deprenyl in both injury models.**After TBI + BEC, l-deprenyl also increased AChE in the dentate molecular layer relative to untreated injured cases. These results suggest that dopaminergic/noradrenergic enhancement facilitates cognitive** recovery after brain injury and that noradrenergic fiber integrity is correlated with enhanced synaptic plasticity in the injured hippocampus. Copyright 2000 Academic Press.

J Neurotrauma. 1992 May;9 Suppl 2:S463-74.**Cholinergic and opioid mediation of traumatic brain injury.**Lyeth BG, Hayes RL.

Psychosom Med. 1976 Jan-Feb;38(1):55-8.**Sudden death in the laboratory rat.**Rosellini RA, Binik YM, Seligman MP. Vulnerability to sudden death was produced in laboratory rats by manipulating their developmental history. Rats who were reared in isolation died suddenly when placed in a stressful swimming situation. Handling of these singly-housed rats from 25 to 100 days of age potentiated the phenomenon. However, animals who were group housed did not die even when they had been previously handled.

J Neurol Neurosurg Psychiatry. 1973 Aug;36(4):581-4. Creutzfeldt-Jakob disease treated with amantidine. A report of two cases. Sanders WL, Dunn TL. The treatment of two cases of Creutzfeldt-Jakob disease with amantidine is described. The first case made a remarkable initial improvement which was sustained for two months, but then deteriorated and died. Histological examination of the brain showed changes consistent with early Creutzfeldt-Jakob disease. The second case which was clinically one of Creutzfeldt-Jakob disease has now been followed for 30 months since the start of treatment and appears to be cured. It is considered that amantidine has a definite effect in this disease and it is suggested that its mode of action, though unknown, is more likely to be metabolic than antiviral. Free PMC Article

Arch Int Pharmacodyn Ther. 1986 Mar;280(1):136-44. Effect of stress and glucocorticoids on the gastrointestinal cholinergic enzymes. Oriaku ET, Soliman KF. (Glucocorticoids lower AChE)

Cardiovasc Res. 1990 Apr;24(4):335-9. Sympathectomy alters acetylcholinesterase expression in adult rat heart. Nyquist Battie C, Moran N.

Harris LW, Garry VF, Jr, Moore RD. Biosynthesis of cholinesterase in rabbit bone marrow cells in culture. Biochem Pharmacol. 1974 Aug;23(15):2155–2163.

Heller M, Hanahan DJ. Human erythrocyte membrane bound enzyme acetylcholinesterase. Biochim Biophys Acta. 1972 Jan 17;255(1):251–272.

J Cell Biol. 1976 June 1; 69(3): 638–646. Bartos EM. Properties of growth-related acetylcholinesterase in a cell line of fibroblastic origin

Behav Brain Res 2000 Jul;112(1-2):33-41 Impaired escape performance and enhanced conditioned fear in rats following exposure to an uncontrollable stressor are mediated by glutamate and nitric oxide in the dorsal raphe nucleus. Grahn RE, Watkins LR, Maier SF. Department of Psychology, Connecticut College, Box 5275, 270 Mohegan Avenue, 06320-4196, New London, CT 06320-4196, USA.regra@conncoll.edu Exposure to uncontrollable aversive events produces a variety of behavioral consequences that do not occur if the aversive event is controllable. Accumulating evidence suggests that exaggerated excitation of serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN) is sufficient to cause these same behaviors, such as poor shuttlebox escape performance and enhanced conditioned fear that occur 24 h after exposure to inescapable tailshock (IS). The aim of the present studies was to explore the possibility that N-methyl-D-aspartate (NMDA) receptor activation and nitric oxide (NO) formation within the DRN might be involved in mediating the behavioral consequences of IS. To this end, either the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (APV) or the nitric oxide synthase inhibitor Nw-nitro-L-arginine methyl ester (L-NAME), was microinjected into the DRN before IS or before testing 24 h later. Blocking NMDA receptors with APV in the DRN during IS prevented the usual impact of IS on escape responding and conditioned fear. However, injection of APV at the time of testing only reduced these effects. The DRN was shown to be the critical site mediating blockade of these behavioral changes since injection of APV lateral to the DRN did not alter the behavioral consequences of IS. Conversely, L-NAME was most effective in reversing the effects of IS when administered at the time of testing. These results suggest that there is glutamatergic input to the DRN at the time of IS that produces long-lasting changes in DRN sensitivity. This plasticity in the DRN is discussed as a possible mechanism by which IS leads to changes in escape performance and conditioned fear responding.

and prolonged depression causes shrinkage of this area. The high cortisol associated with depression is undoubtedly one of the factors causing brain shrinkage during stress. Cushing's disease, in which the adrenal glands produce far too much cortisol, causes shrinkage of the brain, and when the disease is cured by normalizing the level of cortisol, the brain size is restored. There are two very different kinds of stress reaction. The best known "fight or flight reaction" could be called more accurately "struggle to adapt." Another, less discussed kind, might appear to be a "give up and die or get depressed" reaction, but it involves many processes that are protective and adaptive in certain circumstances. tone and heart rate;

drown easily. The role of acetylcholine, (Anisman, et al., 1981).

A situation of extreme restraint causes very rapid damage to the tissues, with bleeding ulcers of the stomach and intestine, shrinking of the thymus gland, and, if the animal survives for a while, atrophy of the brain. (Doi, et al., 1991; Gatón, et al., 1993)

LH, somatotropin, GH, Ach. caffeine progest

Behav Brain Res. 2012 Mar 17;228(2):294-8. doi: 10.1016/j.bbr.2011.11.036. Epub 2011 Dec 8. Parental enrichment and offspring development: modifications to brain, behavior and the epigenome. Mychasiuk R, Zahir S, Schmold N, Ilnytskyy S, Kovalchuk O, Gibb R. University of Lethbridge, Canadian Centre for Behavioural Neuroscience, Canada. r.mychasiuk@uleth.ca

4. Biomed Pharmacother. 2012 Jun;66(4):249-55. doi: 10.1016/j.biopha.2011.11.005. Epub 2011 Dec 21. Cholinesterase activities and biochemical determinations in patients with prostate cancer: influence of Gleason score, treatment and bone metastasis. Battisti V, Bagatini MD, Maders LD, Chiesa J, Santos KF, Gonçalves JF, Abdalla FH, Battisti IE, Schetinger MR, Morsch VM. Departamento de Química, Centro de Ciências Naturais e Exatas, Universidade Federal de Santa Maria, Campus Universitário, 97105-900 Santa Maria, RS, Brazil. battistivanessa@gmail.com Prostate cancer (PCa) is the sixth most common type of cancer worldwide. Cholinesterase is well known as having non-cholinergic functions such as cellular proliferation and differentiation, suggesting a possible influence of cholinesterase in tumorogenesis. Thus, the aim of this study was to investigate the whole blood acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BChE) activities and some biochemical parameters in PCa patients. This study was performed in 66 PCa patients and 40 control subjects. AChE and BChE activities were determined in PCa patients and the influence of the Gleason score; bone metastasis and treatment in the enzyme activities were also verified. Furthermore, we also analyzed possible biochemical alterations in these patients. **AChE and BChE activities decreased in PCa patients in relation to the control group and various biochemical changes were observed in these patients. Moreover, Gleason score, metastasis and treatment influenced cholinesterase activities and biochemical determinations. Our results suggest that cholinesterases activities and biochemical parameters are altered in PCa. These facts support the idea that t**he drop in the cholinesterase activity and the consequent increased amount of acetylcholine could lead to a cholinergic overstimulation and increase the cell proliferation in PCa. Copyright © 2011 Elsevier Masson SAS. All rights reserved.

4. Biomed Pharmacother. 2012 Jun;66(4):249-55. doi: 10.1016/j.biopha.2011.11.005. Epub 2011 Dec 21. Cholinesterase activities and biochemical determinations in patients with prostate cancer: influence of Gleason score, treatment and bone metastasis. Battisti V, Bagatini MD, Maders LD, Chiesa J, Santos KF, Gonçalves JF, Abdalla FH, Battisti IE, Schetinger MR, Morsch VM. Departamento de Química, Centro de Ciências Naturais e Exatas, Universidade Federal de Santa Maria, Campus Universitário, 97105-900 Santa Maria, RS, Brazil. battistivanessa@gmail.com Prostate cancer (PCa) is the sixth most common type of cancer worldwide. Cholinesterase is well known as having non-cholinergic functions such as cellular proliferation and differentiation, suggesting a possible influence of cholinesterase in tumorogenesis. Thus, the aim of this study was to investigate the whole blood acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BChE) activities and some biochemical parameters in PCa patients. This study was performed in 66 PCa patients and 40 control subjects. AChE and BChE activities were determined in PCa patients and the influence of the Gleason score; bone metastasis and treatment in the enzyme activities were also verified. Furthermore, we also analyzed possible biochemical alterations in these patients. AChE and BChE activities decreased in PCa patients in relation to the control group and various biochemical changes were observed in these patients. Moreover, Gleason score, metastasis and treatment influenced cholinesterase activities and biochemical determinations. Our results suggest that cholinesterases activities and biochemical parameters are altered in PCa. These facts support the idea that the drop in the cholinesterase activity and the consequent increased amount of acetylcholine could lead to a cholinergic overstimulation and increase the cell proliferation in PCa. Copyright

1. 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. wxyinwxyin@163.com

2. Mol Reprod Dev. 2012 Oct;79(10):689-96. doi: 10.1002/mrd.22075. Epub 2012 Sep 11. Roles of cytokines and progesterone in the regulation of the nitric oxide generating system in bovine luteal endothelial cells. Yoshioka S, Acosta TJ, Okuda K. Laboratory of Reproductive Physiology, Graduate School of Natural Science and Technology, Okayama University, Okayama, Japan. Nitric oxide (NO) produced by luteal endothelial cells (LECs) plays important roles in regulating corpus luteum (CL) function, yet the local mechanism regulating NO generation in bovine CL remains unclear. The purpose of the present study was to elucidate if tumor necrosis factor-α (TNF), interferon γ (IFNG), and/or progesterone (P4) play roles in regulating NO generating system in LECs. Cultured bovine LECs obtained from the CL at the mid-luteal stage (Days 8-12 of the cycle) were treated for 24 hr with TNF (2.9 nM), IFNG (2.5 nM), or P4 (0.032-32 μM). NO production was increased by TNF and IFNG, but decreased by P4 ($P < 0.05$). TNF and IFNG stimulated the relative steady-state amounts of inducible nitric oxide synthase (iNOS) mRNA and iNOS protein expression ($P < 0.05$), whereas P4 inhibited relative steady-state amounts of iNOS mRNA and iNOS protein expression ($P < 0.05$). In contrast, endothelial nitric oxide synthase (eNOS) expression was not affected by any treatment. TNF and IFNG stimulated NOS activity ($P < 0.05$) and 1400W, a specific inhibitor of iNOS, reduced NO production stimulated by TNF and IFNG in LECs ($P < 0.05$)**. Onapristone, a specific P4 receptor antagonist, blocked the inhibitory effect of P4 on NO** production in LECs ($P < 0.05$). The overall findings suggest that TNF and IFNG accelerate luteolysis by increasing NO production via stimulation of iNOS expression and NOS activity in bovine LECs. P4, on the other hand, may act in maintaining CL function by suppressing iNOS expression in bovine LECs. Mol. Reprod. Dev. 79: 689-696, 2012. ©2012 Wiley Periodicals, Inc. Copyright ©2012 Wiley Periodicals, Inc.

3. J Neurochem. 2012 Jul;122(1):185-95. doi: 10.1111/j.1471-4159.2012.07753.x. Progesterone prevents mitochondrial dysfunction in the spinal cord of wobbler mice. Deniselle MC, Carreras MC, Garay L, Gargiulo-Monachelli G, Meyer M, Poderoso JJ, De Nicola AF. Laboratory of Neuroendocrine Biochemistry, Instituto de Biologia y Medicina Experimental-CONICET, Buenos Aires, Argentina. In the Wobbler mouse, a mutation of the Vps54 protein increases oxidative stress in spinal motoneurons, associated to toxic levels of nitric oxide and hyperactivity of nitric oxide synthase (NOS). Progesterone neuroprotection has been reported for several CNS diseases, including the Wobbler mouse neurodegeneration. In the present study, we analyzed progesterone effects on mitochondrial-associated parameters of symptomatic Wobbler mice. The activities of mitochondrial respiratory chain complexes I, II-III and IV and protein levels of mitochondrial and cytosolic NOS were determined in cervical and lumbar cords from control, Wobbler and Wobbler mice receiving a progesterone implant for 18 days. We found a significant reduction of complex I and II-III activities in mitochondria and increased protein levels of mitochondrial, but not cytosolic nNOS, in the cervical cord of Wobbler mice.**Progesterone treatment prevented the reduction of complex I in the cervical region and the increased level of mitochondrial nNOS.**Wobbler motoneurons also showed accumulation of amyloid precursor protein immunoreactivity and decreased activity and immunostaining of MnSOD. Progesterone treatment avoided these abnormalities. Therefore, administration of progesterone to clinically afflicted Wobblers (i) prevented the abnormal increase of mitochondrial nNOS and normalized respiratory complex I; (ii) decreased amyloid precursor protein accumulation, a sign of axonal degeneration, and (iii) increased superoxide dismutation. Thus, progesterone neuroprotection decreases mitochondriopathy of Wobbler mouse cervical spinal cord. © 2012 The Authors. Journal of Neurochemistry ©2012 International Society for Neurochemistry.

Comp Biochem Physiol C. 1993 Sep;106(1):125-9.**The role of the neurotransmitters acetylcholine and noradrenaline in the pathogenesis of stress ulcers.**Gatón J, Fernández de la Gándara F, Velasco A.

People with Cloninger's "harm avoidance" personality trait, which is closely associated with serotonin (Hansenne, et al., 1999), are more likely to develop dementia (Clément, et al., 2010). These observations are consistent with the stress-susceptibility of people with high serotonin exposure, and to the effects of cortisol on nerves and glucose-derived energy production.

Jpn J Surg. 1991 Jan;21(1):43-9. **Participation of the parasympathetic nervous system in the development of activity-stress ulcers.** Doi K, Iwahashi K, Tsunekawa K.17. J Auton Nerv Syst. 1987 Oct;20(3):265-8. Adrenergic modulation of gastric stress pathology in rats: a cholinergic link. Ray A, Sullivan RM, Henke PG. Department of Psychology, St. Francis Xavier University, Antigonish, Nova Scotia, Canada. The effects of some adrenergic drugs were evaluated on cold restraint-induced gastric ulcers in rats. The beta-adrenergic antagonist, (+/-)-propranolol (1 and 10 mg/kg), as well as the beta-agonist, isoproterenol (0.05 and 0.5 mg/kg) potentiated the gastric pathology. On the other hand, the alpha-agonist, clonidine (0.5 mg/kg) attenuated and the alpha-antagonist, yohimbine (1 mg/kg) aggravated stress ulcer development. The anticholinergic agent, atropine methylnitrate (1 mg/kg), reduced both the frequency and severity of stress ulcers and also antagonized the potentiating effects of (+/-)-propranolol, isoproterenol and yohimbine. The results suggest a cholinergic role in the adrenergic modulation of gastric stress pathology.

Psychopharmacology (Berl). 1981;74(1):81-7. **Cholinergic influences on escape deficits produced by uncontrollable stress.** Anisman H, Glazier SJ, Sklar LS. A series of experiments assessed the potential role of acetylcholine (ACh) in the escape interference produced by inescapable shock.**Treatment with the anticholinesterase, physostigmine, successfully mimicked the effects of inescapable shock.**That is, the drug disrupted performance when escape was prevented for 6 s on any given trial, thereby necessitating sustained active responding. When escape was possible upon shock onset, the drug treatment did not influence performance.**The centrally acting anticholinergic scopolamine hydrobromide antagonized the effects of physostigmine, and when administered prior to escape testing antagonized the disruptive effects of previously administered inescapable shock.**In contrast, the peripherally acting agent scopolamine methylbromide did not influence the effects of these treatments, suggesting that the effects of physostigmine and inescapable shock involved central ACh changes. Scopolamine hydrobromide administered prior to inescapable shock did not prevent the escape interference from subsequently appearing, but this effect could not be attributed to state dependence. It was argued that the interference of escape following uncontrollable stress was due to non-associative motor deficits. Alterations of the escape deficits by scopolamine were due to elimination of the motor disruption.

Curr Opin Oncol. 2005 Jan;17(1):55-60. DNA methylation and cancer therapy: new developments and expectations. Esteller M. Cancer Epigenetics Laboratory, Spanish National Cancer Centre (CNIO) Madrid, Spain.mesteller@cnio.es PURPOSE OF REVIEW: In addition to having genetic causes, cancer can also be considered an epigenetic disease. The main epigenetic modification is DNA methylation, and patterns of aberrant DNA methylation are now recognized to be a common hallmark of human tumors. One of the most characteristic features is the inactivation of tumor-suppressor genes by CpG-island hypermethylation of the CpG islands located in their promoter regions. These sites, among others, are the targets of DNA-demethylating agents, the promising chemotherapeutic drugs that are the focus of this article. RECENT FINDINGS: Four exciting aspects have recently arisen at the forefront of the advancements in this field: first, the development of new compounds with DNA-demethylating capacity that are less toxic (for example, procaine) and may be administered orally (for example, zebularine);

Science. 2013 May 10;340(6133):756-9. **Emergence of individuality in genetically identical mice.** Freund J, Brandmaier AM, Lewejohann L, Kirste I, Kritzler M, Krüger A, Sachser N, Lindenberger U, Kempermann G. CRTD-DFG Research Center for Regenerative Therapies Dresden, Technische Universität Dresden, Dresden, Germany. Comment in Science. 2013 May 10;340(6133):695-6. Brain plasticity as a neurobiological reflection of individuality is difficult to capture in animal models. Inspired by behavioral-genetic investigations of human monozygotic twins reared together, we obtained dense longitudinal activity data on 40 inbred mice living in one large enriched environment. The exploratory activity of the mice diverged over time, resulting in increasing individual differences with advancing age. Individual differences in cumulative roaming entropy, indicating the active coverage of territory, correlated positively with individual differences in adult hippocampal neurogenesis. Our results show that factors unfolding or emerging during development contribute to individual differences in structural brain plasticity and behavior. The paradigm introduced here serves as an animal model for identifying mechanisms of plasticity underlying nonshared environmental contributions to individual differences in behavior.

Neurobiol Aging. 1995 Jul-Aug;16(4):523-30. Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. Breitner JC, Welsh KA, Helms MJ, Gaskell PC, Gau BA, Roses AD, Pericak-Vance MA, Saunders AM.

If each opportunity we have to choose expands our curiosity, we go beyond our inheritance to become something unique but also universal, that is, more fully human.

J Neurobiol. 1976 Jan;7(1):75-85. Effects of environment on morphology of rat cerebral cortex and hippocampus. Diamond MC, Ingham CA, Johnson RE, Bennett EL, Rosenzweig MR. ... strains of rats. KRECH D, ROSENZWEIG MR, BENNETT EL....

19. Pharmacol Biochem Behav. 1986 Sep;25(3):521-6. Cholinergic function and memory: extensive inhibition of choline acetyltransferase fails to impair radial maze performance in rats. Wenk G, Sweeney J, Hughey D, Carson J, Olton D. The present study investigated the effects of a potent inhibitor of choline acetyltransferase (ChAT), BW813U, on the choice accuracy of rats in the radial arm maze. BW813U (100 mg/kg, IP) produced a rapid (within 1 hour) and substantial decrease in ChAT activity throughout the brain, ranging from 66% (hippocampus) to 80% (caudate nucleus) that lasted up to 5 days.**A single injection (50 mg/kg, IP) into rats with lesions (using ibotenic acid) in the nucleus basalis magnocellularis and medial septal area, decreased ChAT activity by 75% and 60% in the cortex and hippocampus, respectively. Lesioned and unlesioned rats were trained on the radial arm maze until they reached a criterion level of performance.**Each rat then received an injection of BW813U (50 or 100 mg/kg, IP). Choice accuracy was not impaired at any time following the injection. The lack of effect on performance may be due to 2 possible factors: The radial maze retention paradigm chosen may not be sufficiently difficult, or the decrease in acetylcholine production was not sufficient to affect behavior. Compensation by non-cholinergic neural systems might account for the insensitivity of the rats to significant cholinergic depletion.

Psychol Aging. 1988 Dec;3(4):399-406. Genotype-environment interaction in personality development: identical twins reared apart. Bergeman CS, Plomin R, McClearn GE, Pedersen NL, Friberg LT. Center for Developmental and Health Genetics, Pennsylvania State University, University Park 16802. The focus of this study is to identify specific genotype-environment (GE) interactions as they contribute to individual differences in personality in later life. In behavioral genetics, GE interaction refers to the possibility that individuals of different genotypes may respond differently to specific environments. A sample of 99 pairs of identical twins reared apart, whose average age is 59 years, has been studied as part of the Swedish Adoption/Twin Study of Aging (SATSA). Hierarchical multiple regression was used to detect interactions between personality and environmental measures after the main effects of genotype and environment were removed. Analyses yield evidence for 11 significant interactions that provide the first evidence for GE interaction in human development using specific environmental measures. Thus, in addition to the main-effect contributions of heredity and environment, GE interactions contribute to individual differences in personality as measured in the second half of the life course.

Wikipedia:**Excitability and inhibition**[edit source|editbeta]

Acetylcholine also has other effects on neurons. One effect is to cause a slowdepolarization[*citation needed*]by blocking a tonically active K+ current, which increases neuronal excitability. Alternatively, acetylcholine can activate non-specific cation conductances to directly excite neurons.[10]An effect upon postsynapticM4-muscarinic ACh receptorsis to openinward-rectifier potassium ion channel(K_{ir}) and cause inhibition.[11]The influence of acetylcholine on specific neuron types can be dependent upon the duration of cholinergic stimulation. For instance, transient exposure to acetylcholine (up to several seconds) can inhibit cortical pyramidal neurons via M1 type muscarinic receptors that are linked to Gq-type G-protein alpha subunits.**M1 receptor activation can induce calcium-release from intracellular stores, which then activate a calcium-activated potassium conductance which inhibits**pyramidal neuron firing.[12]**On the other hand, tonic M1 receptor activation is strongly excitatory.**Thus, ACh acting at one type of receptor can have multiple effects on the same postsynaptic neuron, depending on the duration of receptor activation.[13]Recent experiments in behaving animals have demonstrated that cortical neurons indeed experience both transient and persistent changes in local acetylcholine levels during cue-detection behaviors.[14]

In the cerebral cortex, tonic ACh inhibits layer 4medium spiny neurons, the main targets of thalamocortical inputs while excitingpyramidal cellsin layers 2/3 and layer 5.[11]This filters out weak sensory inputs in layer 4 and amplifies inputs that reach the layers 2/3 and layer L5 excitatory microcircuits. As a result, these layer-specific effects of ACh might function to improve the signal noise ratio of cortical processing.[11]At the same time, acetylcholine acts through nicotinic receptors to excite certain groups of inhibitory interneurons in the cortex, which further dampen down cortical activity.[15]

Role in decision making[edit source|editbeta]

One well-supported function of acetylcholine (ACh) in cortex is increased responsiveness to sensory stimuli, a form ofattention.Phasicincreases of ACh during visual,[16]auditory[17]and somatosensory[18]stimulus presentations have been found to increase the firing rate of neurons in the corresponding primary sensory cortices. When cholinergic neurons in the basal forebrain are lesioned, animals' ability to detect visual signals was robustly and persistently impaired.[19]In that same study, animals' ability to correctly reject non-target trials was not impaired, further supporting the interpretation that phasic ACh facilitates responsiveness to stimuli. Looking at ACh's effect on thalamocortical connections, a known pathway of sensory information, in vitro application of cholinergicagonistcarbacholto mouse auditory cortex enhanced thalamocortical activity.[20]In addition, Gil et al. (1997) applied a different cholinergic agonist,nicotine, and found that activity was enhanced at thalamocortical synapses.[21]This finding provides further evidence for a facilitative role of ACh in transmission of sensory information from the thalamus to selective regions of cortex.

An additional suggested function of ACh in cortex is suppression of intracortical information transmission. Gil et al. (1997) applied the cholinergic agonistmuscarineto neocortical layers and found thatexcitatory post-synaptic potentialsbetween intracortical synapses were depressed.[21]In vitro application of cholinergic agonist carbachol to mouse auditory cortex suppressed intracortical activity as well.[20]Optical recording with a voltage-sensitive dye in rat visual cortical slices demonstrated significant suppression in intracortical spread of excitement in the presence of ACh.[22]

Some forms of learning and plasticity in cortex appear dependent on the presence of acetylcholine. Bear et al. (1986) found that the typical synaptic remapping instriate cortexthat occurs duringmonocular deprivationis reduced when there is a depletion of cholinergic projections to that region of cortex.[23]Kilgard et al. (1998) found that repeated stimulation of thebasal forebrain, a primary source of ACh neurons, paired with presentation of a tone at a specific frequency, resulted in remapping of theauditory cortexto better suit processing of that tone.[24]Baskerville et al. (1996) investigated the role of ACh inexperience-dependent plasticityby depleting cholinergic inputs to thebarrel cortexof rats.[25]The cholinergic depleted animals had a significantly reduced amount of whisker-pairing plasticity. Apart from the cortical areas, Crespo et al. (2006) found that the activation of nicotinic and muscarinic receptors in thenucleus accumbensis necessary for the acquisition of an appetitive task.[26]

ACh has been implicated in the reporting of expected uncertainty in the environment[27]based both on the suggested functions listed above and results recorded while subjects perform a behavioral cuing task.Reaction timedifference between correctly cued trials and incorrectly cued trials,**called the cue validity, was found to vary inversely with ACh**levels in primates with pharmacologically (e.g. Witte et al., 1997) and surgically (e.g. Voytko et al., 1994) altered levels of ACh.[28][29]The result was also found inAlzheimer's diseasepatients (Parasuraman et al., 1992) and smokers after nicotine (an ACh agonist) consumption.[30][31]The inverse covariance is consistent with the interpretation of ACh as representing expected uncertainty in the environment, further supporting this claim.

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1. Pharmacol Res. 2011 Jun;63(6):525-31. Endothelin receptor antagonists: potential in Alzheimer's disease. Palmer J, Love S. Dementia Research Group, Institute of Clinical Neurosciences, School of Clinical Sciences, University of Bristol, Frenchay Hospital, Bristol BS16 1LE, United Kingdom.jen.palmer@bristol.ac.uk Alzheimer's disease (AD) is believed to be initiated by the accumulation of neurotoxic forms of Aβ peptide within the brain. AD patients show reduction of cerebral blood flow (CBF), the extent of the reduction correlating with the impairment of cognition.**There is evidence that cerebral hypoperfusion precedes and may even trigger the onset of dementia in AD. Cerebral hypoperfusion impairs neuronal function, reduces the clearance of Aβ peptide and other toxic metabolites from the brain, and upregulates Aβ production. Studies in animal models of AD have shown the reduction in CBF to be more than would be expected for the reduction in neuronal metabolic activity.**Aβ may contribute to the reduction in CBF in AD, as both Aβâ‚‹â‚„â‚€and Aβâ‚‹â‚„â‚‚induce cerebrovascular dysfunction. Aβâ‚‹â‚„â‚€acts directly on cerebral arteries to cause cerebral smooth muscle cell contraction. Aβâ‚‹â‚„â‚‚causes increased neuronal production and release of endothelin-1 (ET-1), a potent vasoconstrictor, and upregulation of endothelin-converting enzyme-2 (ECE-2), the enzyme which cleaves ET-1 from its inactive precursor. ET-1 and ECE-2 are also elevated in AD, making it likely that upregulation of the ECE-2-ET-1 axis by Aβâ‚‹â‚„â‚‚contributes to the chronic reduction of CBF in AD. At present, only a few symptomatic treatment options exist for AD. The involvement of ET-1 in the pathogenesis of endothelial dysfunction associated with elevated Aβ indicates the potential for endothelin receptor antagonists in the treatment of AD. It has already been demonstrated that the endothelin receptor antagonist bosentan, preserves aortic and carotid endothelial function in Tg2576 mice, and our findings suggest that endothelin receptor antagonists may be beneficial in maintaining CBF in AD. Copyright © 2011 Elsevier Ltd. All rights reserved.

Fiziol Zh SSSR Im I M Sechenova. 1975 Oct;61(10):1466-72. [Amine receptors in brain vessels]. [Article in Russian] Edvinsson L, Owman Ch. Isolated middle cerebral arteries from cats and pial arteries from humans (obtained during lobe resection) were studied in a sensitive in vitro system allowing a detailed pharmacological characterization of various amine receptors and related dissociation constants. It was found that the adrenergic receptors comprise contractile (alpha) and dilatory (beta) receptors.**Acetylcholine induced dilation (at low doses) as well as constriction (at high doses) both responses being inhibited in a comparative way by atropine.**Experiments with selective inhibitors showed the presence of specific histamine H2 (dilatory) receptors;**at high doses histamine contracted the vessels in a non-specific way. 5-Hydroxytryptamine was the most efficient vasoconstrictor agent, and the** response could be blocked by the serotonin-antagonist, methysergide.

Behav Neurosci. 2007 Jun;121(3):491-500. Exposure to enriched environment improves spatial learning performances and enhances cell density**but not choline acetyltransferase activity in the hippocampus of ventral subicular-lesioned rats.** Dhanushkodi A, Bindu B, Raju TR, Kutty BM. Department of Neurophysiology National Institute of Mental Health and Neuro Sciences (NIMHANS Deemed University), Bangalore, India. The authors demonstrated the efficacy of enriched housing conditions in promoting the behavioral recovery and neuronal survival following subicular lesion in rats. Chemical lesioning of the ventral subiculum impaired the spatial learning performances in rats. The lesion also induced a significant degree of neurodegeneration in the CA1 and CA3 areas of the hippocampus and entorhinal cortex. Exposure to enriched housing conditions improved the behavioral performance and partially attenuated the neurodegeneration in the hippocampus. The choline acetyl transferase (ChAT) activity in the hippocampus remained unchanged following ventral subicular lesion and also following exposure to an enriched environment. The study implicates the effectiveness of activity-dependent neuronal plasticity induced by environmental enrichment in adulthood following brain insult.

Horm Behav. 2013 Jul 27. pii: S0018-506X(13)00139-6. Progesterone and vitamin D: Improvement after traumatic brain injury in middle-aged rats. Tang H, Hua F, Wang J, Sayeed I, Wang X, Chen Z, Yousuf S, Atif F, Stein DG. Department of Emergency Medicine, Emory University, Atlanta, GA 30322, USA. Progesterone (PROG) and vitamin D hormone (VDH) have both shown promise in treating traumatic brain injury (TBI). Both modulate apoptosis, inflammation, oxidative stress, and**excitotoxicity.**We investigated whether 21days of VDH deficiency would alter cognitive behavior after TBI and whether combined PROG and VDH would improve behavioral and morphological outcomes more than either hormone alone in VDH-deficient middle-aged rats given bilateral contusions of the medial frontal cortex. PROG (16mg/kg) and VDH (5μg/kg) were injected intraperitoneally 1h post-injury. Eight additional doses of PROG were injected subcutaneously over 7 days post-injury. VDH deficiency itself did not significantly reduce baseline behavioral functions or aggravate impaired cognitive outcomes. Combination therapy showed moderate improvement in preserving spatial and reference memory but was not significantly better than PROG monotherapy. However, combination therapy significantly reduced neuronal loss and the proliferation of reactive astrocytes, and showed better efficacy compared to VDH or PROG alone in preventing MAP-2 degradation. VDH+PROG combination therapy may attenuate some of the potential long-term, subtle, pathophysiological consequences of brain injury in older subjects. © 2013. KEYWORDS:

Yang, glutamate stimulates DNA repair; methylation of dna during stress, hydrophobic

Life Sci 1998;62(17-18):1717-21 Induction of inducible nitric oxide synthase and heme oxygenase-1 in rat glial cells. Kitamura Y, Matsuoka Y, Nomura Y, Taniguchi T Department of Neurobiology, Kyoto Pharmaceutical University, Japan. Recent observations suggest a possible interaction between the nitric oxide (NO)/NO synthases and carbon monoxide (CO)/heme oxygenases systems. We examined the effects of lipopolysaccharide (LPS), interferon-gamma (IFN-gamma), and NO donor such as S-nitroso-N-acetylpenicillamine (SNAP) on induction of inducible NO synthase (iNOS) and heme oxygenase-1 (HO-1) in mixed glial cells and in rat hippocampus. In in vitro glial cells, treatment with LPS induced the expression of 130-kDa iNOS after 6 h, and NO2- accumulation and enhancement of the protein level of 33-kDa HO-1 after 12 h. In addition, treatment with SNAP induced HO-1 expression after 6 h. Although a NOS inhibitor, such as N(G)-nitro-L-arginine (NNA), did not change LPS-induced iNOS expression, the inhibitor s**uppressed both NO2- accumulation and the enhancement of HO-1.**Immunocytochemistry showed that LPS-treatment induced iNOS-immunoreactivity predominantly in microglia, while this treatment induced HO-1-immunoreactivity in both microglia and astrocytes. These results suggest that endogenous NO production by iNOS in microglia causes autocrine- and paracrine-induction of HO-1 protein in microglia and astrocytes in rat brain.

4. Proc Soc Exp Biol Med. 1994 Oct;207(1):43-7. Dietary restriction modulates the norepinephrine content and uptake of the heart and cardiac synaptosomes. Kim SW, Yu BP, Sanderford M, Herlihy JT. Department of Physiology, University of Texas Health Science Center at San Antonio 78284. The present study was designed to examine the effects of long-term dietary restriction on cardiac sympathetic nerves and neurotransmitter. The food intake of male, 6-week-old Fischer 344 rats was reduced to 60% of the intake of control rats fed ad libitum. The body and heart weights of rats diet restricted for 4.5 months were less than those of the ad libitum fed animals, while the heart weight to body weight ratios were higher**. The norepinephrine (NE) content of hearts from restricted rats (1073 +/- 84 ng/g wet wt) was higher than controls (774 +/- 38 ng/g wet wt), although the total amoun**t of NE per heart was unchanged. Similarly, the cardiac synaptosomal P2 fraction from restricted rats possessed a higher NE content (24.1 +/- 2.4 ng/mg protein) than the P2 fraction of ad libitum fed controls (13.7 +/- 1.3 ng/mg protein). The desmethylimipramine-sensitive norepinephrine uptake of the P2 fraction from restricted rats was significantly higher than that of control rats (9.44 +/- 1.33 vs 4.75 +/- 0.35 ng/mg protein/hr). The NE uptakes of the two groups were similar when uptake was normalized to endogenous NE levels. These results demonstrate that long-term dietary restriction affects cardiac sympathetic nerve endings and suggest that part of the beneficial action of life-long dietary restriction on the age-related decline in cardiovascular regulation may be related to changes in cardiac sympathetic nerves.

Int J Cancer. 1985 Apr 15;35(4):493-7. Muscarinic cholinergic receptors in pancreatic acinar carcinoma of rat. Taton G, Delhaye M, Swillens S, Morisset J, Larose L, Longnecker DS, Poirier GG. The active enantiomer of tritiated quinuclidinyl benzilate (3H(-)QNB) was used as a ligand to evaluate the muscarinic receptors. The 3H(-)QNB binding characteristics of muscarinic cholinergic receptors obtained from normal and neoplastic tissues were studied to determine changes in receptor properties during neoplastic transformation. Saturable and stereospecific binding sites for 3H(-)QNB are present in homogenates of rat pancreatic adenocarcinoma. The proportions of high- and low-affinity agonist binding sites are similar for neoplastic and normal tissues. The density of muscarinic receptors is higher in neoplastic (200 femtomoles/mg protein) than in normal pancreatic homogenates (80 femtomoles/mg protein). The muscarinic binding sites of the neoplastic and fetal pancreas show similar KD values which are higher than those observed for normal pancreas.

17: Cancer Res. 1986 Nov;46(11):5706-14. Muscarinic receptor coupling to intracellular calcium release in rat pancreatic acinar carcinoma. Chien JL, Warren JR. Analysis by sodium dodecyl sulfate-polyacrylamide gel electrophoresis of cholinergic receptor protein affinity labeled with the muscarinic antagonist [3H]propylbenzilylcholine mustard revealed a major polypeptide with molecular weight of 80,000-83,000 in both acinar carcinoma and normal acinar cells of rat pancreas. Muscarinic receptor protein is therefore conserved in pancreatic acinar carcinoma. A small but significant difference was detected in the affinity of carcinoma cell receptors (Kd approximately 0.6 nM) and normal cell receptors (Kd approximately 0.3 nM) for reversible binding of the muscarinic antagonist drug, N-methylscopolamine. In addition, carcinoma cell muscarinic receptors displayed homogeneous binding of the agonist drugs carbamylcholine (Kd approximately 31 microM) and oxotremorine (Kd approximately 4 microM), whereas normal cell receptors demonstrated heterogeneous binding, with a minor receptor population showing high affinity binding for carbamylcholine (Kd approximately 3 microM) and oxotremorine (Kd approximately 160 nM), and a major population showing low affinity binding for carbamylcholine (Kd approximately 110 microM) and oxotremorine (Kd approximately 18 microM). Both carcinoma and normal cells exhibited concentration-dependent carbamylcholine-stimulated increases in cytosolic free Ca2+, as measured by 45Ca2+ outflux assay and intracellular quin 2 fluorescence. However, carcinoma cells were observed to be more sensitive to Ca2+ mobilizing actions of submaximal carbamylcholine concentrations, demonstrating 50% maximal stimulation of intracellular Ca2+ release at a carbamylcholine concentration (approximately 0.4 microM) approximately one order of magnitude below that seen for normal cells. These results indicate altered muscarinic receptor coupling to intracellular Ca2+ release in acinar carcinoma cells, which manifests as a single activated receptor state for agonist binding, and increased sensitivity of Ca2+ release in response to muscarinic receptor stimulation.

1: Anticancer Drugs. 2008 Aug;19(7):655-71. Neurotransmission and cancer: implications for prevention and therapy. Schuller HM. Experimental Oncology Laboratory, Department of Pathobiology, College of Veterinary Medicine, University of Tennessee, 2407 River Drive, Knoxville, TN 37996, USA.hmsch@utk.edu Published evidence compiled in this review supports the hypothesis that the development, progression, and responsiveness to prevention and therapy of the most common human cancers is strongly influenced, if not entirely orchestrated, by an imbalance in stimulatory and inhibitory neurotransmission. The neurotransmitters acetylcholine, adrenaline, and noradrenaline of the autonomic nervous system act as powerful upstream regulators that orchestrate numerous cell and tissue functions, by releasing growth factors, angiogenesis factors and metastasis factors, arachidonic acid, proinflammatory cytokines, and local neurotransmitters from cancer cells and their microenvironment. In addition, they modulate proliferation, apoptosis, angiogenesis, and metastasis of cancer directly by intracellular signaling downstream of neurotransmitter receptors. Nicotine and the tobacco-specific nitrosamines have the documented ability to hyperstimulate neurotransmission by both branches of the autonomic nervous system. The expression and function of these neurotransmitter pathways are cell type specific. Lifestyle, diet, diseases, stress, and pharmacological treatments modulate the expression and responsiveness of neurotransmitter pathways. Current preclinical testing systems fail to incorporate the modulating effects of neurotransmission on the responsiveness to anticancer agents and should be amended accordingly. The neurotransmitter gamma-aminobutyric acid has a strong inhibitory function on sympathicus-driven cancers whereas stimulators of cyclic adenosine monophosphate/protein kinase A signaling have strong inhibitory function on parasympathicus-driven cancers. Marker-guided restoration of the physiological balance in stimulatory and inhibitory neurotransmission represents a promising and hitherto neglected strategy for the prevention and therapy of neurotransmitter-responsive cancers.

Psychological stress in IBD: new insights into pathogenic and ... www.ncbi.nlm.nih.gov › Journal List › Gut › v.54(10); Oct 2005 by JE Mawdsley - 2005 - Cited by 255 - Related articles Psychological stress has long been reported anecdotally to increase disease ..... atropine and was more marked in cholinesterase deficient Wistar-Kyoto rats.

Neuropsychopharmacology. 2002 May;26(5):672-81. Sexual diergism of hypothalamo-pituitary-adrenal cortical responses to low-dose physotigmine in elderly vs. young women and men. Rubin RT, Rhodes ME, O'Toole S, Czambel RK. Center for Neurosciences Research, MCP Hahnemann University School of Medicine, Allegheny General Hospital, Pittsburgh, PA 15212, USA.rubin@wpahs.org We previously demonstrated that the reversible cholinesterase inhibitor, physostigmine (PHYSO), administered to normal young adult women and men (average age 35 years) at a dose that produced few or no side effects, resulted in a sex difference (sexual diergism) in hypothalamo-pituitary-adrenal cortical (HPA) axis responses: Plasma**ACTH(1-39), cortisol, and arginine vasopressin (AVP) concentrations increased to a significantly greater extent in the men than in the women.**To explore the effect of age on these sexually diergic hormone responses, in the present study we used the same dose of PHYSO (8 microg/kg IV) to stimulate ACTH(1-39), cortisol, and AVP secretion in normal elderly, non-estrogen-replaced women and elderly men (average ages 73 years and 70 years, respectively). The subjects underwent three test sessions 5-7 days apart: PHYSO, saline control, and a second session of PHYSO. Serial blood samples were taken for hormone analyses before and after pharmacologic challenge.As with the previously studied younger subjects, PHYSO administration produced no side effects in about half the elderly subjects and mild side effects in the other half, with no significant female-male differences.**The hormone responses were 2-5 fold greater in the elderly subjects t**han in the younger subjects, but in contrast to the younger subjects, the elderly men did not have significantly greater hormone responses to PHYSO administration than did the elderly women. The ACTH(1-39) and AVP responses to PHYSO for the two sessions were significantly positively correlated in the men (+0.96, +0.91) but not in the women. None of the hormone responses was significantly correlated with the presence or absence of side effects in either group of subjects.These results indicate**a greater sensitivity of the HPA axis to low-dose PHYSO, and a loss of overall sex differences in hormone responses, in elderly compared with younger subjects.**The lack of a difference in side effects between the elderly women and men and the lack of significant correlations between presence or absence of side effects and hormone responses suggest that the increase in hormone responses with aging is due to correspondingly increased responsiveness of central cholinergic systems and/or the HPA axis, and not to a nonspecific stress response.

Horm Behav. 2013 Feb;63(2):284-90. Progesterone and neuroprotection. Singh M, Su C. Department of Pharmacology and Neuroscience, Institute for Aging and Alzheimer's Disease Research, Center FOR HER, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX 76107, USA.meharvan.singh@unthsc.edu Numerous studies aimed at identifying the role of estrogen on the brain have used the ovariectomized rodent as the experimental model. And while estrogen intervention in these animals has, at least partially, restored cholinergic, neurotrophin and cognitive deficits seen in the ovariectomized animal, it is worth considering that the removal of the ovaries results in the loss of not only circulating estrogen but of circulating progesterone as well. As such, the various deficits associated with ovariectomy may be attributed to the loss of progesterone as well. Similarly, one must also consider the fact that the human menopause results in the precipitous decline of not just circulating estrogens, but in circulating progesterone as well and as such, the increased risk for diseases such as Alzheimer's disease during the postmenopausal period could also be contributed by this loss of progesterone. In fact, progesterone has been shown to exert neuroprotective effects, both in cell models, animal models and in humans.**Here, we review the evidence that supports the neuroprotective effects of progesterone and discuss the various mechanisms that are thought to mediate these protective effects.**We also discuss the receptor pharmacology of progesterone's neuroprotective effects and present a conceptual model of progesterone action that supports the complementary effects of membrane-associated and classical intracellular progesterone receptors.**In addition, we discuss fundamental differences in the neurobiology of progesterone and the clinically used, synthetic progestin, medroxyprogesterone acetate that may offer an explanation for the negative findings of the combined estrogen/progestin arm of the Women's Health Initiative-Memory Study (WHIMS) and suggest that the type of progestin used may dictate the outcome of either pre-clinical or clinical studies that addresses brain function.**

Brain Res. 2005 Jul 5;1049(1):112-9.**Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury.**Pettus EH, Wright DW, Stein DG, Hoffman SW. Department of Cell Biology, Emory University, Atlanta, GA 30322, USA. Progesterone given after traumatic brain injury (TBI) has been shown to reduce the initial cytotoxic surge of inflammatory factors. We used Western blot techniques to analyze how progesterone might affect three inflammation-related factors common to TBI: complement factor C3 (C3), glial fibrillary acidic protein (GFAP), and nuclear factor kappa beta (NFkappaB). One hour after bilateral injury to the medial frontal cortex, adult male rats were given injections of progesterone (16 mg/kg) for 2 days. Brains were harvested 48 h post-TBI, proteins were extracted from samples, each of which contained tissue from both the contused and peri-contused areas, then measured by Western blot densitometry. Complete C3, GFAP, and NFkappaB p65 were increased in all injured animals. However, in animals given progesterone post-TBI,**NFkappaB p65 and the inflammatory metabolites of C3 (9 kDa and 75 kDa)**were decreased in comparison to vehicle-treated animals.

J Leukoc Biol 1996 Mar;59(3):442-50 Progesterone inhibits inducible nitric oxide synthase gene expression and nitric oxide production in murine macrophages. Miller L, Alley EW, Murphy WJ, Russell SW, Hunt JS Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, USA. The purpose of this study was to determine whether the female hormones estradiol-l7 beta (E2) and progesterone (P4) influence inducible nitric oxide synthase (iNOS) and the production of nitric oxide (NO) by interferon-gamma(IFN-gamma)- and lipopolysaccharide (LPS)-activated mouse macrophages. Treatment with P4 alone caused a time- and dose-dependent inhibition of NO production by macrophage cell lines (RAW 264.7, J774) and mouse bone marrow culture-derived macrophages as assessed by nitrite accumulation. RAW 264.7 cells transiently transfected with an iNOS gene promoter/luciferase reporter-gene construct that were stimulated with IFN-gamma/LPS in the presence of P4 displayed reduced luciferase activity and NO production. Analysis of RAW 264.7 cells by Northern blot hybridization revealed concurrent P4-mediated reduction in iNOS mRNA. These observations suggest that P4-mediated inhibition of NO may be an important gender-based difference within females and males that relates to macrophage-mediated host defense.

J Reprod Immunol 1997 Nov 15;35(2):87-99 Female steroid hormones regulate production of pro-inflammatory molecules in uterine leukocytes. Hunt JS, Miller L, Roby KF, Huang J, Platt JS, DeBrot BL Department of Anatomy and Cell Biology, University of Kansas Medical Center, Kansas City 66160-7400, USA.jhunt@kumc.edu Estrogens and progesterone could be among the environmental signals that govern uterine immune cell synthesis of pro-inflammatory substances. In order to investigate this possibility, we first mapped expression of the inducible nitric oxide synthase (iNOS) and tumor necrosis factor-alpha (TNF-alpha) genes in the leukocytes of cycling and pregnant mouse uteri, then tested the ability of estradiol-17 beta (E2) and progesterone to influence gene expression. Immunohistochemistry, in situ hybridization, and other experimental approaches, revealed that the iNOS and TNF-alpha genes are expressed in mouse uterine mast cells, macrophages and natural killer cells (uNK). Gene expression in each cell type was noted to be dependent upon stage of the cycle or stage of gestation, implying potential relationships with levels of female hormones and state of cell differentiation or activation. Further in vivo and in vitro experiments showed that individual hormones have cell type-specific effects on synthesis of iNOS and TNF-alpha that are exerted at the level of transcription. In uterine mast cells, iNOS and TNF-alpha are promoted by E2 whereas preliminary studies in macrophages suggest that transcription and translation of the two genes are unaffected by E2 but are inhibited by progesterone.

Hypothyroidism increases NO; T3, vs helpless; hypothyroid, escape deficit, Levine, et 1990. **choline is increased in AD CSF Elble R;, Carriere;**

Genes Nutr. 2009 December; 4(4): 309–314.**Dietary polyunsaturated fatty acids improve cholinergic transmission in the aged brain**Willis LM, Shukitt-Hale B, Joseph JA. 28. Bloj B, Morero RD, Farias RN, Trucco RE (1973) Membrane lipid fatty acids and regulation of membrane-bound enzymes. Allosteric behaviour of erythrocyte Mg 2+-ATPase (Na++ K+)-ATPase and acetylcholinesterase from rats fed different fat-supplemented diets. Biochim Biophys Acta 311:67–79. [PubMed] 29. Vajreswari A, Narayanareddy K (1992) Effect of dietary fats on erythrocyte membrane lipid composition and membrane-bound enzyme activities. Metabolism 41:352–358. [PubMed] 30. Vajreswari A, Rupalatha M, Rao PS (2002) Effect of altered dietary n-6-to-n-3 fatty acid ratio on erythrocyte lipid composition and membrane-bound enzymes. J Nutr Sci Vitaminol 48:365–370. [PubMed] 31. Foot M, Cruz TF, Clandinin MT (1983)**Effect of dietary lipid on synaptosomal acetylcholinesterase activity.**Biochem J 211:507–509. [PMC free article] [PubMed]

33. Srinivasarao P, Narayanareddy K, Vajreswari A, Rupalatha M, Prakash PS, Rao P (1997) Influence of dietary fat on the activities of subcellular membrane-bound enzymes from different regions of the brain. Neuochem Int 31:789–794. [PubMed]

The protective effect of anticholinergic drugs, such as atropine or scopolamine, against various degenerative brain processes might lead a person to wonder whether the Berkeley enrichment experiments might not have been neurologically exactly the opposite of the stress experiments of Richter and Seligman, that is, reducing cholinergic processes with enrichment, increasing them with impoverishment of choices and experience. A drug, pilocarpine,

USING THE BRAIN FOR LIFE Living is development; the choices we make create our individuality. If genetically identical mice grow up in a large and varied environment, small differences in their experience will affect cell growth in their brains, leading to large differences in their exploratory behavior as they age (Freund, et al., 2013). Geneticists used to say that "genes determine our limits," but this experiment shows that an environment can provide both limitations and opportunities for expanding the inherited potential. If our environment restricts our choices, our becoming human is thwarted, the way rats' potentials weren't discovered when they were kept in the standard little laboratory boxes. An opportunity to be complexly involved in a complex environment lets us become more of what we are, more humanly differentiated.

A series of experiments that started at the University of California in 1960 found that rats that lived in larger spaces with various things to explore were better at learning and solving problems than rats that were raised in the standard little laboratory cages (Rosenzweig, 1960). Studying their brains, they found that the enzyme cholinesterase, which destroys the neurotransmitter, acetylcholine, was increased. They later found that the offspring of these rats were better learners than their parents, and their brains contained more cholinesterase. Their brains were also larger, with a considerable thickening of the cortex, which is considered to be the part mainly responsible for complex behavior, learning and intelligence.

These processes aren't limited to childhood. For example, London taxi drivers who learn all the streets in the city develop a larger hippocampus, an area of the brain involved with memory.

The 1960s research into environmental enrichment coincided with political changes in the US, but it went against the dominant scientific ideas of the time. Starting in 1945, the US government had begun a series of projects to develop techniques of behavior modification or mind control, using drugs, isolation, deprivation, and torture. In the 1950s, psychiatry often used lobotomies (about 80,000, before they were generally discontinued in the 1980s) and electroconvulsive "therapy," and university psychologists tortured animals, often as part of developing techniques for controlling behavior.

The CIA officially phased out their MKultra program in 1967, but that was the year that Martin Seligman, at the University of Pennsylvania, popularized the idea of "learned helplessness." He found that when an animal was unable to escape from torture, even for a very short time, it would often fail to even try to escape the next time it was tortured. Seligman's lectures have been attended by psychologists who worked at Guantanamo, and he recently received a no-bid Pentagon grant of $31,000,000, to develop a program of "comprehensive soldier fitness," to train marines to avoid learned helplessness.

Curt Richter already in 1957 had described the "hopelessness" phenomenon in rats ("a reaction of hopelessness is shown by some wild rats very soon after being grasped in the hand and prevented from moving. They seem literally to give up,") and even how to cure their hopelessness, by allowing them to have an experience of escaping once (Richter, 1957). Rats which would normally be able to keep swimming in a tank for two or three days, would often give up and drown in just a few minutes, after having an experience of "inescapable stress." Richter made the important discovery that the hearts of the hopeless rats slowed down before they died, remaining relaxed and filled with blood, revealing the dominant activity of the vagal nerve, secreting acetylcholine.

The sympathetic nervous system (secreting noradrenaline) accelerates the heart, and is usually activated in stress, in the "fight or flight" reaction, but this radically different (parasympathetic) nervous activity hadn't previously been seen to occur in stressful situations. The parasympathetic, cholinergic, nervous system had been thought of as inactive during stress, and activated to regulate processes of digestion, sleep, and repair. Besides the cholinergic nerves of the parasympathetic system, many nerves of the central nervous system also secrete acetylcholine, which activates smooth muscles, skeletal muscles, glands, and other nerves, and also has some inhibitory effects. The parasympathetic nerves also secrete the enzyme, cholinesterase, which destroys acetylcholine. However, many other types of cell (red blood cells, fibroblasts, sympathetic nerves, marrow cells), maybe all cells, can secrete acetylcholine.

Because cholinergic nerves have been opposed to the sympathetic, adrenergic, nerves, there has been a tendency to neglect their nerve exciting roles, when looking at causes of excitotoxicity, or the stress-induced loss of brain cells. Excessive cholinergic stimulation, however, can contribute to excitotoxic cell death, for example when it's combined with high cortisol and/or hypoglycemia.

Drugs that block the stimulating effects of acetylcholine (the anticholinergics) as well as chemicals that mimic them, such as the organophosphate insecticides, can impair the ability to think and learn. This suggested to some people that age-related dementia was the result of the deterioration of the cholinergic nerves in the brain. Drugs to increase the stimulating effects of acetylcholine in the brain (by inactivating cholinesterase) were promoted as treatment for Alzheimer's disease.

Although herbal inhibitors were well known, profitable new drugs, starting with Tacrine, were put into use. It was soon evident that Tacrine was causing serious liver damage, but wasn't slowing the rate of mental deterioration.

As the failure of the cholinergic drug Tacrine was becoming commonly known, another drug, amantadine (later, the similar memantine) was proposed for combined treatment. In the 1950s, the anticholinergic drug atropine was proposed a few times for treating dementia, and amantadine, which was also considered anticholinergic, was proposed for some mental conditions, including Creutzfeldt-Jacob Disease (Sanders and Dunn, 1973). It must have seemed odd to propose that an anticholinergic drug be used to treat a condition that was being so profitably treated with a pro-cholinergic drug, but memantine came to be classified as an anti-excitatory "NMDA blocker," to protect the remaining cholinergic nerves, so that both drugs could be prescribed simultaneously. The added drug seems to have a small beneficial effect, but there has been no suggestion that this could be the result of its previously-known anticholinergic effects.

Over the years, some people have suspected that Alzheimer's disease might be caused partly by a lack of purpose and stimulation in their life, and have found that meaningful, interesting activity could improve their mental functioning. Because the idea of a "genetically determined hard-wired" brain is no longer taught so dogmatically, there is increasing interest in this therapy for all kinds of brain impairment. The analogy to the Berkeley enrichment experience is clear, so the association of increasing cholinesterase activity with improving brain function should be of interest.

The after-effect of poisoning by nerve gas or insecticide has been compared to the dementia of old age. The anticholinergic drugs are generally recognized for protecting against those toxins. Traumatic brain injury, even with improvement in the short term, often starts a long-term degenerative process, greatly increasing the likelihood of dementia at a later age. A cholinergic excitotoxic process is known to be involved in the traumatic degeneration of nerves (Lyeth and Hayes, 1992), and the use of anticholinergic drugs has been recommended for many years to treat traumatic brain injuries (e.g., Ward, 1950: Ruge, 1954; Hayes, et al., 1986).

In 1976 there was an experiment (Rosellini, et al.) that made an important link between the enrichment experiments and the learned helplessness experiments. The control animals in the enrichment experiments were singly housed, while the others shared a larger enclosure. In the later experiment, it was found that the rats "who were reared in isolation died suddenly when placed in a stressful swimming situation," while the group-housed animals were resistant, effective swimmers. Enrichment and deprivation have very clear biological meaning, and one is the negation of the other.

The increase of acetylcholinesterase, the enzyme that destroys acetylcholine, during enrichment, serves to inactivate cholinergic processes. If deprivation does its harm by increasing the activity of the cholinergic system, we should expect that a cholinergic drug might substitute for inescapable stress, as a cause of learned helplessness, and that an anticholinergic drug could cure learned helplessness. Those tests have been done: "Treatment with the anticholinesterase, physostigmine, successfully mimicked the effects of inescapable shock." "The centrally acting anticholinergic scopolamine hydrobromide antagonized the effects of physostigmine, and when administered prior to escape testing antagonized the disruptive effects of previously administered inescapable shock." (Anisman, et al., 1981.)

This kind of experiment would suggest that the anticholinesterase drugs still being used for Alzheimer's disease treatment aren't biologically helpful. In an earlier newsletter I discussed the changes of growth hormone, and its antagonist somatostatin, in association with dementia: Growth hormone increases, somatostatin decreases. The cholinergic nerves are a major factor in shifting those hormones in the direction of dementia, and the anticholinergic drugs tend to increase the ratio of somatostatin to growth hormone. Somatostatin and cholinesterase have been found to co-exist in single nerve cells (Delfs, et al., 1984).

Estrogen, which was promoted so intensively as prevention or treatment for Alzheimer's disease, was finally shown to contribute to its development. One of the characteristic effects of estrogen is to increase the level of growth hormone in the blood. This is just one of many ways that estrogen is associated with cholinergic activation. During pregnancy, it's important for the uterus not to contract. Cholinergic stimulation causes it to contract; too much estrogen activates that system, and causes miscarriage if it's excessive. An important function of progesterone is to keep the uterus relaxed during pregnancy. In the uterus, and in many other systems, progesterone increases the activity of cholinesterase, removing the acetylcholine which, under the influence of estrogen, would cause the uterus to contract.

Progesterone is being used to treat brain injuries, very successfully. It protects against inflammation, and in an early study, compared to placebo, lowered mortality by more than half. It's instructive to consider its anticholinergic role in the uterus, in relation to its brain protective effects. When the brain is poisoned by an organophosphate insecticide, which lowers the activity of cholinesterase, seizures are likely to occur, and treatment with progesterone can prevent those seizures, reversing the inhibition of the enzyme (and increasing the activity of cholinesterase in rats that weren't poisoned) (Joshi, et al., 2010). Similar effects of progesterone on cholinesterase occur in women (Fairbrother, et al., 1989), implying that this is a general function of progesterone, not just something to protect pregnancy. Estrogen, with similar generality, decreases the activity of cholinesterase. DHEA, like progesterone, increases the activity of cholinesterase, and is brain protective (Aly, et al., 2011).

Brain trauma consistently leads to decreased activity of this enzyme (Östberg, et al., 2011; Donat, et al., 2007), causing the acetylcholine produced in the brain to accumulate, with many interesting consequences. In 1997, a group (Pike, et al.) created brain injuries in rats to test the idea that a cholinesterase inhibitor would improve their recovery and ability to move through a maze. They found instead that it reduced the cognitive ability of both the injured and normal rats. An anticholinergic drug, selegeline (deprenyl) that is used to treat Parkinson's disease and, informally, as a mood altering antiaging drug, was found by a different group (Zhu, et al., 2000) to improve cognitive recovery from brain injuries.

One of acetylcholine's important functions, in the brain as elsewhere, is the relaxation of blood vessels, and this is done by activating the synthesis of NO, nitric oxide. (Without NO, acetylcholine constricts blood vessels; Librizzi, et al., 2000.) The basic control of blood flow in the brain is the result of the relaxation of the wall of blood vessels in the presence of carbon dioxide, which is produced in proportion to the rate at which oxygen and glucose are being metabolically combined by active cells. In the inability of cells to produce CO_2 at a normal rate, nitric oxide synthesis in blood vessels can cause them to dilate. The mechanism of relaxation by NO is very different, however, involving the inhibition of mitochondrial energy production (Barron, et al., 2001). Situations that favor the production and retention of a larger amount of carbon dioxide in the tissues are likely to reduce the basic "tone" of the parasympathetic nervous system, as there is less need for additional vasodilation.

Nitric oxide can diffuse away from the blood vessels, affecting the energy metabolism of nerve cells (Steinert, et al., 2010). Normally, astrocytes protect nerve cells from nitric oxide (Chen, et al., 2001), but that function can be altered, for example by bacterial endotoxin absorbed from the intestine (Solà, et al., 2002) or by amyloid-beta (Tran, 2001), causing them to produce nitric oxide themselves.

Nitric oxide is increasingly seen as an important factor in nerve degeneration (Doherty, 2011). Nitric oxide activates processes (Obukuro, et al., 2013) that can lead to cell death. Inhibiting the production of nitric oxide protects against various kinds of dementia (Sharma & Sharma, 2013; Sharma & Singh, 2013). Brain trauma causes a large increase in nitric oxide formation, and blocking its synthesis improves recovery (Hüttemann, et al., 2008; Gahm, et al., 2006). Organophosphates increase nitric oxide formation, and the protective anticholinergic drugs such as atropine reduce it (Chang, et al., 2001; Kim, et al., 1997). Stress, including fear (Campos, et al., 2013) and isolation (ZlatkoviÄ‡ and FilipoviÄ‡, 2013) can activate the formation of nitric oxide, and various mediators of inflammation also activate it. The nitric oxide in a person's exhaled breath can be used to diagnose some diseases, and it probably also reflects the level of their emotional well-being.

The increase of cholinesterase by enriched living serves to protect tissues against an accumulation of acetylcholine. The activation of nitric oxide synthesis by acetylcholine tends to block energy production, and to activate autolytic or catabolic processes, which are probably involved in the development of a thinner cerebral cortex in isolated or stressed animals. Breaking down acetylcholine rapidly, the tissue renewal processes are able to predominate in the enriched animals.

Environmental conditions that are favorable for respiratory energy production are protective against learned helplessness and neurodegeneration, and other biological problems that involve the same mechanisms. Adaptation to high altitude, which stimulates the formation of new mitochondria and increased thyroid (T3) activity, has been used for many years to treat neurological problems, and the effect has been demonstrated in animal experiments (Manukhina, et al., 2010). Bright light can reverse the cholinergic effects of inescapable stress (Flemmer, et al., 1990).

During the development of learned helplessness, the T3 level in the blood decreases (Helmreich, et al., 2006), and removal of the thyroid gland creates the "escape deficit," while supplementing with thyroid hormone before exposing the animal inescapable shock prevents its development (Levine, et al., 1990). After learned helplessness has been created in rats, supplementing with T3 reverses it (Massol, et al., 1987, 1988).

Hypothyroidism and excess cholinergic tone have many similarities, including increased formation of nitric oxide, so that similar symptoms, such as muscle inflammation, can be produced by cholinesterase inhibitors such as Tacrine, by increased nitric oxide, or by simple hypothyroidism (Jeyarasasingam, et al., 2000; Franco, et al., 2006).

Insecticide exposure has been suspected to be a factor in the increased incidence of Alzheimer's disease (Zaganas, et al., 2013), but it could be contributing to many other problems, involving inflammation, edema, and degeneration. Another important source of organophosphate poisoning is the air used to pressurize airliners, which can be contaminated with organophosphate fumes coming from the engine used to compress it.

Possibly the most toxic component of our environment is the way the society has been designed, to eliminate meaningful choices for most people. In the experiment of Freund,*et al.*, some mice became more exploratory because of the choices they made, while others' lives became more routinized and limited. Our culture reinforces routinized living. In the absence of opportunities to vary the way you work and live to accord with new knowledge that you gain, the nutritional, hormonal and physical factors have special importance.

Supplements of thyroid and progesterone are proven to be generally protective against the cholinergic threats, but there are many other factors that can be adjusted according to particular needs. Niacinamide, like progesterone, inhibits the production of nitric oxide, and also like progesterone, it improves recovery from brain injury (Hoane, et al., 2008). In genetically altered mice with an Alzheimer's trait, niacinamide corrects the defect (Green, et al., 2008). Drugs such as atropine and antihistamines can be used in crisis situations. Bright light, without excess ultraviolet, should be available every day.

The cholinergic system is much more than a part of the nervous system, and is involved in cell metabolism and tissue renewal. Most people can benefit from reducing intake of phosphate, iron, and polyunsaturated fats (which can inhibit cholinesterase; Willis, et al., 2009), and from choosing foods that reduce production and absorption of endotoxin. And, obviously, drugs that are intended to increase the effects of nitric oxide and acetylcholine should be avoided.