Ray Peat's Newsletter

November 2001

Some issues related to the stress of winter:

"Winter sickness" occurs when there isn't enough daylight to allow us to recover from nocturnal stress. The stress related hormones rise at night, and winter nights are long.

The inadequate light produces thyroid and progesterone deficiencies.

A progesterone or thyroid deficiency, or estrogen and polyunsaturated fat excess, causes serotonin to increase. Cold, dark, and even minor stresses cause increased serotonin.

The amino acid tryptophan can be metabolized into serotonin, which can be converted into melatonin.

More than twenty years ago, tryptophan was being promoted as a sedative, even though it was known to be the only amino acid that is carcinogenic. In excess, it suppresses the function of the thyroid gland. A protein deficiency releases tryptophan from muscles.

A "serotonin deficiency" was often said to cause depression. Hydroxy tryptophan (5-HTP) is sold as a serotonin precursor that is supposed to improve mood. Many kinds of stress cause serotonin's activity to increase.

Melatonin has been sold as a sleeping pill, longevity pill, and anticancer agent. Its production in the body is stimulated by stress and darkness.

Light, especially red light, penetrates into the body, and suppresses free radical activity and activates the crucial respiratory enzyme, cytochrome oxidase, which is activated by thyroid, and which is inactivated by polyunsaturated fats.

Serotonin released from platelets causes blood clotting and vascular spasms, and stimulates cell division. It and histamine are mediators of inflammation that cause blood vessels to leak.

Serotonin triggers the release of the stress hormones, ACTH, cortisol, and prolactin.

People often gain weight during the winter; in the far north, blood tryptophan is elevated in the winter; depressed women have increased melatonin, alcohol lowers melatonin; alcohol consumption is increased by darkness.

The use of antiserotonin drugs in alleviating stroke, hypertension, heart failure, diabetes, depression, obesity, rheumatoid arthritis, lupus (SLE), fibrosis, wheezing, and migraine suggests the importance of hyperserotonemia in causing disease.

Postpartum, premenstrual, and seasonal serotonin soaks: Hints about aging, insomnia and diabetes

When I read, in the early 1950s, about the cyclical peaks of mortality in the early morning hours and winter months, that had been evident in actuarial tables for a long time, it wasn't hard to accept that light was good for us, and that darkness was harmful. "Chronobiology," the awareness that biological responses are dependent on the time of day, was firmly established by the 1950s.

"...Tryptophan transport was increased in the major depressions and in the dysthymic disorders." D. Pringuey, et al., 1986.

"...We propose that there is a hyperserotonergic state in the hippocampal formation of some subjects with schizophrenia...."
E. Scarr, D.L. Copolov, B. Dean, L. Rebecca.

"...a hyperserotonemic condition has been documented in preeclampsia."
Carrasco, et al., 2000.

"Both melatonin and serotonin were potent inhibitors of progesterone release."
Schaeffer and Sirotkin, 1997.

Beginning in the 1950s, when I would spend the summers working in the woods, I noticed effects of sunlight that I didn't understand, such as the worsening of acne in proportion to the amount of sun exposure, as well as during times of stress. In 1965, I noticed that even incandescent light exposure during the night could immediately provoke my acne, so I realized that ultraviolet irritation wasn't the essential factor. First I thought the eyes' consumption of vitamin A might be responsible, since taking additional vitamin A would control my acne, but then I realized that an

extended photoperiod stimulated the sex hormones, and that this increased demands for vitamin A.

When I moved to the northern US from Mexico in 1965, I began noticing other interesting hormonal and nutritional effects relating to the seasons. In the winter of 1966-67 I began referring to "winter sickness" as the consequence of the hormonal changes produced by a lack of light exposure. Women who moved from a sunny climate to cloudy Eugene, and who often lived in gloomy basement apartments while they were at the university, described premenstrual depression and other symptoms that they had never experienced before. Many serious diseases had their onset during these times of light deprivation and hormonal upset.

I submitted some of my observations on winter sickness to various journals, and didn't get any responses from most of the editors, except for occasional sarcastic remarks about how ridiculous it is to suggest that ***light*** would have biological or psychological effects on humans.

Since 1966 I had been including a discussion of light's effects in my classes on nutrition and hormones and aging, and in the early seventies I began travelling around to talk to health-food, alternative medicine, and church groups, and to talk on occasional radio and television programs, where I would emphasize the importance of good light along with good nutrition. I found that the general public, and especially so-called "conservative" people, were remarkably receptive to ideas of interactions between organism and environment, and between mood and chemistry. I think their receptiveness had to do with the attitude called "paranoia," an attitude that has its positive features, as Salvador Dalí observed.

Professional people, especially journal editors, on the other hand, seemed to suffer from a mental rigidity that was the polar opposite of paranoia, a belief that nothing was happening outside of the set of beliefs residing in their own minds. This is a psychiatric condition that can be called "editorness," or simply "professionalism."

Although no journal or magazine had responded favorably to my articles on winter sickness and light therapy, some of those editors later began publishing similar observations by themselves or others, and by 1985 "Seasonal Affective Disorder" was becoming something like a "movement," with people arguing about the proper use of "light panels" and phase-shifting of melatonin, and even direct supplementation of melatonin. When its factors are reduced to a minimum, usually two, a new thought can sometimes penetrate into the professional mentality, though they are likely to get one or both of those factors wrong, as often as not. The use of bright light to treat depression should have made people realize that a melatonin excess contributed to depression, but that simple idea has been generally evaded.

The reluctance to see any connection between mood and hormones, or between light and health, probably resulted from an education in which there was already an explanation for everything. Now that medicine accepts a role for light and hormones in mood and behavior, it is within a culture dominated by Estrogen Replacement Therapy and Selective Serotonin Reuptake Inhibitors, such as Prozac. When there is a product for everything, explanations are degraded, and professionalism reaches a new low. The use of Prozac and similar drugs to treat PMS is an example of how product-professionalism works. (Its action in PMS is probably the result of increasing a brain steroid, compensating for a progesterone deficiency, exactly contrary to the doctrine that it acts by increasing serotonin availability.)

People who believe that there is a "biological clock" in the brain think that light signals entering through the eye provide the cues that set the clock, and that the brain then organizes the behavior that's appropriate for the season and time of day. But pigeons wearing opaque hoods can sense environmental light if the rest of their body is uncovered. The same sort of bodily sensitivity to light was demonstrated by shining light onto the back of a person's knee.

Instead of a "clock" that consists of some procedure for counting enzyme reactions or DNA oscillations or something of the sort, for which there is not even a clear theory, I think the evidence supports the idea that physiological

states reflect the organism's relation to the environment, and that, in the absence of the necessary amount of light and heat from the environment, energy stores in the form of glycogen become depleted, creating hunger and a variety of stress reactions. It takes some time to deplete glycogen stores, and it takes time to assimilate food, and so hunger and satiation tend to be cyclic, but it isn't productive to call these processes "a biological clock."

Mitochondria change their shape and function during the night, becoming radically less effective at producing energy. Light regenerates the crucial cytochrome oxidase enzyme, creating the energy needed to repair mitochondria. During darkness, glycogen stores in the liver, brain and other tissues are used rapidly, because of the mitochondrial respiratory inefficiency. Fats are mobilized from storage under the influence of adrenalin that rises when glucose is scarce. Rapid eye movement sleep, the phase of active dreaming, increases with hunger, and the arousal subsides cyclically as adrenalin is suppressed by other adjustments, including increased cortisol, melatonin, GABA, and many other regulatory substances and processes.

Light suppresses melatonin and serotonin, but its action is biological and biochemical, not just informational--it's a component of our metabolism, not just a "cue." Our biological rhythms, of approximately 24 hours, do have a learned component, but Frank A. Brown's experiments in the 1960s made it clear that there are important rhythmic environmental influences other than the cycle of light and dark. Brown's biological experiments were complemented by Alexandre Rothen's physical experiments which made it clear that the diurnal cycles aren't just light cues. In the university's hamster house where I worked, the cycles of light and dark were automatically controlled, air temperature was kept constant, and there were no windows, but in the winter the hamsters' thymus glands practically disappeared, and then in the summer they were restored. The infrared and microwave radiation of the environment, that can penetrate walls, must be constant to avoid biological stress.

Winter, at least in some species, causes serotonin to increase. (Philo and Reiter, 1980) In the winter, and in the morning, intraocular pressure (IOP) increases (Qureshi, et al., 1999), and drugs that antagonize serotonin reduce IOP. Women, on average, have higher IOP than men, and estrogen increases IOP (and serotonin).

Serotonin is a mediator of inflammation that suppresses metabolism, disturbs blood pressure, and promotes clotting, so it would be a Manichean-seeming misfortune if it was also essential to have lots of it to experience eupohoria. But in reality a state of "serotonergia" is a state of torpor, discomfort, and depression, rather than a state of alert pleasure. Its levels are above normal in autism, attention deficit disorder, and some forms of mental retardation, as well as in various types of depression.

A mediator of stress transduces an infinite range of harmful influences into a stereotyped response, mobilizing the adaptive antistress systems. A relatively harmless stress, such as overheating, chilling, oxygen deficiency or exertion, can leave the organism stronger as a result of its adaptation, but other kinds of challenge, such as prolonged darkness, leave the organism more vulnerable despite its mobilization of its antistress systems. The difference seems to be that passivity allows a generalized catabolism, while an active response strengthens the functional system that is being challenged. Winter stress is a prolonged passive stress. The passive responses of hibernation, over-eating, lethargy or depression probably represent the best biological response under the circumstances, which have impaired the capacity for energetic response.

Depression, like inflammation, is a costly reaction for an organism that can't achieve a better adaptation. Serotonin is a mediator of both depression and inflammation. On the cellular level, serotonin depresses respiration, and on the organismic level it depresses body temperature which depresses biochemical reactions generally. For mood and mental function, it's probably significant that serotonin depresses blood circulation in the brain (Mendelow, et al., 1977; Eidelman, et al., 1978). There is no question about serotonin's being a mediator of depression, except

for the stereotype that got its start in the 1960s that wants to see it as a sedative euphoriant, a deficiency of which produces many psychological problems. The tryptophan and melatonin industries were built up around this serotonin myth.

Aging and the degenerative diseases involve combinations of metabolic depression and inflammation. Anti-serotonin agents are coming to be recognized as treatments for a wide variety of degenerative diseases.

Minks that have mated in the winter don't implant the fertilized ovum in the uterus until the spring equinox, when progesterone rises suddenly, and allows both the uterus and the embryo to begin the process of pregnancy and gestation. Progesterone provides the oxygen needed for the successful implantation of the embryo, while estrogen and serotonin lower the intrauterine oxygen.

Under good conditions, the (premenstrual) luteal phase of the monthly cycle resembles pregnancy, as a period of progesterone dominance, in which the abundance of progesterone causes cells to decrease their estrogen content. The luteal phase is actually the first stage of pregnancy, and if there is implantation of an embryo all of the processes that begin at ovulation progress continuously until childbirth occurs. When there is no implantation, the luteal phase progesterone dominance is terminated, allowing estrogen to enter tissues and producing menstruation. The sudden decrease of progesterone production before menstruation is similar to the decrease of hormone production just before childbirth. The same conditions that produce the premenstrual syndrome, if they aren't corrected by the placenta's massive production of progesterone, will produce preeclampsia, toxemia of pregnancy, eclampsia, and postpartum depression. They are also related to the problems that become so common at menopause. Whenever the production of progesterone falls, tissues are susceptible to estrogen.

There are several common causes of a progesterone deficiency. Deficiencies of thyroid, vitamin A, and cholesterol are often responsible for a progesterone deficiency. Inadequate light exposure can cause it. Excess polyunsaturated fats, interfering with gonads and thyroid, can cause it. And excess serotonin can cause it.

Serotonin is a precursor of melatonin, which tends to be produced at night. Because of the books published during the intensive marketing campaign for melatonin, many people are familiar with the work of Maestroni and Pierpaoli, who reported that treatment with melatonin, or with the transplantation of pineal glands from young animals, would extend the life span of mice and prevent cancer. Melatonin is often called the "pineal hormone," though there are other hormones in the pineal, and many other tissues can produce melatonin.

Mice and rats are nocturnal animals, so they are notoriously inappropriate for evaluating the nocturnal hormones as they might relate to humans and other animals that are active in the daytime. Although melatonin sometimes antagonizes serotonin in a protective way, in itself it can lower body temperature and alertness, ***suppressing thyroid and progesterone.*** (Sirotkin, 1997) Women who are depressed have been found to have higher daytime melatonin levels. (Danilenko, et al., 1994) While the popular books have given the impression that there is no question about the protective nature of melatonin, it turns out that **in only five out of 36 strains of inbred mice can melatonin be demonstrated in the pineal glands. The famous cancer prone strain, in which mammary cancer kills practically all the females, is one of these. When they are given melatonin the development of tumors is accelerated. When their pineal gland is removed, their life span is extended.**

Estrogen and stress increase free fatty acids, and unsaturated free fatty acids cause serotonin release; serotonin, at least under some circumstances, can be lipolytic, increasing the free circulating fatty acids.

Darkness creates stress, by free radical inactivation of the respiratory enzyme, cytochrome oxidase, and light restores the activity of that enzyme, and probably also has a variety of anti-free-radical actions. Free fatty acids rise in the darkness, intensifying free radical production and

suppressing respiration. Progesterone synthesis is suppressed by darkness. The serotonin liberated by the fatty acids suppresses progesterone by inhibiting the secretion of luteinizing hormone (LH) which stimulates progesterone synthesis, and also seems to act directly on the ovary to suppress progesterone secretion (Wilson, et al., 1975). While estrogen increases serotonin's actions, progesterone antagonizes them.

Serotonin depletes glycogen stores, much the way estrogen and histamine do. This can cause hyperglycemia. Thyroid, carbon dioxide, and caffeine, which inhibit serotonin release, all tend to protect glycogen stores. Under the influence of carbon dioxide, noradrenaline can still liberate glucose from glycogen, but serotonin's effect is inhibited by carbon dioxide.

Serotonin interferes with slow-wave sleep, creating a situation resembling that of depression or old age. Brain glycogen is depleted in old age, and this depletion contributes to inefficient brain metabolism. Serotonin's stimulation of ACTH, which stimulates the adrenal cortex, and its direct stimulation of cortisone production by the adrenals, is probably involved in the chronic excess of cortisone seen in depression and old age, which contributes to insulin resistance and diabetes, and to the atrophy of all tissues including the brain. (People who are studying chronic inflammatory processes are gathering data that will be meaningful for understanding depression and aging, but it seems that psychiatrists don't know about their work.)

Anti-serotonin drugs such as bromocriptine have been found to correct diabetes, apparently because serotonin interferes with the use of sugar, acting on cells' metabolism to decrease its use, and preventing the secretion of insulin. Bromocriptine's correction of obesity also seems to be the result of its correction of glucose metabolism.

In the 1970s, it was established that darkness increases the appetite for alcohol. More recently (Lin and Hubbard, 1995) it has been found that the antiserotonin drugs prevent the dark-induced appetite for alcohol. Alcohol is probably a self-medication to alleviate serotonin-related depression. Alcohol, like progesterone, is neuroprotective in brain trauma. Alcohol increases formation of the sedative neurosteroid ("THP") derived from progesterone (VanDoren, et al., 2000), and alcohol increases brain circulation, countering serotonin's effect.

Progesterone withdrawal and alcohol withdrawal are so closely related that one can alleviate the symptoms of the other.

Isolation might be another factor contributing to depression and alcoholism, since it decreases the formation of the protective neurosteroid.

The "brain fog" that is often described in depressed people (and people with other serotonin syndromes, such as the fibromyalgia syndrome) is probably produced by a combination of factors, including hypothyroidism, low body temperature, and hyperserotonemia. The amnesia produced by shock was found to be prevented by antiserotonin drugs (Montanaro, et al., 1979). The same researchers suggested that the drugs had an "antipunishment" effect, in effect making the animals less fearful.

There is more confusion in the medical literature regarding the actions of serotonin than there is about practically any other subject.

For example, there is clear evidence from both animal and human studies that serotonin, like estrogen, is associated with aggression, but the dominating stereotype is that serotonin is the agent of serenity and peace. In an epidemiological study (Moffitt, et al., 1998), a record of violence was clearly associated with above-average blood serotonin levels. Animal studies show that darkness stimulates both aggression and eating (Russell and Singer, 1983), and that serotonin increases, while antiserotonin drugs decrease, aggression (Carlini and Lindsey, 1983).

When lysergic acid derivatives came onto the pharmaceutical market, the spirit of the times caused them to be described as dopamine agonists, rather than as serotonin antagonists, but the latter would be at least as descriptive of their effects. Bromocriptine fulfills many of the requirements of being a serotonin antagonist, for example by suppressing prolactin. As a class, the serotonin antagonists have a very interesting place in pharmaceutical medicine, because the broad spectrum of their therapeutic activity suggests the

great variety of problems caused by excess serotonin.

The documentation of extensive government-supported fraud in research on LSD and marihuana should make us question subsequent research that plows the same or similar furrows. My inclination is to believe that incompetence can't account for the glaring errors in research on serotonin-related questions. Commercial commitments to particular theories of drug action have undoubtedly contributed to the crazy quality of the psychiatric serotonin literature.

In the case of some antiserotonin drugs, there is commercial support for research, so they might come into general use in spite of the mythic stature of tryptophan/serotonin/melatonin. But thyroid, protein, magnesium, thiamine, progesterone and light are natural factors that keep serotonin under control, and that don't have the side effects of the synthetic antiserotonergic agents. Knowledge of serotonin's harmful actions can guide our use of the natural protective factors. For example, whey protein contains much more tryptophan than whole milk or cheese does, and would tend to suppress the thyroid and activate the whole serotonin-stress system. Whey might be good food for fattening pigs, but its acceptance in the health food industry as a powdered protein supplement is just another example of the harmful effects of the serotonin mythology.

(Some comments on research methods:)

"Serotonin activity" may be judged by the response of prolactin to serotonin or to a drug that is thought to mimic serotonin, or by serotonin metabolites in cerebrospinal fluid, or by the total amount of serotonin in the blood, or by its efflux from platelets, or the ratio of its concentration in the plasma and in the platelets. It isn't very clear whether serotonin's concentration or its turnover rate is most important, and the number and sensitivity of the many "serotonin receptors" varies, and presumably changes the meaning of any given quantity of serotonin. When serotonin's activity is judged indirectly, interpretation and subjectivity are involved.

Even the "synaptic reuptake inhibitors," such as fluoxetine, sometimes relieve symptoms that are believed to be caused by an excess of serotonin (C. Advokat and V. Kutlesic, 1995, Neurosci Biobehav Rev 1995 Spring;19(1):59-66 Pharmacotherapy of the eating disorders: a commentary.)

But the actual injection of serotonin, or of serotonin antagonists that are known to approximately neutralize serotonin's effects, and the examination of the basal concentrations of the hormones known to be regulated by serotonin, are much less likely to be distorted by arbitrary interpretations.

When a "receptor" is first proposed or "discovered," it is always "a protein," though because of the idea of a barrier (semipermeable) membrane around cells, "membrane lipids" are sometimes invoked. But after a few years of research, the "receptor" becomes a more and more complex system of interacting molecules. The doctrine of the "receptor" is intended to explain why cells have a specific response to a specific substance. Gradually, a receptor becomes a "response element," but the "element," in its complexity, begins to shade off into the system "membrane/cytoplasm/nucleus," which is to say, the cell. ***The cell is the response element.*** *The "transmitter substance" interacts with various agonists, antagonists, inverse agonists and binding competitors to produce an effect that is a summation of influences. A single protein or protein system can serve as a "receptor" for antagonistic substances.*

REFERENCES

Int J Circumpolar Health 1998;57 Suppl 1:386-8. **Seasonal variation of the amino acid, L-tryptophan, in interior Alaska.** Levine ME, Duffy LK The seasonal pattern of L-tryptophan was studied in a Fairbanks, Alaska, population that was unadapted to the extreme light variations of the North. Previously, this population was shown to exhibit seasonal behavior effects such as increases in fatigue and sleep duration, as well as endocrine effects such as increases in melatonin levels and phase shifting. Caloric and macronutrient intake have been reported to vary seasonally in humans, thereby potentially

influencing the plasma levels of L-tryptophan, which is a precursor of serotonin and melatonin. Plasma levels of L-tryptophan from volunteers, whose average duration of stay in Alaska was eight months, were determined by automated amino acid analysis. Prominent results included finding increased levels in the winter **at several different diurnal time points. These findings support hypotheses which relate underlying physiological adaptations to the North to the increased incidence of behavioral disorders such as depression and alcoholism.**

Epidemiology 2000 Nov;11(6):660-5. **Alcohol consumption and urinary concentration of 6-sulfatoxymelatonin in healthy women.** Stevens RG, Davis S, Mirick DK, Kheifets L, Kaune W **"We found that the nocturnal urinary concentration of the primary metabolite of melatonin (6-sulfatoxymelatonin) decreased in a dose-dependent manner with increasing consumption of alcoholic beverages in the preceding 24-hour period, after taking into account the independent effects on melatonin of age, hours of darkness, use of medications that affect melatonin levels, and body mass index. A categorical analysis revealed no effect of one drink, but a 9% reduction with two drinks, a 15% reduction with three drinks, and a 17% reduction with four or more drinks."**

Fertil Steril 1993 Apr;59(4):896-900. **Baboon corpus luteum: the effect of melatonin on in vitro progesterone production.** Khan-Dawood FS, Dawood MY **"Melatonin (0.01 to 1.0 ng/mL) inhibited basal P production in all the CL (41.8 +/- 9.9 ng P without melatonin compared with 32.2 +/- 2.0 ng P, 28.4 +/- 2.1 ng with 0.01 and 1.0 ng/mL melatonin, respectively). Human chorionic gonadotropin-stimulated P production was significantly inhibited with as little as 0.01 ng of melatonin** (150.8 +/- 11.4 ng with 10 IU hCG versus 120.3 +/- 6.4 ng with 10 IU hCG and 1.0 ng melatonin). The degree of inhibition in the hCG-stimulated cells was greater than in the nonstimulated cells. Melatonin at a concentration of 0.001 ng/mL did not affect P production in both stimulated and nonstimulated cells. Serotonin in similar concentrations had no effect on luteal cell P production." "These findings indicate that melatonin exerts a suppressive effect on baboon dispersed luteal cell P production and thus may play a role in luteal function."

Experientia 1980 Jun 15;36(6):664-5. **A circannual rhythm in bovine pineal serotonin.** Philo R, Reiter RJ.

Exp Clin Endocrinol Diabetes, 1997, 105:2, 109-12. **Melatonin and serotonin regulate the release of insulin-like growth factor-I, oxytocin and progesterone by cultured human granulosa cells.** Schaeffer HJ; Sirotkin AV.

Physiol Behav 1983 Jan;30(1):23-7. **Relations between muricide, circadian rhythm and consummatory behavior.** Russell JW, Singer G Three forms of behavior--muricide, eating, and drinking--have been studied at six photic periods during a 12/12 hr light/dark circadian cycle to which the subjects have been habituated. One hundred and eight rats served as subjects, 18 per photic period. The frequency of muricide was recorded for each period and subsequent food and water intakes were measured during a 1 hr test period. **Results show a significantly higher frequency of muricide during the dark than during periods of light.** Food intake covaried significantly with the incidence of muricide rs = 0.89, p less than 0.05), while no such relationship was found between muricide and water intake (rs = 0.17, p less than 0.05). **The findings are consistent with reports of circadian changes in other rodent behaviors, including rhythmicity in home-cage and in shock-induced aggression.** Covariation of muricide and eating does not establish a causal relation between the two. Three models of physiological mechanisms which might provide substrates for the covariance are discussed.

Semin Clin Neuropsychiatry 2000 Apr;5(2):125-31. **Serotonin and amino acids: partners in delirium pathophysiology?** van der Mast RC, Fekkes D "Serotonin is one of the neurotransmitters that may play an important role in medical and surgical delirium. Normal serotonin synthesis and release in the human brain is, among others, dependent on the availability of its precursor tryptophan (Trp) from blood. **The essential amino acid Trp competes with the other large neutral amino acids (LNAA) tyrosine, phenylalanine, valine, leucine, and isoleucine for transport** across the blood-brain barrier. This competition determines its uptake into the brain, represented by the ratio of the plasma level of Trp to the sum of the other LNAA. The plasma ratio of Trp/LNAA, plasma level of Trp, and serotonin in plasma and platelets have been used as indirect peripheral measures for central serotonergic functioning. Both increased and decreased serotonergic activity have been associated with delirium. **Serotonin agonists can induce psychosis, both elevated Trp availability and increased cerebral serotonin have been associated with hepatic encephalopathy, and excess serotonergic brain activity has been related to the development of the serotonin syndrome of which delirium is a main symptom.** On the other hand, alcohol withdrawal delirium, delirium in levodopa-treated Parkinson patients, and postoperative delirium have been related to reduce cerebral Trp availability from plasma suggesting diminished serotonergic function. Rick factors for delirium such as severe illness, surgery, and trauma can induce immune activation and a physical stress response comprising increased activity of the limbic-hypothalamic-pituitary-adrenocortical axis, the occurrence of a low T3 syndrome, and, possibly, changes in

the permeability of the blood-brain barrier. There are indications that these changes have their effect on plasma amino acid concentrations, e.g., Trp, and multiple cerebral neurotransmitters, including serotonin. This stress response may be different depending on the stage of illness being acute or chronic."

J Neurosci 2000 Mar 1;20(5):1982-9. **Neuroactive steroid 3alpha-hydroxy-5alpha-pregnan-20-one modulates electrophysiological and behavioral actions of ethanol.** VanDoren MJ, Matthews DB, Janis GC, Grobin AC, Devaud LL, Morrow AL Neuroactive steroids are synthesized de novo in brain, yet their physiological significance remains elusive. We provide biochemical, electrophysiological, and behavioral evidence that several specific actions of alcohol (ethanol) are mediated by the neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one (3alpha,5alpha-THP; allopregnanolone). **Systemic alcohol administration elevates 3alpha, 5alpha-THP levels in the cerebral cortex to pharmacologically relevant concentrations.** The elevation of 3alpha,5alpha-THP is dose- and time-dependent. Furthermore, there is a significant correlation between 3alpha,5alpha-THP levels in cerebral cortex and the hypnotic effect of ethanol. **Blockade of de novo biosynthesis of 5alpha-reduced steroids using the 5alpha-reductase inhibitor finasteride prevents several effects of ethanol.** Pretreatment with finasteride causes no changes in baseline bicuculline-induced seizure threshold but reverses the anticonvulsant effect of ethanol. Finasteride pretreatment also reverses ethanol inhibition of spontaneous neural activity in medial septal/diagonal band of Broca neurons while having no direct effect on spontaneous firing rates. Thus, elevation of 3alpha,5alpha-THP levels by acute ethanol administration represents a novel mechanism of ethanol action as well as an important modulatory role for neurosteroids in the CNS.

Clin Exp Pharmacol Physiol 2001 Jan; 28(1-2):70-3. **A proposed pathological model in the hippocampus of subjects with schizophrenia.** E. Scarr, D.L. Copolov, B. Dean, L. Rebecca.

Braz J Med Biol Res 1982 Oct;15(4-5):281-3. **Effect of serotonergic drugs on the aggressiveness induced by delta 9-tetrahydrocannabinol in rem-sleep-deprived rats.** Carlini EA, Lindsey CJ **1. delta 9-Tetrahydrocannabinol (THC) induced aggressive behavior in rats previously deprived of REM sleep. This aggressiveness was significantly potentiated by tryptophan and fluoxetine, drugs which increase brain serotonin** availability. 2. Conversely, **drugs which decrease serotonergic function such as D,L-p-chlorophenylalanine, cinanserin and cyproheptadine strongly blocked the aggressive behavior**. 3. On the basis of previous data indicating an involvement of dopaminergic mechanisms in this type of aggressiveness and the present results showing a role for serotonin, it is concluded that REM deprivation-THC aggression is under the control of at least these two neurotransmitters.

Endocrinol Exp 1979 Mar;13(1):9-18. **Inhibitory role of brain stem serotoninergic neuron system on thyroid function in rat.** Ruzsas C, Jozsa R, Mess B Thyroid function was investigated in adult male rats following the use experimental procedures which inhibit the activity of serotoninergic neuron system. Pharmacological blockade of the biosynthesis of sertonin by repeated administration of para-chlorophenylalanine (pCPA), or interruption (by Halasz knife) of the serotoninergic pathways of the brain stem which terminate on hypothalamic nuclei equally resulted in an augmentation of the following **parameters of hypothalamo-hypophysial-thyroid activity: T/S ratio, pituitary and blood TSH levels and blood thyroxine concentration as well as TRH content of the hypothalamus. The results suggest that the central nervous serotoninergic neuron system plays an inhibitory role in the regulation of TSH secretion, presumably** acting upon the hypothalamus, thereby inhibiting hypothalamic TRH secretion.

Vopr Onkol 2000;46(3):311-9. **[The effect of melatonin on the indices of biological age, on longevity and on the development of spontaneous tumors in mice].** Anisimov VN, Zavarzina NI, Zabezhinskii MA, Popovich IG, Anikin IV, Zimina OA, Solov'ev MV, Shtylik AV, Arutiunian AV, Oparina TI, Prokopenko VM, Khavinson VK Fifty female CBA mice were given melatonin with drinking water (20 mg/l) for 5 consecutive days monthly, beginning from the age of 6 months, until natural death. Another 50 intact mice were used as controls. Melatonin failed to significantly influence body weight or food consumption. **Age-related switching-off of estrus function was delayed, body temperature decreased. Somewhat decreased motor activity did not affect physical one or endurance. Increase in life span led to higher spontaneous tumor incidence.** Another experiment using 20 animals of the same line showed melatonin to inhibit free-radical processes. A conclusion was drawn that caution should be exercised before melatonin is recommended for long-term administration as a geroprotector.

Am J Psychiatry 1983 Jan;140(1):26-30. **Hyperserotonemia and platelet serotonin uptake and release in schizophrenia and affective disorders.** Stahl SM, Woo DJ, Mefford IN, Berger PA, Ciaranello RD **The authors found that platelet serotonin concentrations were significantly elevated in patients with chronic schizophrenia and in patients with bipolar major depressive disorder. High-affinity serotonin uptake was significantly reduced only in patients with bipolar major depressive disorder.** Thrombin-induced release of serotonin from platelets in any patient group was not

different from that of normal control subjects. Platelet serotonin storage in chronic schizophrenic patients was also not different from that in normal control subjects. These platelet findings could not be explained by age, sex, or medication variables. The authors suggest that the pharmacodynamics of platelet serotonin may be different in chronic schizophrenia than in bipolar major depressive disorder.

Arctic Med Res 1994 Jul;53(3):137-45 **Diurnal and seasonal variations of melatonin and serotonin in women with seasonal affective disorder.** Danilenko KV, Putilov AA, Russkikh GS, Duffy LK, Ebbesson SO In winters 1990-1991 and 1991-1992 women with and without seasonal affective disorder, winter type, were treated by light at 2500 lux either in the morning (0800h-1000h) or afternoon (1600h-1800h). In winter before light treatment, **melatonin levels in serum in daytime (1200h and 1600h) were higher in patients compared to controls ($p < 0.05$). This difference disappeared in the summer or** after light treatment in the winter. Also, light treatment and change in season resulted in a phase advance shift of melatonin rhythm in patients. The decline in melatonin levels correlated with the decline in specific SAD symptoms of hyperphagia and carbohydrate craving. In winter, neither patients nor controls showed significant diurnal variations in levels of whole blood serotonin. In both patients and controls, levels of serotonin were higher in summer as compared with winter, especially at 2000h. Our data suggest that elevated daytime melatonin can be a state marker of winter depression, and that seasonal change of photoperiod may also affect the circadian amplitude and daytime levels of blood serotonin.

Lik Sprava 1994 Jul-Aug;(7-8):88-90. **[The effect of an increased intensity of light on changes in the serotonin and melatonin content in patients with depression].** [Article in Russian] Bozhko GK, Tsaritsinskii VI, Kostiukovskaia LS, Kulabukhov VM Study into the effect of **light of increased intensity shows that in patients with anxious depression a high level of melatonin excretion declines to normal,** its low level in melancholic depression remaining unchanged. Blood **concentrations of serotonin in depressive patients are higher as compared with the healthy persons** and do not change with increasing in the brightness of the illumination **except for a decrease in a portion of patients showing maximum levels of serotonin and melanin.**

Brain Res Bull 1994;33(6):633-8. **The increased ethanol preference in rats induced by choice, darkness, or drugs is reduced by ritanserin.** Lin N, Hubbard JI We tested the hypothesis that ritanserin, a serotonin S2 antagonist, reduces voluntary and induced forms of ethanol drinking. We gave 10 mg/kg ritanserin IP or SC to groups of rats given either a) a free choice between 3% ethanol and water, or b) kept in the dark for 5 weeks and given a choice between a range of ethanol concentrations (3-25%) and water, or c) implanted with osmotic pumps filled with tetrahydro-beta carboline and given a choice between a range of ethanol concentrations and water. In each case, ritanserin significantly reduced ethanol consumption and ethanol preference for 8-10 days after the last injection.

Neuropsychobiology 1979;5(3):174-80. **Bromolysergide and methysergide protection against ECS-induced retrograde amnesia.** Montanaro N, Dall'Olio R, Gandolfi O Bromolysergide (BOL 148) and methysergide (UML 491), 2 mg/kg intraperitoneally, and saline were administered to rats 45 min before one-trial passive-avoidance conditioning followed by electroconvulsive shock (ECS) or sham-ECS (ECS). On test session (24 h later), the groups treated with both BOL 148 and UML 491 exhibited a clear-cut retention in comparison to saline-ECS rats. On the other hand, all drugged groups, regardless of their submission to ECS, showed a little less pronounced consolidation than saline-ECS rats. The antiamnestic effect **brought about by the two drugs was discussed in terms of receptor antagonism against ECS-released brain serotonin, whereas the lower passive-avoidance level** observed in treated animals was considered in relation to a possible **antipunishment effect of antiserotoninergic treatment.**

J Neural Transm 1981;50(1):1-12. **Depletion in amygdaloid 5-hydroxytryptamine concentration and changes in social and aggressive behaviour.** File SE, James TA, MacLeod NK 5,7-Dihydroxytryptamine (10 and 20 microgram) was microinjected bilaterally into **the amygdaloid complex of rats and resulted in 55% and 80% depletion in 5-hydroxytryptamine concentration, respectively. The lesioned animals exhibited fewer dominance behaviours and submitted more often to an intruder into their home-cages than did the vehicle-injected controls. The lesioned rats were also more submissive than were the controls when they were intruding into another** rat's territory. Only the higher dose of toxin altered social investigatory behaviour when this was measured in an arena in which neither rat had established territory. The lesioned rats displayed less social interaction and had reduced levels of motor activity. The results are compared with those of other studies in which there

has been regional or general depletion of brain 5-hydroxytryptamine concentration.

J Neuroimmunol 2000 Aug 1;108(1-2):131-5. **The pineal gland and cancer. I. Pinealectomy corrects congenital hormonal dysfunctions and prolongs life of cancer-prone C3H/He mice.** Bulian D, Pierpaoli W. **Hormonal derangements almost invariably anticipate and signal the onset of tumors.** Chronic, nocturnal melatonin administration delays aging in normal strains of mice. **On the contrary it promotes and accelerates the onset of tumors in the cancer-prone strain of C3H/He mice.** Grafting of a young pineal gland into aging mice prolongs their longevity and maintains juvenile circadian hormonal functions while pinealectomy (Px) does the opposite. We investigated if Px in C3H/He mice would modify their congenitally deranged pituitary function and affect their longevity. It was found that contrarily to Px in normal mice, Px in **C3H/He mice remarkably maintains juvenile night levels of thyroid hormones and lipids, preserves a cell-mediated immune response and significantly prolongs their life. The pineal gland and its pathology may be the key for understanding,** not only the causes of metabolic aging, but also the origin of those congenital or progressive aging-related hormonal alterations preceding onset of all tumors and thus allow preventive corrective interventions with pineal-derived agents.

J Pineal Res 1989;7(2):195-204. **Melatonin content of the pineal gland in different mouse strains.** Goto M, Oshima I, Tomita T, Ebihara S. Pineal melatonin content at several times during the day and night was measured in 36 inbred strains of mice (Mus musculus) kept under LD 12:12 cycles. The **results have indicated that only five inbred strains have pineal melatonin content, with higher levels during the night and lower levels during the day; the other 31 strains do not contain detectable melatonin in their pineal gland at any of times examined.** The former group includes two commonly used strains (C3H/He and CBA/Ms) and three wild-derived strains (Mol-A, Mol-Nis, MOM). C3H and CBA mice showed a similar pattern of pineal melatonin rhythm with a peak at 2 hours before lights on. The peak levels were about 150 pg/gland in both strains. The rhythmic patterns of melatonin content in Mol-A, Mol-Nis, and MOM were slightly different from those in CBA and C3H. In the wild-derived strains, the peak of melatonin content did not occur at 2 hours before lights on but tended to occur at midnight. The peak levels were 67-91 pg/gland at the highest point in these strains.

Am J Obstet Gynecol 1985 Sep 15;153(2):130-4. **The effect of serotonergic blockade in postpartum preeclamptic patients.** Montenegro R, Knuppel RA, Shah D, O'Brien WF Thirty postpartum preeclamptic patients from the University of South Florida Obstetrical Service were enrolled in a placebo-controlled, randomized, double-blind study to test the effectiveness of ketanserin in lowering the blood pressure. **An intravenous bolus of ketanserin resulted in a significant drop in the mean arterial blood pressure. The decrease in the blood pressure could be maintained by a continuous infusion of ketanserin.** Hypertension returned after the medication was discontinued. These observations suggest that ketanserin, a selective blocker of type II serotonin receptors, may be effective in **acutely reducing elevated postpartum blood pressure in preeclamptic patients,** and that serotonin may play a role in the pathogenesis of preeclampsia, but not be important as a mediator in the severity of the disease.

Eur J Pharmacol 1985 May 8;111(2):211-20. **Maternal aggression in mice: effects of treatments with PCPA, 5-HTP and 5-HT receptor antagonists.** Ieni JR, Thurmond JB Drug treatments which influence brain serotonergic systems were administered to lactating female mice during the early postpartum period, and their effects on aggressive behavior, locomotor activity and brain monoamines were examined. P-chlorophenylalanine (200 and 400 mg/kg) and 5-hydroxytryptophan (100 mg/kg) inhibited fighting behavior of postpartum mice toward unfamiliar male intruder mice. These drug-treated postpartum females showed increased latencies to attack male intruders and also reduced frequencies of attack. In addition, postpartum **mice treated with the serotonin receptor antagonists, mianserin (2 and 4 mg/kg), methysergide (4 mg/kg) and methiothepin (0.25 and 0.5 mg/kg), displayed significantly less aggressive behavior than control mice, as measured by reduced** number of attacks. Whole brain monoamine and monoamine metabolite levels were measured after drug treatments. The behavioral results are discussed in terms of drug-induced changes in brain chemistry and indicate a possible role for serotonin in the mediation of maternal aggressive behavior of mice.

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