Estrogen and brain aging in men and women: Depression, energy, stress

---

From the original article in 2009. Author: Ray Peat.

Although the incidence of Alzheimer's disease is 2 or 3 times as high among women as among men, there is a major campaign under way to convince the public that taking estrogen supplements will prevent the disease. Estrogen is now mainly promoted to prevent osteoporosis (another problem that is more common in women) and heart disease (which is more common in men).

This substance, which came into medical use as "the female hormone" for the treatment of "female problems," especially for improving fertility, and then for preventing fertility as the oral contraceptive, is now being aimed primarily at the post-reproductive population, for problems that are essentially unrelated to femininity. It is, in fact, being presented to the public as something to prevent major age-related conditions.

Brain degeneration, like osteoporosis, takes years to develop. Analysis of letters written by young women, for example, showed limited mental functioning in those who many years later developed Alzheimer's disease, and young women who have small bones are the ones most likely to develop osteoporosis later. **It seems clear that the course of degenerative aging processes is set in young adulthood (or even earlier), and that it is never too early to be concerned with correcting processes that are going in the wrong direction.** (See Walker, et al., 1988, and Smith, et al., 1992.)

In "The Biological Generality of Progesterone" (1979) I proposed that the life-long trajectory of energy production and longevity was strongly influenced by prenatal nutrition and progesterone. This idea was based on work by people such as Marion Diamond, who showed that prenatal progesterone enlarges the cortex of the brain, and that estrogen makes it smaller, and Leonell Strong, who showed that a treatment that lowered the estrogen function in a young mouse could produce cancer-free offspring for several generations. Strong's work was very encouraging, because it showed that biological problems that had been "bred in" over many generations could be corrected by some simple metabolic treatments.

Seeing these profoundly toxic long-range effects of estrogen, which shaped the animal's growth, development, function, and even its heredity, made it important to learn how estrogen works, because such fundamental changes covering the whole range of biology, produced by a simple little molecule, promised to reveal interesting things about the nature of life.

Aging is an energy problem, and in the brain, which has extremely high energy requirements, interference with the energy supply quickly causes cells to die.

I believe that estrogen's "principle," in all of its actions, is to interfere with the respiratory mode of energy production. This is an integrating principle that explains estrogen's immediate, direct effects on cells and organisms, which aren't explained by the idea that it acts on the genes through a specific "estrogen receptor." (It's hard to imagine, for example, how the "estrogen receptor" doctrine could explain the fact that a single injection of estrogen can kill a large portion of brain cells.) It explains why estrogen causes cells to take up water, allowing calcium to enter, activating various enzymes and cell division. On the organismic level, it explains why estrogen mimics "shock," releasing histamine and activating the nervous and glandular stress response system. The inefficiency of metabolism which doesn't use oxygen in the normal way causes glucose to be used rapidly, and this in itself is enough to trigger the release of pituitary ACTH and adrenal cortisol. The ACTH, and related hormones, liberate free fatty acids, which cells take up instead of glucose, and this (in the so-called Randall cycle) further limits the body's ability to oxidize glucose.

People have spoken of "cascades" in relation to the adrenal glucocorticoids (e.g., cortisol) and estrogen, leading to cell damage, but really both of these hormonal cascades have to be seen as part of a more general collapse of adaptive systems, as a result of both chronic and immediate inadequacies of energy production.

Estrogen activates the adrenal stress reaction by way of the hypothalamus and pituitary, by direct actions on the adrenal glands, and by a variety of indirect effects, such as the increase of free fatty acids. It activates the excitotoxic glutamic acid pathway, and interferes with protective adenosine inhibition of nerves. It has both direct and indirect ways of promoting the formation of nitric oxide and carbon monoxide. These, and other estrogen-promoted factors, quickly and seriously interfere with mitochondrial respiration. Many of these effects contribute to increased intracellular calcium and free radical production, contributing to both the excitatory excess and the energy deficit.

The biochemical details of these cascades are mainly interesting because they show how many different kinds of stress converge on a few physiological processess--mitochondrial energy production, cellular excitation, and intercellular communication--which, when damaged thousands of times, lead to the familiar states of old age. These few functions, damaged by an infinite variety of stresses, have their own complexly adaptive ways of deteriorating, producing the various degenerative diseases.

This perspective brings dementia, heart failure, autoimmunity, immunodeficiency and other diseases of aging together, in ways that allow generalized therapeutic and preventive approaches.

The antistress, antiestrogen approaches become fundamental to prevention of aging.

The pro-estrogenic nature of the unsaturated fatty acids is probably the biggest barrier to the radical elimination of degenerative diseases. Various saturated fatty acids, including butyric, octanoic, and palmitic, have protective effects on

mitochondrial respiration.

Progesterone is the basic brain-protective antiestrogen. It works to protect the brain at many levels (preventing lipid peroxidation, exitotoxicity, nitric oxide damage, energy deficit, edema, etc.) and it promotes repair and recovery.

Progesterone in most cases has effects opposite to estrogen's, improving mitochondrial energy production while preventing excessive excitation. Along with pregnenolone, progesterone is recognized as a neurosteroid with anti-excitotoxic actions, with the ability to promote repair and regeneration of the nervous system. (Roof, Stein, Faden; Schumacher, et al.; Baulieu.)

The use of aspirin, which reduces inflammation and inhibits the formation of neurotoxic prostaglandins, is known to be associated with a lower incidence of Alzheimer's disease, and in other contexts, it offers protection against estrogen. Naloxone, the antiendorphin, has been found to reverse some of the cumulative effects of stress, restoring some pituitary and ovarian function, and it promotes recovery after brain injury; in a variety of ways, it corrects some of estrogen's toxic effects.

Adenosine helps to maintain brain glycogen stores, which are lost in stress and aging. Vitamin B12 protects against nitric oxide, and improves alertness.

Pyruvic acid has brain-protective effects, apparently through its decarboxylation (producing carbon dioxide) rather than through its use as an energy source, since other ketoacids are similarly protective. (The ketoacids occur in some natural foods.) The directly brain-protective effect of carbon dioxide offers many clues that should be interpreted in relation to estrogen's toxicity, since many of their effects on nerves are opposite. **Estrogen blocks the production of energy while it stimulates nerve cells to use energy more rapidly, and carbon dioxide promotes the production of energy, while restraining the excitation which expends energy.** The presence of carbon dioxide is an indicator of proper mitochondrial respiratory functioning.

Pharmaceutical blockers of glutamic acid transmission, and of calcium and sodium uptake, prevent some deterioration following brain injury, but the most physiological way to protect against those toxic processes is to maintain metabolic energy at a high level. Magnesium, which is protective against excitatory damage and is a calcium antagonist, tends to be retained in proportion to the activity of thyroid hormone.

As I have discussed previously, progesterone alone has brought people out of post-epileptic dementia and senile dementia, but it is reasonable to use a combined physiological approach, including thyroid.

Besides providing new insights into biological energy and aging, the recognition that estrogen activates the stress hormone system--the pituitary-adrenal system--also provides clear insights into other problems, such as the polycystic ovary syndrome, hirsutism, adrenal hyperplasia, Cushing's disease, etc.

References

[The references are clustered into groups, showing estrogen's indirect toxicity through its activation of the adrenal hormones, its direct brain-toxicity, and some of the interactions between these and fats, nitric oxide, etc.]

Stress 1996 Jul;1(1):1-19 **Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion.** Sapolsky RM Department of Biological Sciences, Stanford University, Stanford, CA 94305. **An extensive literature demonstrates that glucocorticoids (GCs), the adrenal steroids secreted during stress, can have a broad range of deleterious effects in the brain. The actions occur predominately, but not exclusively, in the hippocampus, a structure rich in corticosteroid receptors and particularly sensitive to GCs. The first half of this review considers three types of GC effects: a) GC-induced atrophy, in which a few weeks' exposure to high GC concentrations or to stress causes reversible atrophy of dendritic processes in the hippocampus; b) GC neurotoxicity where, over the course of months, GC exposure kills hippocampal neurons; c) GC neuroendangerment, in which elevated GC concentrations at the time of a neurological insult such as a stroke or seizure impairs the ability of neurons to survive the insult. The second half considers the rather confusing literature as to the possible mechanisms underlying** these deleterious GC actions. Five broad themes are discerned: a) that GCs induce a metabolic vulnerability in neurons due to inhibition of glucose uptake; b) that GCs exacerbate various steps in a **damaging cascade of glutamate excess, calcium mobilization and oxygen radical generation. In a review a number of years ago, I concluded that these two components accounted for the deleterious GC effects. Specifically, the energetic vulnerability induced by GCs left neurons metabolically compromised, and less able to carry out the costly task of containing glutamate, calcium and oxygen radicals. More recent work has shown this conclusion to be simplistic, and GC actions are shown to probably involve at least three additional components: c) that GCs impair a variety of neuronal defenses against neurologic insults; d) that GCs disrupt the mobilization of neurotrophins; e) that GCs have a variety of electrophysiological effects which can damage neurons.** The relevance of each of those mechanisms to GC-induced atrophy, neurotoxicity and neuroendangerment is considered, as are the likely interactions among them.

J Clin Endocrinol Metab 1996 Oct;81(10):3639-43 **Short-term estradiol treatment enhances pituitary-adrenal axis and sympathetic responses to psychosocial stress in healthy young men.** Kirschbaum C, Schommer N, Federenko I, Gaab J, Neumann O, Oellers M, Rohleder N, Untiedt A, Hanker J, Pirke KM, Hellhammer DH Center for Psychobiological, University of Trier, Germany. **Evidence from animal studies and clinical observations suggest that the activity of the pituitary-adrenal axis is under significant influence of sex steroids. The present study investigated how a short term elevation of estradiol levels affects ACTH, cortisol, norepinephrine, and heart rate responses to mental stress in healthy men.** In a double blind study, 16 men received a patch delivering 0.1 mg estradiol/day transdermally, and age- and body mass index-matched control subjects received a placebo patch. Twenty-four to 48 h later, they were exposed to a brief psychosocial stressor (free speech and mental arithmetic in front of an audience). In response to the psychosocial stressor, ACTH, cortisol, norepinephrine, and heart rate were increased in both experimental groups (all $P < 0.0001$). However, the **estradiol-treated subjects showed exaggerated peak ACTH ($P < 0.001$) and cortisol ($P < 0.002$) responses compared to the placebo group. Also, the norepinephrine area under the response curve was greater in the estradiol group** ($P < 0.05$). Although heart rate responses differences failed to reach statistical significance, they, too, tended to be larger in the estradiol group. Neither mood ratings before or after the stressor, nor ratings of the perception of the stressor could explain the observed endocrine response differences. In conclusion, **short term estradiol administration resulted in hyperresponses of the**

pituitary-adrenal axis and norepinephrine to psychosocial stress in healthy young men independent of psychological effects, as assessed in this study.

J Appl Physiol 1996 Mar;80(3):931-9 **Treadmill exercise training and estradiol increase plasma ACTH and prolactin after novel footshock.** White-Welkley JE, Warren GL, Bunnell BN, Mougey EH, Meyerhoff JL, Dishman RK "We examined whether rats that were treadmill exercise trained (Tr) or chronically immobilized (CI) had similar responses by the hypothalamic-pituitary-adrenal (HPA) cortical axis to acute stress and whether the HPA responses interacted with the hypothalamic-pituitary-gonadal (HPG) axis." **"[ACTH] and [prolactin**] after **footshock were higher in Tr rats with E2 compared with CI and sedentary rats without E2;** recovery levels for sedentary animals were higher after Run compared with Im. The elevation in [corticosterone] from minute 1 to 15 of recovery was higher after the familiar Run and Im conditions. Our findings are consistent with an increased responsiveness of the HPA axis to novel footshock after treadmill exercise training that is additionally modulated by the HPG axis."

Endocrinology 1992 Sep;131(3):1261-9. **Chronic estrogen-induced alterations in adrenocorticotropin and corticosterone secretion, and glucocorticoid receptor-mediated functions in female rats.** Burgess LH, Handa RJ "The effect of estrogen (E) on the hypothalamic-pituitary-adrenal axis was investigated in female Sprague-Dawley rats." "...the ACTH and CORT secretory responses to ether stress could be suppressed by exogenous RU 28362 (a specific glucocorticoid receptor agonist; 40 micrograms/100 g BW for 4 days) in OVX controls (P less than 0.05), **but not in E-treated animals.** These data suggest that E can impair glucocorticoid receptor-mediated delayed o r slow negative feedback." "Thus, E **treatment results in a loss of the glucocorticoid receptor's ability to autoregulate; this suggests that E may cause a functional impairment of the glucocorticoid receptor even though receptor binding appears normal. These findings suggest that hyperactivation of the hypothalamic-pituitary-adrenal axis after stress in E-treated rats is due in part to impaired glucocorticoid receptor-mediated slow negative feedback."**

Am J Physiol 1994 Jul;267(1 Pt 1):E32-8 **Lesions of hypothalamic paraventricular nuclei do not prevent the effect of estradiol on energy and fat balance.** Dagnault A, Richard D. **"Plasma levels of corticosterone and ACTH were higher in E2-treated rats than in animals receiving the placebo treatment. The present results provide evidence that the hypothalamic PVH is not an essential neuroanatomical structure in the effects of E2 on energy and fat balances."**

Fertil Steril 1994 Oct;62(4):738-43 **Ovarian suppression reduces clinical and endocrine expression of late-onset congenital adrenal hyperplasia due to 21-hydroxylase deficiency.** Carmina E, Lobo RA "OBJECTIVE: To determine the effectiveness of GnRH-agonist (GnRH-a) treatment in women with late onset congenital adrenal hyperplasia." "CONCLUSIONS: Suppression of the ovary with GnRH-a treatment was beneficial in these patients with late-onset congenital adrenal hyperplasia. An ovarian influence on the clinical and biochemical findings of the disorder is suggested."

Life Sci 1995;57(9):833-7. **Effects of sex hormones on the steroidogenic activity of dispersed adrenocortical cells of the rat adrenal cortex.** Nowak KW, Neri G, Nussdorfer GG, Malendowicz LK "The effect of 17 beta-estradiol and testosterone on glucocorticoid secretion were studied in vitro by using dispersed inner adrenocortical cells obtained from gonadectomized female and male rats. Independently of the sex of animals, estradiol enhanced basal, but not ACTH-stimulated corticosterone (B) secretion; conversely, testosterone inhibited ACTH-stimulated, but not basal B output." "Testosterone inhibited by about 30% ACTH-stimulated PREG production and by about 54% total post-PREG secretion (B was decreased to 56% of the control value, and other steroid hormones were below the limit of sensitivity of our assay system). These findings indicate that sex hormones directly affect rat adrenocortical secretion, **mainly by acting on the rate-limiting step of steroidogenesis (i.e. the conversion of cholesterol to PREG); moreover, they suggest that testosterone is also able depress the activity of the enzymes operating distally to cholesterol side-chain cleavage."**

J Endocrinol 1995 Feb;144(2):311-21 **The influence of ovarian steroids on hypothalamic-pituitary-adrenal regulation in the female rat.** Carey MP, Deterd CH, de Koning J, Helmerhorst F, de Kloet ER "The present study examined the association between hypothalamic- pituitary-adrenal (HPA) and hypothalamic-pituitary-ovarian axes. HPA activity determined by plasma levels of adrenocorticotropin (ACTH) and corticosterone (B) was assessed in intact female rats as a function of oestrous cycle stage under resting conditions and after exposure to a 20 min restraint stress. To delineate the roles of oestradiol and progesterone in HPA axis modulation, plasma concentrations of ACTH and B were determined in ovariectomised (OVX) animals treated with oestradiol and/or progesterone under resting conditions and during exposure to the stress of a novel environment. The effects of these steroid treatments on the transcription and/or binding properties of the two corticosteroid receptors, the mineralocorticoid (MR) and glucocorticoid (GR) receptors, were also examined in hippocampal tissue, (i) Fluctuations in basal and **stress-induced plasma ACTH and B concentrations were found during the oestrous cycle with highest levels at late pro-oestrus. (ii) In OVX steroid-replaced animals, basal and stress-induced activity was enhanced in oestradiol and oestradiol plus progesterone-treated animals compared with OVX controls."** "In conclusion, we find that sex steroids modulate HPA activity and **suggest that the observed effects of these steroids on hippocampal MR may underlie their concerted mechanism of action in inducing an enhanced activity at the period of late pro-oestrus."**

J Clin Endocrinol Metab 1995 Feb;80(2):603-7 **The impact of estrogen on adrenal androgen sensitivity and secretion in polycystic ovary syndrome.** Ditkoff EC, Fruzzetti F, Chang L, Stancyzk FZ, Lobo RA **"Adrenal hyperandrogenism is a common feature of patients with polycystic ovary syndrome (PCO).** This may be due to enhanced adrenal sensitivity to ACTH. **Because enhanced ovarian androgen secretion does not appear to explain this phenomenon, we explored the role of estrogen in inducing enhanced adrenal sensitivity, in that a state of relative hyperestrogenism exists in PCO."** "Steroid ratio **responses to oCRH suggested that 17,20-desmolase activity (delta maximum change in the ratio of A4/17-hydroxyprogesterone) was lowered with estrogen suppression and increased again after transdermal E2 administration."** "In conclusion, these data provide **evidence that estrogen is at least one factor that influences adrenal androgen sensitivity in PCO and may help explain the frequent finding of adrenal hyperandrogenism in this syndrome."**

Endocrinology 1993 Nov;133(5):2284-91 **Estrogen and hydroxysteroid sulfotransferases in guinea pig adrenal cortex: cellular and subcellular distributions.** Whitnall MH, Driscoll WJ, Lee YC, Strott CA "The high concentration of EST immunoreactivity in nuclei suggests that EST may play a role in modulating the **ability of active estrogens to regulate gene expression in ACTH-responsive cells. The distribution of HST labeling suggests that sulfonation of adrenocortical 3-hydroxysteroids takes place largely within smooth endoplasmic reticulum in the zona reticularis in adult guinea pigs."**

J Clin Endocrinol Metab 1993 Sep;77(3):754-8. **Interaction of insulin-like growth factor-II and estradiol directs steroidogenesis in the human fetal adrenal toward dehydroepiandrosterone sulfate production.** Mesiano S, Jaffe RB

J Clin Endocrinol Metab 1993 Aug;77(2):494-7. **Estradiol stimulates cortisol production by adrenal cells in estrogen-dependent primary adrenocortical nodular dysplasia.** Caticha O, Odell WD, Wilson DE, Dowdell LA, Noth RH, Swislocki AL, Lamothe JJ, Barrow R. Adrenal glands from a patient with ACTH-independent Cushing's syndrome, whose symptoms worsened during pregnancy and oral contraceptive use, were cultured in different concentrations of estradiol. Estradiol stimulated cortisol secretion in a dose-response manner in the absence of ACTH." . "This is the first description of estradiol stimulation of cortisol production by cultured adrenal cells in ACTH-independent Cushing's syndrome."

Endocrinology 1992 Nov;131(5):2430-6 **Effects of gonadectomy and sex hormone therapy on the endotoxin-stimulated hypothalamo-pituitary-adrenal axis: evidence for a neuroendocrine-immunological sexual dimorphism.** Spinedi E, Suescun MO, Hadid R, Daneva T, Gaillard RC "Bacterial lipopolysaccharide (LPS) stimulates the hypothalamo-pituitary-adrenal axis by a mechanism involving the release of cytokines, which activate the CRH-ACTH system and, as a result, increase glucocorticoid secretion. **In the present study we investigated the possibility that endogenous sex hormones modulate the in vivo endotoxin-stimulated adrenal and immune responses in adult BALB/c mice."** "Our results indicate that 1) **randomly cycling female mice have significantly more pronounced corticosterone secretion than males 2 h after endotoxin** injection, although the tumor necrosis factor responses were similar....".

J Neurosci Res 1995 Oct 1;42(2):228-35 **Activation of the hypothalamo-anterior pituitary corticotropin- releasing hormone, adrenocorticotropin hormone and beta-endorphin systems during the estradiol 17 beta-induced plasma LH surge in the ovariectomized monkey.** Kerdelhue B, Jones GS, Gordon K, Seltman H, Lenoir V, Melik Parsadaniantz S, Williams RF, Hodgen GD. "These results suggest that there **may be a marked activation of the hypothalamo-anterior pituitary-adrenal axis during the negative and positive feedback phases of the E2B-induced LH surge in the ovariectomized monkey."**

Biol Reprod 1995 Nov;53(5):996-1002 **Activation of the baboon fetal pituitary-adrenocortical axis at midgestation by estrogen: responsivity of the fetal adrenal gland to adrenocorticotropic hormone in vitro.** Berghorn KA, Albrecht ED, Pepe G.J.

Fertil Steril 1996 May;65(5):950-3 **Ovarian hyperstimulation augments adrenal dehydro- epiandrosterone sulfate secretion.** Casson PR, Kristiansen SB, Umstot E, Carson SA, Buster JE.

Hinyokika Kiyo 1997 Apr;43(4):275-8 **[A case of concurrent bilateral adrenocortical adenoma causing Cushing's syndrome].** Koga F, Sumi S, Umeda H, Maeda S, Honda M, Hosoya Y, Yano M, Konita A, Suzuki S, Yoshida K. "All 14 previously reported cases of bilateral adrenocortical adenoma (BAA) causing Cushing's syndrome as well as the present case were **concurrent and dominant in females of reproductive age. This suggests that some cofactors other than ACTH, such as estrogen, contribute to the pathogenesis of BAA."**

Endocrinology 1991 Nov;129(5):2503-11 **Variations in the hypothalamic-pituitary-adrenal response to stress during the estrous cycle in the rat.** Viau V, Meaney MJ. **"In cycling rats, we found significantly higher peak ACTH (P less than 0.01) and B (P less than 0.05) responses to stress during proestrus** compared to the estrous and diestrous phases." "In response to **stress, ACTH levels were higher (P less than 0.01) in the E' group compared to the EP' and O' groups.** Although the peak B response was similar in all groups, the E' and EP' groups secreted more B after the termination of stress than did the O' group. Within the 20 min stress period, **ACTH levels in the E' group were significantly (P less than 0.05) higher at 5, 10, and 15 min after the onset of stress, compared to the EP' and O' groups. Plasma B levels were significantly higher in the E' group at 5 and 10 min (P less than 0.05 and P less than 0.01, respectively) compared to the EP' and O' group. beta-endorphin-like immunoreactive responses to restraint stress were also significantly higher in the E' group compared to the EP' (P less than 0.05) and O'** (P less than 0.01) groups. In contrast to the effect seen at 24 h, ACTH responses to stress 48 h after E2 injection in the E' group were comparable to O' animals. There was no effect of E2 on ACTH clearance, whereas B clearance was enhanced in E' treated animals vs. O'-treated animals. These results indicate that the HPA axis in the female rat is most sensitive to stress during proestrous. Such enhanced HPA responses to stress are limited to the early portion of proestrous, **as progesterone appears to inhibit the facilitatory effects of estrogen on ACTH release during stress.** Taken together, these results suggest an ovarian influence on both activational and inhibitory components of HPA activity."

Semin Reprod Endocrinol 1997 May;15(2):137-57 **Adrenal involvement in polycystic ovary syndrome.** Gonzalez F. "Whereas 17,20 lyase hyperactivity diagnosed by defined criteria in response to pharmacological ACTH may be an intrinsic genetic defect, **increases in 17,20 lyase activity and adrenal androgen hyper-responsiveness to ACTH in response to physiological ACTH may be promoted by the functional elevation of estrogen of ovarian origin in PCOS.** The latest in vitro data suggest the estrogen may elicit its effect on the adrenal cortex through a receptor mediated mechanism."

Metabolism 1997 Aug;46(8):902-7. **Mild adrenal and ovarian steroidogenic abnormalities in hirsute women without hyperandrogenemia: does idiopathic hirsutism exist?** Escobar-Morreale HF, Serrano-Gotarredona J, Garcia-Robles R, Sancho J, Varela C **"Basal and ACTH-stimulated 17OHP and delta 4-A, and stimulated DHEA concentrations were reduced with ovarian suppression,** but their net increment and ratio to the increase of F in response to ACTH remained unchanged, **reflecting the ovarian contribution to the secretion of these steroids."**.

Am J Physiol 1997 Apr;272(4 Pt 2):R1128-34. **Modulation of ovine fetal adrenocorticotropin secretion by androstenedione and 17beta-estradiol.** Saoud CJ, Wood CE "Parturition in sheep is initiated by increases in activity of the fetal hypothalamic-pituitary-adrenal axis. We **have previously reported that cortisol negative feedback efficacy is decreased at the end of gestation.** The present study was designed to test the hypothesis that **increasing plasma estrogen and/or androgen concentrations in the fetus might increase plasma adrenocorticotropic hormone (ACTH) concentration, either by stimulating ACTH secretion or by altering the negative feedback** effect of cortisol on ACTH." "We conclude that increased fetal cortisol and ACTH secretion at the end of gestation may be due to the combined effects of the gonadal steroids in that **estradiol increases basal plasma ACTH secretion while androstenedione reduces cortisol negative feedback efficacy."**

J Clin Endocrinol Metab 1998 Sep;83(9):3083-8. **Menstrual abnormalities in women with Cushing's disease are correlated with hypercortisolemia rather than raised circulating androgen levels.** Lado-Abeal J, Rodriguez-Arnao J, Newell-Price JD, Perry LA, Grossman AB, Besser GM, Trainer PJ.

Eur J Endocrinol 1998 Apr;138(4):430-5. **Hypothalamo-pituitary-adrenal axis and adrenal function before and after ovariectomy in premenopausal women.** De Leo V, la Marca A, Talluri B, D'Antona D, Morgante G **The hypothalamo-pituitary-adrenal (HPA) axis is modulated by sex hormones. Few data exist on the relation between acute estrogen deficit and HPA axis response to corticotropin-releasing hormone (CRH).** The effects of a sudden drop in estradiol levels on basal and CRH-stimulated levels of ACTH, cortisol, testosterone, androstenedione and 17-hydroxyprogesterone (17-OHP) were assessed in nine premenopausal women (44-48 years of age), before and after ovariectomy. The CRH test was performed before and 8 days after ovariectomy. **A significant reduction in ACTH and adrenal steroids but not in cortisol response to CRH was observed after ovariectomy.** The ratio of deltamax androstenedione/17-OHP after CRH stimulation was substantially the same before and after ovariectomy, whereas **deltamax 17-OHP/cortisol was significantly lower in ovariectomized** women showing increased 21- and 11beta-hydroxylase activity. The results show that the acute estrogen deficit induces changes in the HPA xis characterized by **reduced stimulated secretion of ACTH and steroids** but normal stimulated cortisol production.

Biokhimiia 1987 Sep;52(9):1501-11 **[Activation of lipolysis and ketogenesis in tumor-bearing animals as a reflection of chronic stress states].** [Article in Russian] Chekulaev VA, Shelepov VP, Pasha-zade GR, Shapot VS In order to elucidate the peculiarities of brain metabolism in tumour-bearing organisms, the arterio-venous (A-V) content of glucose, acetoacetate (Ac-Ac), beta-hydroxybutyrate (beta-HB) and non-esterified fatty acids (NEFA) in growing Zajdela ascite hepatoma (ZAH) and solid hepatoma 27 (H-27) was compared. Analysis of

metabolic patterns of healthy, starving and fed recipients (ZAH and H-27) revealed the inadequacy of the concepts on anorexia as being the cause of carbohydrate-lipid metabolic disturbances. In tumour-bearing organisms **lipolysis and ketogenesis reflect the tumour-induced chronic stress.** Absorption of beta-HB and release of Ac-Ac by brain were observed at all stages of malignant growth. **This is probably due to a partial switch-over of brain metabolism to non-carbohydrate energy sources.** Besides, certain stages of tumour growth are associated with **active assimilation of NEFA by brain.** A correlation between the A-V difference with respect to glucose and Ac-Ac as well as between the glucose and NEFA contents was established. It was assumed that the A-V difference in glucose is the main regulator of ketone body metabolism.

R. Sanchez Olea, et al., **"Inhibition by polyunsaturated fatty acids of cell volume regulation and osmolyte fluxes in astrocytes,"** Amer. J. of Physiology--cell physiology 38(1), C96-C102, 1995. **"...potent blockers of regulatory volume decrease and of the swelling-activated efflux of taurine, D-aspartate,** inositol, and I-125 (used as marker of Cl). **...oleic and ricinoleic acids and saturated fatty acids were ineffective." "...polyunsaturated fatty acids directly inhibit the permeability pathways correcting cell volume after swelling in cultured astrocytes."**

P. H. Chan and R. A. Fishman, "**Brain edema: Induction in cortical slices by polyunsaturated fatty acids**," Science 201, 358-369, 1978. "This cellular edema was specific, since **neither saturated fatty acids nor a fatty acid containing a single double bond had such effect**."

Endocrinology 1992 Aug;131(2):662-8 **Estradiol selectively regulates agonist binding sites on the N-methyl-D-aspartate receptor complex in the CA1 region of the hippocampus.** Weiland NG. Laboratory of Neuroendocrinology, Rockefeller University. **"Estradiol alters cognitive function and lowers the threshold for seizures in women and laboratory animals. Both of these activities are modulated by the excitatory neurotransmitter glutamate in the hippocampus. To assess the hypothesis that estradiol increases the sensitivity of the hippocampus to glutamate activation by increasing glutamate binding sites, the densities of N-methyl-D-aspartate (NMDA) agonist sites...."** "Two days of estradiol treatment increased the density of NMDA agonist, but not of competitive nor noncompetitive NMDA antagonist binding sites exclusively in the CA1 region of the hippocampus." **"The increase in NMDA agonist sites with ovarian hormone treatment should result in an increase in the sensitivity of the hippocampus to glutamate activation which may mediate some of the effects of estradiol on learning and epileptic seizure activity."**

J Neurochem 1994 Sep;63(3):953-62 **Corticosterone regulates heme oxygenase-2 and NO synthase transcription and protein expression in rat brain.** Weber CM, Eke BC, Maines MD. **"We suggest that glucocorticoid-mediated deficits in hippocampal functions may reflect their negative effect on messenger-generating systems."**

Gen Pharmacol 1993 Nov;24(6):1383-6 **Changes in microtubular tau protein after estrogen in a cultured human neuroblastoma cell line.** Lew GM. **"4. The estrogen (10(-7) M) also caused a 31% reduction in the total number of cells."**

Rodriguez, P; Fernandez-Galaz, C; Tejero, A. **Controlled neonatal exposure to estrogens: A suitable tool for reproductive aging studies in the female rat.** Biology of Reproduction, v.49, n.2, (1993): 387-392.

O'Rourke, M T; Lipson, S F; Ellison, P T. **Ovarian function in the latter half of the reproductive lifespan.** American Journal of Human Biology, v.8, n.6, (1996): 751-759.

Schumacher, M; Robel, P; Baulieu, E-E. **Development and regeneration of the nervous system: A role for neurosteroids.** Developmental Neuroscience, v.18, n.1-2, (1996): 6-21.

Life Sci 1996;58(17):1461-7 **The endogenous estrogen metabolite 2-methoxyestradiol induces apoptotic neuronal cell death in vitro.** Nakagawa-Yagi Y, Ogane N, Inoki Y, Kitoh N. "We examined the effects of 2-methoxyestradiol, a metabolite of estradiol, on cell death in retinoic acid (RA)-differentiated neuroblastoma SH-SY5Y cell cultures. **Cell death was induced by 2-methoxyestradiol in a concentration- dependent manner**." **[**Provides evidence] **"...for an endogenous neuroactive steroid metabolite in the etiology of some neurodegenerative diseases."**

Recent Prog Horm Res 1997;52:279-303 **Aging of the female reproductive system: a window into brain aging.** Wise PM, Kashon ML, Krajnak KM, Rosewell KL, Cai A, Scarbrough K, Harney JP, McShane T, Lloyd JM, Weiland NG **"The menopause marks the permanent end of fertility in women. It was once thought that the exhaustion of ovarian follicles was the single, most important explanation for the transition to the menopause. Over the past decade, this perception has gradually changed with the realization that there are multiple pacemakers of reproductive senescence. We will present evidence that lends credence to the hypothesis that the central nervous system is a critical pacemaker of reproductive aging and that changes at this level** contribute to the timing of the menopause."

Neuroendocrinology 1989 Nov;50(5):605-612 **N-methyl-aspartic acid lesions of the arcuate nucleus in adult C57BL/6J mice: a new model for age-related lengthening of the estrous cycle.** May PC, Kohama SG, Finch CE. "We report a new effect of the excitotoxin N-methyl-aspartic acid (NMA) on adult mice. Besides confirming cell loss in the arcuate nucleus of animals treated as adults, we also observed lengthened estrous cycles. Cycling female C57BL/6J mice were treated with subcutaneous injections of NMA and estrous cycles monitored for 30 days. NMA treatment lengthened average estrous cycle length by 1 day, to 5.6 days." **"Consistent with the regional pattern of cell loss, little specific binding of any glutamatergic ligand was observed in the VMN. NMA caused weight gain in all age groups." "The transition from 4-day to 5- and 6-day estrous cycles produced by NMA treatment mimics the early age-related changes in estrous cycle patterns in rodents."** This new model will be useful in analyzing the contributions of neuroendocrine changes in the arcuate nucleus to reproductive senescence."

Pathologic effect of estradiol on the hypothalamus. Brawer JR; Beaudet A; Desjardins GC; Schipper HM. Biol Reprod, 1993 Oct, 49:4, 647-52. "In addition to its multiple physiological actions, we have shown that estradiol is also selectively cytotoxic to beta-endorphin neurons in the hypothalamic arcuate nucleus. The mechanism underlying this neurotoxic action appears to involve the conversion of estradiol to catechol estrogen and subsequent oxidation to o-semiquinone free radicals. The estradiol-induced loss of beta-endorphin neurons engenders a compensatory increment in mu opioid binding in the medial preoptic area rendering this region supersensitive to residual beta-endorphin or to other endogenous opioids. The consequent persistent opioid inhibition results in a cascade of neuroendocrine deficits that are ultimately expressed as a chronically attenuated plasma LH pattern to which the ovaries respond by becoming anovulatory and polycystic. This neurotoxic action of estradiol may contribute to a number of reproductive disorders in humans and in animals in which aberrant hypothalamic function is a major component."

Vitamin E protects hypothalamic beta-endorphin neurons from estradiol neurotoxicity. Desjardins GC; Beaudet A; Schipper HM; Brawer JR. Endocrinology, 1992 Nov, 131:5, 2482-4 **"Estradiol valerate (EV) treatment has been shown to result in the destruction of 60% of beta-endorphin neurons in the hypothalamic arcuate nucleus."**

Estrogen-induced hypothalamic beta-endorphin neuron loss: a possible model of hypothalamic aging. Desjardins GC; Beaudet A; Meaney MJ; Brawer JR. Exp Gerontol, 1995 May-Aug, 30:3-4, 253-67 Over the course of normal aging, all female mammals with regular

cycles display an irreversible arrest of cyclicity at mid-life. Males, in contrast, exhibit gametogenesis until death. **Although it is widely accepted that exposure to estradiol throughout life contributes to reproductive aging, a unified hypothesis of the role of estradiol in reproductive senescence has yet to emerge.** Recent evidence derived from a rodent model of chronic estradiol-mediated accelerated reproductive senescence now suggests such a hypothesis. It has been shown that chronic estradiol exposure results in the **destruction of greater than 60% of all beta-endorphin neurons in the arcuate nucleus** while leaving other neuronal populations spared. This loss of opioid neurons is prevented by treatment with antioxidants indicating that it results from **estradiol-induced formation of free radicals. Furthermore, we have shown that this beta-endorphin cell loss is followed by a compensatory upregulation of mu opioid receptors in the vicinity of LHRH cell bodies.** The increment in mu opioid receptors presumably renders the opioid target cells supersensitive to either residual beta-endorphin or other endogenous mu ligands, such as met-enkephalin, thus resulting in chronic opioid **suppression of the pattern of LHRH release, and subsequently that of LH.** Indeed, prevention of the neuroendocrine effects of estradiol by antioxidant treatment also **prevents the cascade of neuroendocrine aberrations resulting in anovulatory acyclicity.** The loss of beta-endorphin neurons along with the paradoxical opioid supersensitivity which ensues, provides a unifying framework in which to interpret the diverse features that characterize the reproductively senescent female.

The 21-aminosteroid antioxidant, U74389F, prevents estradiol-induced depletion of hypothalamic beta-endorphin in adult female rats. Schipper HM; Desjardins GC; Beaudet A; Brawer JR. Brain Res, 1994 Jul 25, 652:1, 161-3 **"A single intramuscular injection of 2 mg estradiol valerate (EV) results in neuronal degeneration and beta-endorphin depletion in the hypothalamic arcuate nucleus of adult female rats."**

J Neurochem 1998 Sep;71(3):1187-93 **Energy dependency of glucocorticoid exacerbation of gp120 neurotoxicity.** Brooke SM, Howard SA, Sapolsky RM "The HIV envelope glycoprotein, gp120, a well documented neurotoxin, may be involved in AIDS-related dementia complex. gp120 works through an NMDA receptor- and calcium-dependent mechanism to damage neurons. We have previously demonstrated that both natural and synthetic glucocorticoids (GCs) exacerbate gp120-induced neurotoxicity and calcium mobilization in hippocampal mixed cultures. GCs, steroid hormones secreted during stress, are now shown to work in conjunction with gp120 to decrease ATP levels and to work synergistically with gp120 to decrease the mitochondrial potential in hippocampal cultures. **Furthermore, energy supplementation blocked the ability of GCs to worsen gp120's effects on neuronal survival and calcium mobilization.** A GC-induced reduction in glucose transport in hippocampal neurons, as previously documented, may contribute to this energetic dependency. These results may have clinical significance, considering the common treatment of severe cases of Pneumocystis carinii pneumonia, typical of HIV infection, with large doses of synthetic GCs."

Acta Otolaryngol Suppl (Stockh) 1990;476:32-6. **Glutamate neurotoxicity in the cochlea: a possible consequence of ischaemic or anoxic conditions occurring in ageing.** Pujol R, Rebillard G, Puel JL, Lenoir M, Eybalin M, Recasens M.

Br J Pharmacol 1996 Jan;117(1):189-95. **Metabotropic glutamate receptors, transmitter output and fatty acids: studies in rat brain slices.** Lombardi G, Leonardi P, Moroni F. "The requirement of both unsaturated fatty acids and 1S,3R-ACPD in the facilitation of transmitter exocytosis may play an important role in the regulation of synaptic plasticity."

Adv Exp Med Biol 1992;318:147-58 **A role for the arachidonic acid cascade in fast synaptic modulation: ion channels and transmitter uptake systems as target proteins.** Volterra A, Trotti D, Cassutti P, Tromba C, Galimberti R, Lecchi P, Racagni G. "Recent evidence indicates that arachidonic acid (AA) and its metabolites play a fast messenger role in synaptic modulation in the CNS." "Other types of K+ channels in vertebrate excitable cells have been found to be **sensitive to arachidonic acid, lipoxygenase products, and polyunsaturated fatty acids (PUFA). In the mammalian CNS, arachidonic acid is released upon stimulation of N-methyl-D-aspartate (NMDA)-type glutamate receptors." "Polyunsaturated fatty acids mimic arachidonate with a rank of potency parallel to the degree of unsaturation. Since the effect of glutamate on the synapses is terminated by diffusion and uptake, a slowing of the termination process may potentiate glutamate synaptic efficacy. However, excessive extracellular accumulation of glutamate may lead to neurotoxicity."**

J Neurochem 1999 Jan;72(1):129-38**. Transient inhibition of glutamate uptake in vivo induces neurodegeneration when energy metabolism is impaired.** Sanchez-Carbente MR, Massieu L. "Impairment of glutamate transport during ischemia might be related to the elevation of the extracellular concentration of glutamate and ischemic neuronal damage. Additionally, impairment of energy metabolism in vivo leads to neurodegeneration apparently mediated by a secondary excitotoxic mechanism. In vitro observations show that glucose deprivation and inhibition of energy metabolism exacerbate the toxic effects of glutamate." **"Our results show that glutamate uptake inhibition leads to marked neuronal damage in energy-deficient rats but not in intact animals...."**

J Neurochem 1998 Nov;71(5):1993-2005. **Glia modulate NMDA-mediated signaling in primary cultures of cerebellar granule cells.** Beaman-Hall CM, Leahy JC, Benmansour S, Vallano ML "Nordihydroguaiaretic acid, a lipoxygenase inhibitor, blocked NMDA-mediated toxicity in astrocyte-poor cultures, raising the possibility **that glia effectively reduce the accumulation of highly diffusible and toxic arachidonic acid metabolites in** neurons. Alternatively, glia may alter neuronal development/phenotype in a manner that selectively reduces susceptibility to NR-mediated toxicity."

J Neurosci 1997 Dec 1;17(23):9060-7**. Pyruvate protects neurons against hydrogen peroxide-induced toxicity.** Desagher S, Glowinski J, Premont J**. "Pyruvate strongly protected neurons against both H2O2 added to the external medium and H2O2 endogenously produced through the redox cycling of the experimental quinone menadione. The neuroprotective effect of pyruvate appeared to result rather from the ability of alpha-ketoacids to undergo nonenzymatic decarboxylation in the presence of H2O2 than from an improvement of energy metabolism. Indeed, several other alpha-ketoacids, including alpha-ketobutyrate, which is not an energy substrate, reproduced the neuroprotective effect of pyruvate. In contrast, lactate, a neuronal energy substrate, did not protect neurons from H2O2."** "Together, these results indicate that pyruvate efficiently protects neurons against both exogenous and endogenous H2O2. Its low toxicity and its capacity to cross the blood-brain barrier open a new therapeutic perspective in brain pathologies in which H2O2 is involved."

J Neurosci 1998 Jan 1;18(1):156-63**. Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's disease.** Matthews RT, Yang L, Jenkins BG, Ferrante RJ, Rosen BR, Kaddurah-Daouk R, Beal MF **.**

M. C. Diamond, ***Enriching Heredity: The Importance of the Environment on the Anatomy of the Brain.*** Free Press, N.Y., 1988.

C. Finch and L. Hayflick, ***Handbook of the Biology of Aging.*** Van Nostrand Reinhold, N.Y., 1977.

Swanson RA **Physiologic coupling of glial glycogen metabolism to neuronal activity in brain.** Can J Physiol Pharmacol, 1992, 70 Suppl:, S138-44. Brain glycogen is localized almost exclusively to glia, where it undergoes continuous utilization and resynthesis. We have shown that glycogen utilization increases during tactile stimulation of the rat face and vibrissae. **Conversely, decreased neuronal activity during hibernation and anesthesia is accompanied by a marked increase in brain glycogen content**. These observations support a link between neuronal activity and glial glycogen metabolism. The energetics of glycogen metabolism suggest that glial glycogen is mobilized to meet increased metabolic demands of glia rather than to serve as a substrate for neuronal activity. An advantage to the use of glycogen may be the potentially faster generation of ATP from glycogen than from glucose. Alternatively, glycogen could be utilized

if glucose supply is transiently insufficient during the onset of increased metabolic activity. Brain glycogen may have a **dynamic role as a buffer between the abrupt increases in focal metabolic demands that occur during normal brain activity and the compensatory changes in focal cerebral blood flow or oxidative metabolism.**

"Free fatty acids activate the hypothalamic-pituitary-adrenocortical axis in rats." Widmaier EP; Rosen K; Abbott B. *Endocrinology,* 1992 Nov, 131:5, 2313-8. "Intravenous administration of Intralipid 10% increases blood levels of essential free fatty acids." "Since corticosterone, the final secretory product of the rat hypothalamic-pituitary-adrenocortical (HPA) axis, is also lipolytic, we tested the hypothesis that FFA would inhibit the HPA axis." "At 60 min, plasma ACTH levels were significantly elevated to over 1500 pg/ml in Intralipid-infused rats, but were unchanged in saline controls. **This dose of Intralipid increased corticosterone levels by nearly 20-fold at 120 min. At 180 min, corticosterone levels were still significantly greater** than those in saline controls. Lower doses of Intralipid also significantly elevated both FFA and corticosterone levels, but by 180 min, levels of both were similar to those in controls." "The results suggest that high circulating FFA levels activate, rather than inhibit, the HPA axis in rats. Since stress activates glucocorticoid production and **increases FFA levels due to lipolysis, it is possible that FFA and the HPA axis constitute a previously unrecognized positive feedback loop."**

"Impairment of glucose disposal by infusion of triglycerides in humans: role of glycemia," Felley CP; Felley EM; van Melle GD; Frascarolo P; Jéquier E; Felber JP, Am J Physiol, 1989 Jun, 256:6 Pt 1, E747-52. **"These results suggest the existence of physiological regulatory mechanisms by which 1) the rise in plasma free fatty acid inhibits both oxidative and nonoxidative glucose disposal, and 2) the rise in glycemia stimulates predominantly nonoxidative glucose disposal."**

Nature 1998 Jan 15;391(6664):281-5**. Prostaglandins stimulate calcium-dependent glutamate release in astrocytes.** Bezzi P, Carmignoto G, Pasti L, Vesce S, Rossi D, Rizzini BL, Pozzan T, Volterra A**.** Astrocytes in the brain form an intimately associated network with neurons. They respond to neuronal activity and synaptically released glutamate by raising intracellular calcium concentration ([Ca2+]i), which could represent the start of back-signalling to neurons. **Here we show that coactivation of the AMPA/kainate and metabotropic glutamate receptors (mGluRs) on astrocytes stimulates these cells to release glutamate through a Ca2+-dependent process mediated by prostaglandins. Pharmacological inhibition of prostaglandin synthesis prevents glutamate release, whereas application of prostaglandins (in particular PGE2) mimics and occludes the releasing action of GluR agonists. PGE2 promotes Ca2+-dependent glutamate release from cultured astrocytes and also from acute brain slices under conditions that suppress neuronal exocytotic release.** When applied to the CA1 hippocampal region, PGE2 induces increases in [Ca2+]i both in astrocytes and in neurons. The [Ca2+]i increase in neurons is mediated by glutamate released from astrocytes, because it is abolished by GluR antagonists. **Our results reveal a new pathway of regulated transmitter release from astrocytes and outline the existence of an integrated glutamatergic cross-talk between neurons and astrocytes in situ that may play critical roles in synaptic plasticity and in neurotoxicity.**

Prog Neurobiol 1998 Jan;54(1):99-125**. Microglia as effector cells in brain damage and repair: focus on prostanoids and nitric oxide.** Minghetti L, Levi G. "The present article deals with two classes of compounds that activated microglial cells can produce in large amounts: prostanoids (that derive from arachidonic acid through the cyclooxygenase pathway), and nitric oxide (that is synthesized from arginine by nitric oxide synthase). Prostanoids and nitric oxide have a number of common targets, on which they may exert similar or opposite actions, and have a crucial role in the regulation of inflammation, immune responses and cell viability. Their synthesis can massively increase when the inducible isoforms of cyclooxygenase and nitric oxide synthase are expressed."

In Vitro Cell Dev Biol Anim 1998 Mar;34(3):265-74**. Prostaglandins act as neurotoxin for differentiated neuroblastoma cells in culture and increase levels of ubiquitin and beta-amyloid.** Prasad KN, La Rosa FG, Prasad JE**.** "Although chronic inflammatory reactions have been proposed to cause neuronal degeneration associated with Alzheimer's disease (AD), the role of prostaglandins (PGs), one of the secretory products of inflammatory reactions, in degeneration of nerve cells has not been studied. Our initial observation that **PGE1-induced differentiated neuroblastoma (NB) cells degenerate in vitro more rapidly than those inducedby RO20-1724, an inhibitor of cyclic nucleotide phosphodiesterase, has led us to postulate that PGs act as a neurotoxin.** This study has further investigated the effects of PGs on differentiated NB cells in culture. Results showed that PGA1 was more effective than PGE1 in causing degeneration of differentiated NB cells as shown by the cytoplasmic vacuolation and fragmentation of soma, nuclei, and neurites. Because increased levels of ubiquitin and beta-amyloid have been implicated in causing neuronal degeneration, we studied the effects of PGs on the levels of these proteins during degeneration of NB cells in vitro...." "Results showed that PGs increased the intracellular levels of ubiquitin and beta-amyloid prior to degeneration, whereas the degenerated NB cells had negligible levels of these proteins. **These data suggest that PGs act as external neurotoxic signals** which increase levels of ubiquitin and beta-amyloid that represent one of the intracellular signals for initiating degeneration of nerve cells."

Brain Res Bull 1998 Apr;45(6):637-40. **The fatty acid composition of maternal diet affects the response to excitotoxic neural injury in neonatal rat pups.**Valencia P, Carver JD, Wyble LE, Benford VJ, Gilbert-Barness E, Wiener DA, Phelps C **Fatty acids and their derivatives play a role in the response to neural injury.** The effects of prenatal and postnatal dietary fatty acid composition on excitotoxic neural injury were investigated in neonatal rat pups."

Proc Soc Exp Biol Med 1998 Nov;219(2):120-5**. Prostaglandins as putative neurotoxins in Alzheimer's disease.** Prasad KN, Hovland AR, La Rosa FG, Hovland PG**.** "Chronic inflammatory reactions in the brain appear to be one of the primary etiological factors in the pathogenesis of Alzheimer's disease (AD). This is supported by the fact that the secretory products of inflammatory reactions, which include cytokines, complement proteins, adhesion molecules, and free radicals, are neurotoxic. We have recently reported that prostaglandins (PGs), which are also released during inflammatory reactions, cause rapid degenerative changes in differentiated murine neuroblastoma cells (NB) in culture." "The mechanisms underlying Abeta-induced neuronal degeneration have been under intense investigation, and several mechanisms of action have been proposed. We postulate that PG-induced elevation of Abeta may lead to an increased binding of Abeta to the 20S proteasome, resulting in a reduction of 20S proteasome-mediated degradation of ubiquitin-conjugated proteins. This is predicted to lead to an increase in an accumulation of abnormal proteins, which ultimately contribute to neuronal degeneration and death. Based on our hypothesis and on studies published by others, we propose that a combination of nonsteroidal anti-inflammatory drugs, which inhibit the synthesis of PGs, and antioxidant vitamins, which quench free radicals and both of which have been recently reported to be of some value in AD treatment when used-individually, may be much more effective in the prevention and treatment of AD than the individual agents alone."

Mol Chem Neuropathol 1998 May;34(1):79-101**. Effects of EGb 761 on fatty acid reincorporation during reperfusion following ischemia in the brain of the awake gerbil.** Rabin O, Drieu K, Grange E, Chang MC, Rapoport SI, Purdon AD**.**

Regulation of arcuate nucleus synaptology by estrogen. Leedom L; Lewis C; Garcia-Segura LM; Naftolin F. Ann N Y Acad Sci, 1994 Nov 14, 743:, 61-71 "Estrogen modulates the synaptology of the hypothalamic arcuate nucleus during sexual differentiation of the rat brain in both males and females. In **males, testosterone of gonadal origin is converted to estrogen in the brain** by an enzyme, aromatase, which is also present in females. The exposure of the male's hypothalamus to relatively high levels of estrogen (following a perinatal testosterone surge) leads to the development of a pattern of synaptogenesis **which does not support an estrogen-induced gonadotrophin surge in the adult.** In female rats, hypothalamic development **occurs with permissively low levels** of estrogen, enabling a midcycle estrogen-induced gonadotrophin surge and ovulation in adulthood. During adult reproductive life in female rats,

circulating estrogen modulates the synaptology of the arcuate nucleus. **The most physiological example of this is the 30-50% loss of axosomatic synapses following the preovulatory estrogen surge on diestrus-proestrus.** Studies on post-synaptic membranes of the arcuate nucleus reveal sex differences in membrane organization and protein content which are estrogen-dependent. **Estrogen apparently stimulates endocytosis of areas of post-synaptic membrane that are dense with small intramembranous protein particles, resulting in a reduction in the number of small intramembranous particles. This also appears to be the physiologic mechanism of neuronal changes in females during the estrus cycle.** Repeated exposure to preovulatory levels of estrogen may lead to an age-related decline in reproductive capacity in female rats. Aging females lose the estrogen-induced gonadotrophin surge responsible for ovulation. **This loss of function may result from a cumulative estrogen effect during the repeated ovarian cycles which results in a reorganization of the synaptology** on which regulates the estrogen-induced gonadotrophin surge.""...recent research has shown that GABA, the monoamines, and several neuropeptides are participants in the estrogen-sensitive network which regulates GNRH secretion. In this regard, present work shows estrogen-induced changes in GABA and dopamine synapses in the arcuate nucleus."

17 beta Estradiol-induced increase in brain dopamine D-2 receptor: antagonism by MIF-1. Rajakumar G; Chiu P; Chiu S; Johnson RL; **Mishra RK** Department of Psychiatry, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada. Peptides, 1987 Nov-Dec, 8:6, 997-1002 Animal behavioral and neurochemical studies implicate dopaminergic systems **in the neurological sequelae induced by estrogen.** In the present study, we demonstrated for the first time that MIF-1, a neuropeptide unrelated to classical dopamine agonists, when given prior to, concurrently with, and after 17 beta-estradiol, antagonized significantly the estrogen-induced increase in the **density of dopamine D-2 receptor** both in the striatum and the mesolimbic area of male rat brain. The current findings have implications for the prophylactic and therapeutic potential for MIF-1 in **extrapyramidal motor disorders caused by estrogen imbalance in humans.**

Eur J Clin Invest 1984 Dec;14(6):431-4 **Effect of ovulation on haem metabolism in rabbits.** Lindahl J, Werner B, Lerner R**. "To investigate the origin of the cyclic changes in the rate of endogenous carbon-monoxide production (nCO) during the menstrual cycle, haem turnover was determined before and after chorion gonadotropic hormone-induced ovulation in six female rabbits. 14C-labelled delta-aminolevulinic acid and glycine were administered and the excretion rate of 14CO (A14CO) was measured for determination of hepatic and** bone-marrow haem turnover, respectively."**". . . nCO was increased 34% (P less than 0.05) during the post-ovulation period. As the increase in 'unassigned' haem turnover was small and may be unaccompanied by a contemporary increase in bilirubin/CO production, it was concluded that the increase in nCO during the post-ovulation period essentially depends on increased destruction of circulating red cells in the rabbit."**

J Neurotrauma 1993 Winter;10(4):373-84. **Beneficial effect of the nonselective opiate antagonist naloxone hydrochloride and the thyrotropin-releasing hormone (TRH) analog YM-14673 on long-term neurobehavioral outcome following experimental brain injury in the rat.** McIntosh TK, Fernyak S, Hayes RL, Faden AI

J Neurosci 1990 Nov;10(11):3524-30. **Opiate antagonist nalmefene improves intracellular free Mg2+, bioenergetic state, and neurologic outcome following traumatic brain injury in rats.** Vink R, McIntosh TK, Rhomhanyi R, Faden AI. "Treatment of CNS trauma with the opiate antagonist naloxone improves outcome, though the mechanisms of action remain speculative."

Brain Res 1989 Mar 20;482(2):252-60. **Magnesium protects against neurological deficit after brain injury.** McIntosh TK, Vink R, Yamakami I, Faden AI.

Adv Neurol 1988;47:531-46. **Role of thyrotropin-releasing hormone and opiate receptor antagonists in limiting central nervous system injury.** Faden AI. "Opiate antagonists, including receptor antagonists and physiologic antagonists, have been shown to produce beneficial effects in a variety of models of CNS injury and in a variety of species. Opiate antagonists improve spinal cord blood flow, electrical conduction of the spinal cord, pathological changes, and motor recovery following traumatic spinal cord injury in cats. TRH appears to be superior to naloxone in this regard, although direct comparisons between receptor-selective opiate receptor antagonists and TRH have not been made."

Exp Neurol 1994 Sep;129(1):64-9.**Progesterone facilitates cognitive recovery and reduces secondary neuronal loss caused by cortical contusion injury in male rats.** Roof RL, Duvdevani R, Braswell L, Stein DG.

Exp Neurol 1996 Apr;138(2):246-51. **Progesterone rapidly decreases brain edema: treatment delayed up to 24 hours is still effective.** Roof RL, Duvdevani R, Heyburn JW, Stein DG.

Mol Chem Neuropathol 1997 May;31(1):1-11. **Progesterone protects against lipid peroxidation following traumatic brain injury in rats.** Roof RL, Hoffman SW, Stein DG.

Jiang N, et al. **Progesterone is neuroprotective after transient middle cerebral artery occlusion in male rats.** Brain Res. 1996 Sep 30;735(1):101-7.

Roof RL, et al. **Progesterone rapidly decreases brain edema: treatment delayed up to 24 hours is still effective.** Exp Neurol. 1996 Apr;138(2):246-51.

Duvdevani R, et al. **Blood-brain barrier breakdown and edema formation following frontal cortical contusion: does hormonal status play a role?** J Neurotrauma. 1995 Feb;12(1):65-75.

Exp Neurol 1997 Dec;148(2):453-63. **Endogenous repair after spinal cord contusion injuries in the rat.** Beattie MS, Bresnahan JC, Komon J, Tovar CA, Van Meter M, Anderson DK, Faden AI, Hsu CY, Noble LJ, Salzman S, Young W. **"In addition to signs of regeneration, we noted evidence for the proliferation of cells located in the ependymal zone surrounding the central canal at early times following contusion injuries."**
