The Serotonin Connection: A Study of Social Adversity, Stress, Depression, Pain and Serotonin Neurotransmission

I. Introduction

Concepts of illness and body image as they relate to health are constantly shifting, incorporating older ideas from rediscovered ancient health traditions and newer ideas often introduced by medical and scientific discoveries about the body. The germ theory strongly influenced notions of hygiene in protecting oneself from external invaders in the 1940s. Later the changing biomedical understanding about the role of the immune system shifted the focus from the outside to what was happening on the inside with a marked interest in nutrition, vitamins, and trace minerals as immune modulating factors and agents (Martin 1994). The late 20th century is best regarded as the molecular age of clinical medicine. The ongoing scientific advances provided detailed and precise knowledge of the workings of the human body at the molecular level. Most recently much progress has been made in the field of neuroscience in regard to the structural aspects of the brain and its function. The developments in neurocognitive imagery (fMRI, PET, EEG and the like) have made some of the workings of the brain accessible to observation. With increasingly detailed knowledge of the brain's activities it looks like science will help us understand the biological pathways through which environmental and social factors have their effects on the body. Even if much of the boundaries between the physiological and the cognitive remain elusive, increasing understanding of the brain's functions help us answer some of the problems posed by the mind-body problem.

One area of interest in the field of neuroscience and mind-body medicine is stress and the ways in which humans respond to stress. The body's reaction to stress is determined by the interplay of several physiological systems (immune, neural, and endocrine). Recent advances in these different fields have led to a clearer understanding of the connections among these systems, revealing possible mechanisms by which the host response to environmental and social stresses is mediated. One modulator of stress and important variable in the link between the environment and individual body is the neurotransmitter serotonin. It's effect has been linked to depression, schizophrenia, suicidality, aggressive behavior, chronic pain, and social dominance.

II. Stress and the Serotonin System

The practices of modern mind-body medicine are based on the current understanding of the functioning of the human mind (Churchland, 1986). The neuron is the fundamental cellular communication unit of the nervous system. Neurons communicate by producing chemical substances called neurotransmitters that are sent across the synapse (Kalat 2001). The action of these neurotransmitters (e.g. serotonin) is the basis for brain functioning. These chemicals have been linked to behaviors as diverse as learning and memory, motor activity, thirst, pain, thermo-regulation, pleasure, stress, emotions, mood and sexual receptivity (Kalat 2001).

Life course factors interact with contemporary circumstances on a moment-by-moment basis and over time. The systematic differences in the quality of environment and life courses shape the sculpting and neurochemistry of the central nervous system. Animal studies have shown that one's immune system can be conditioned by outer events (Ader & Cohen, 1975). They convincingly

demonstrate that how one feels about the world can directly influence the competence of one's immune system. Moreover, the observation that the immune system can be conditioned implies that these effects can endure beyond the precipitating event. Thus, the nervous system which interprets the environment influences the long term functions of the immune, hormone, and clotting systems.

The two main organ sites for this "biological embedding" (Hertzman 1999) of human experience are the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (HPA). They mediate the adaptive response to stress by first initiating an increase in circulating catecholamines (e.g. adrenaline or epinephrine) and glucocorticoids (e.g. cortisol) that alter the structure and function of a variety of cells and tissues. When a threat to physical or psychological well-being is detected, the hypothalamus amplifies production of corticotropin-releasing factor (CRH), which induces the pituitary to secrete ACTH. ACTH then instructs the adrenal gland atop each kidney to release cortisol. Together all the changes prepare the body to fight or flee and cause it to shut down activities that would distract from self-protection. For instance, cortisol enhances the delivery of fuel to muscles. At the same time, CRH depresses the appetite for food and sex and heightens alertness. Chronic activation of the HPA axis, however, may lay the ground for illness. For each organ system of the body these stress mediators have both short term adaptive and protective and long term damaging effects if the stress response is overextended. Examples of adaptive reactions are: adjustment of heart rate and blood pressure, increased retention of memories of emotionally charged events, and the movement of immune cells to organs and tissues where they are needed to fight an infection or another challenge. Examples of long term damaging reactions are: persistent high blood

pressure and increased risk of atherosclerosis, increased risk of Type II diabetes, cognitive dysfunction, and increased risks of autoimmune and inflammatory disorders.

Two new terms have been used to describe these physiological stress responses: “allostasis” for the adaptive maintenance of stability through change and “allostatic load” for the wear and tear that the body experiences due to over stimulation of allostatic cycles (McEwen & Seeman 1999). Allostatic load represents the biological signature of cumulative psychosocial adversity. Various physiologic parameters (e.g. systolic and diastolic blood pressure, waist-hip-ratio, serum HDL and total cholesterol, overnight urinary cortisol excretion) have been investigated as measures of allostatic load.

Then, recent animal and human findings shed new light into the neurobiology of stress through the HPA axis and the serotonin system. Adrenal glucocorticoids and serotonin receptors have been shown to interact during conditions of chronic stress, or severe "allostatic load" (McEwen, 1987; Chalmers et al., 1993; López et al., 1999) (see details below). Further, serotonin is important for adequate coping with stress. As mentioned above, aberrant serotonin function is implicated in the aetiology of, for example, major depression and anxiety disorders. This dysregulation of the hypothalamic-pituitary-adrenocortical axis, involving elevated corticotropin-releasing hormone (CRH) activity and the chain of downward reaction, plays an important role in stress-related illnesses (Linthorst, Penalva, Flachskamm, Holsboer & Reul 2002).

Walker and DiForio (1997) document that activation of the hypothalamic-pituitary-adrenal (HPA) axis is one of the primary manifestations of the stress response. The hypothalamus of the brain lies at

the top of the hierarchy regulating hormone secretion. It manufactures releasing and inhibiting hormones (e.g. CRH) that reach the anterior pituitary at the base of the brain through the portal vascular system. They bind to specific cell membrane receptors and initiate sequences of metabolic steps, stimulating or inhibiting the pituitary's release of various hormones into the blood. These hormones – among them adrenocorticotropic hormone (ACTH) – control the release of other hormones from target glands (e.g. glucocorticoids or cortisol in primates from the adrenal cortex). In addition to functioning outside the nervous system, the hormones released in response to pituitary hormones feed back to the pituitary and hypothalamus. There they deliver inhibitory signals that keep hormone manufacture from becoming excessive. Studies measuring glucocorticoids show that stressors of sufficient magnitude can produce a sensitization (an increase in response to mild stimuli (Kalat 2001)) effect instead of the expected habituation effect. "When exposure to stressors persists and heightened glucocorticoid release is chronic, there can be permanent changes in the HPA axis. Most notably, the negative feedback system that serves to dampen HPA activation is impaired" (p. 670).

For example, child abuse researchers believe the activation of the HPA axis and the resulting peripheral release of hormones including ACTH, epinephrine (adrenaline), and cortisol are key components in the sensitization of the stress response in traumatized children (Perry and Pate 1994). Further, evidence is now emerging that the HPA changes induced by traumatic events in childhood can persist into adulthood. Women (ages 18-45) who have suffered abuse exhibit increased pituitary-adrenal and autonomic responses to stress compared to nonabused women: "Our findings suggest that hypothalamic-pituitary-adrenal axis and autonomic nervous system hyperreactivity, presumably

due to cortical releasing factor hypersecretion, is a persistent consequence of childhood abuse that may contribute to the diathesis for adulthood psychopathological conditions" (Heim et al. 2000, p. 592). In addition, exposure to "adverse rearing conditions" (including both neglect, in the form of low levels of praise and encouragement, and abuse, as measured by frequent parental anger and physical punishment) is related to lower density serotonin receptors and to dysfunctional serotonin response (Pine et al. 1997).

Higher allostatic load scores or stress in humans were also found to predict increased risks of cardiovascular disease as well as increased risks for decline in physical and cognitive functioning and for mortality (Seeman, Singer, Rowe, Horwitz, &. McEwen 1997). Finally, a study of more than a thousand male Vietnam veterans 20 years after combat exposure suggests a strong link between severe stress exposures and a broad spectrum of human diseases (circulatory, digestive, musculoskeletal, endocrine-nutritional-metabolic, nervous system, respiratory, and nonsexually transmitted infectious diseases) (Boscarino, 1997).

The hippocampus contains a high density of glucocorticoid receptors and plays a vital role in the feedback system that modulates the activation of the HPA axis. It is one brain site where the HPA system converges with the serotonin system. In particular, the hippocampus, and the paraventricular nucleus of the hypothalamus (PVN), are anatomical regions in which components of the HPA axis and the serotonin systems have a rich representation. These regions are also part of the limbic system, an area implicated in the regulation of several vegetative functions (arousal, sleep, appetite and hedonic capacity) as well as in the control of mood. The hippocampus is also crucial for learning

and memory. It is very sensitive to stress and under certain stress conditions, its capacity to dampen the reactivity of the HPA axis can be permanently reduced (Walker and DiForio 1997). Stress of sufficient magnitude permanently alters the modulation of the HPA axis, such that CRH release is augmented and hippocampal glucocorticoid receptors are changed. The recognition that the hippocampus is an integral component of the HPA axis has led some investigators to refer to this neuroendocrine system as the "Limbic"-Hypothalamic-Pituitary-Adrenal (LHPA) axis.

The Limbic-Hypothalamic-Pituitary-Adrenal Axis and Stress

The LHPA is the classic neuroendocrine system that responds to stress. Perception of stress by an organism results in a series of events, the final result of which is in part the secretion of glucocorticoids (cortisol in humans) from the adrenal cortex (Dallman et al., 1987). Activation and termination of the adrenocortical stress response is critical for adaptation and survival. Inhibition of stress responsiveness is partly achieved by the binding of circulating glucocorticoids to specific cytoplasmic receptors in hypothalamus, where they inhibit corticotropin releasing hormone (CRH) and consequently pituitary adrenocorticotropin (ACTH) secretion. Additional modulation of the system is apparently achieved in limbic structures, especially the hippocampus, a structure that is linked to the hypothalamus through neuronal connections that converge on the paraventricular nucleus of the hypothalamus (PVN), where the stress responsive CRH neurons reside (López et al., 1991).

There are several lines of evidence that highlight the importance of the hippocampus for LHPA feedback mechanisms (McEwen, 1991). Pioneer work by McEwen demonstrated that the

hippocampus contains a high abundance of two types of glucocorticoid receptors which are thought to control negative feedback: Type I (also known as Mineralocorticoid Receptor, or "MR") and Type II (also known as Glucocorticoid receptors or "GR"). These two glucocorticoid receptors complement each other and modulate LHPA responses. This puts the hippocampus in a central position to control aspects of cognitive and behavioral functions and modulate simultaneously the neuroendocrine and cognitive response of the organism to stress.

Interaction Between the LHPA Axis and Serotonin

Another level of complexity is added by the fact that serotonin and the LHPA axis interact at multiple levels. Many brain areas that express serotonin receptors also have abundant concentrations of corticosteroid receptors. In the limbic system in particular, the hippocampus has high concentrations of serotonin(1a) in the same neurons that contain abundant GR and MR receptor levels, and the prefrontal cortex is rich in serotonin(2a) receptors (Pazos, Probst & Palacios, 1987), as well as GR receptors. Then, some of the serotonin neurons arising from the nucleus raphe dorsalis and nucleus raphe magnus of the formatio reticularis project to the PVN of the hypothalamus and synapse onto CRH neurons (Fuller, 1992). Serotonin neurons also project to other brain areas, such as the amygdala and the suprachiasmatic nucleus, which are thought to modulate the function of the PVN (Tork, 1990). Furthermore, the co-localization of MR and GR in prefrontal cortex suggest that both of these receptors are capable of modulating higher brain functions, such as mood, social behavior, and cognitive processing, perhaps by interacting with serotonin receptors.

Serotonin and corticosteroid receptors not only interact anatomically, but also functionally. It has been reported that administration of serotonin can up-regulate GR in the hippocampus, and that conversely, pharmacological destruction of serotonergic projections decreases GR and MR mRNA levels in the hippocampus (Betitto et al., 1990; Seckl et al., 1990). Regulation in the other direction, i.e. glucocorticoid regulation of serotonin receptors, has also been reported. Animal studies have demonstrated that adrenalectomy and corticosteroid administration powerfully regulate serotonin(1a) receptor number and mRNA in the hippocampus (Chalmers et al., 1992, 1994; Kuroda et al., 1994).

Stress, Serotonin and the LHPA axis

Both the LHPA and serotonin systems are critical contributors to the neurobiology of stress (McEwen 1987). Chronic stress leads to LHPA overactivity and increases in peripheral glucocorticoids. (Chappel et al., 1996; Armario et al., 1988). Chronic stress and circulating glucocorticoids further influences the serotonin receptor system (López et al., 1997, 1998,1999b). Lopez (1998) found that rats subjected to chronic stress show significant changes in serotonin mRNA and MR mRNA levels in the hippocampus and prefrontal cortex. It is not clear if these serotonin receptor changes are due to a direct effect of corticosteroids on the receptor themselves, or if they are secondary to corticosteroid induced changes in serotonin synthesis and turnover. However, the effects of chronic stress on these serotonin receptors are prevented if the stress-related glucocorticoid increase is abolished.

III. Stress, Serotonin and Depression

Depression, with its feelings of intense sadness, worthlessness, pessimism and reduced emotional well-being, afflicts more than 18 million Americans. In reviewing the clinical, psychological and biological literature on depressive illness, one factor that emerges as being closely associated with depression is stress. Stress and depression have been linked in a variety of ways: For example, both physical and psychological stressors have been shown to be temporally (and perhaps causally) related to the onset of depressive episodes (Post 1992). Some studies have suggested that the association with stressful life events is more common in "non-endogenous depression" (Frank et al., 1994). Other studies have found that stressful life events are significantly correlated even with the first episode of psychotic/endogenous depression (Brown et al., 1994). This is not to say that stress "causes" depression in people. Rather, stress is very likely interacting with an endogenous genetic predisposition, such that in some vulnerable individuals, a stressor can precipitate a mood disorder (i.e. vulnerability + stress = depression). In fact, studies in twins by Kendler (1994) have demonstrated a clear interaction between genetic susceptibility and a recent stressful life event in the precipitation of a depressive episode: the more the genetic "loading" for depression, the more likely a stressful event will trigger an episode. There are of course cases in which the genetic "loading" or predisposition is so high, that an episode of depression can occur in the absence of any apparent precipitating factors.

Under normal circumstances, as I mentioned above, CRH production in the brain helps manage your internal response to daily stressful situations. Many believe that it puts your guard up. You may feel extra vigilant, fearful or anxious. It also sets off a sequence of events that includes the release of two other stress hormones, adrenocorticotropic hormone (ACTH) and cortisol. These hormones arouse

various body systems and prepare them to cope with a challenge. They also facilitate the body's return to a normal state. An increase in circulating catecholamines (through ACTH activation) and glucocorticoids alters the structure and function of a variety of cells and tissues. As mentioned earlier, for each organ system of the body these stress mediators have both short term adaptive and protective and long term damaging effects if the stress response is overextended. Researchers have long suspected that this complex stress system may be overactive in people with depression.

Thus, excessive stress makes the CRH system go awry. For example, severe stress in early life increases the production of CRH in adult animals. Recently, researchers also found that compared with their healthy counterparts, depressed women with a history of abuse experienced a six-fold increase in ACTH levels following a mild stressful situation, which they believe signals CRH problems. A number of researchers contend that malfunctions in the CRH system often underlie depression.

Deeper investigation of the phenomenon has now revealed alterations at each level of the HPA axis in depressed patients. For instance, both the adrenal gland and the pituitary are enlarged, and the adrenal gland hypersecretes cortisol. But many researchers have become persuaded that aberrations in CRH-producing neurons of the hypothalamus and elsewhere bear most of the responsibility for HPA-axis hyperactivity and the emergence of depressive symptoms.

The Limbic-Hypothalamic-Pituitary-Adrenal Axis in Depression

Hyperactivity of the LHPA axis is a well documented phenomena in depression. Historically, the presence of LHPA overactivity in patients with depression was believed by many to be a "secondary" phenomena of the illness. However, over the past few years, it has become clearer that the LHPA abnormalities in depression are intimately linked to the pathohysiology of the disease. This change in perspective was stimulated in part by the increased awareness that glucocorticoids, the final products of the LHPA axis have been shown to have profound effects on mood and behavior (McEwen 1987). For example, a high incidence of depression is linked to pathologies involving elevated corticosteroid levels, such as Cushing's syndrome. This corticosteroid-induced depression usually disappears when corticosteroid levels return to normal (Kathol 1985; Murphy 1991). In fact, it has become increasingly clear, from both animal and clinical studies, that circulating glucocorticoid levels provide important hormonal control of affect, which may be mediated by steroid-induced modulation of central limbic circuitry (McEwen 1987). The precise mechanism by which corticosteroids exert this influence on affect is not well understood. However, this mechanism is likely to involve interactions with brain neurotransmitters, since we know that central control of affect is intimately associated with the actions of the monoamines serotonin, norepinephrine and dopamine.

Serotonin Receptors and Depression

The serotonin system has been widely investigated as a key element in the pathophysiology of depression (Meltzer, 1989), and of suicide (Mann et al., 1989), and as a mediator of the therapeutic action of antidepressants (Berendsen, 1995). Several investigators have proposed that a disturbed balance of postsynaptic serotonin receptors (in the prefrontal cortex and hippocampus) may be

contributing to the pathophysiology of depression (Berendsen, 1995), and that restoring this balance is necessary for antidepressant action (Borsini, 1994). Among the findings supporting a link between low synaptic serotonin levels and depression is that cerebrospinal fluid in depressed, and especially in suicidal patients contains reduced amounts of serotonin metabolites. Moreover, the density of at least one form of serotonin receptor is greater in postmortem brain tissue of depressed patients. This up-regulation is suggestive of a compensatory response to too little serotonin in the synaptic cleft.

Interplay Between Stress, the LHPA Axis, Serotonin, and Antidepressants

The interplay between stress, the LHPA axis, serotonin receptors, and their potential interactions in suicide and depression may can be summarized as follows: 1) Depressed patients, as well as suicide victims, show evidence of overactivity of the LHPA axis. 2) Chronic stress and/or high steroid levels in rats result in an alteration of specific serotonin receptors. 3) Many human studies show the same receptor changes in the brain of suicide victims as also found in hypercorticoid states. 4) Chronic antidepressant administration causes opposite serotonin receptor changes to those seen with chronic stress. 5) Antidepressant administration reverses the overactivity of the LHPA axis.

If indeed the serotonin receptors have at least a partial role in controlling affective states (either directly or secondarily through other systems), then their modulation by corticosteroids provides a potential mechanism by which these hormones may regulate mood. This of course does not exclude the possibility that stress can be simultaneously acting through other systems, such as the CRH receptors, thereby synergistically affecting mood and behavior. Antidepressants can counteract this

phenomenon by affecting serotonin receptor function directly and by simultaneously regulating stress induced corticosteroid secretion.

It is not known exactly how inhibition of serotonin reuptake would lead to normalization of the HPA axis. Even so, the finding implies that serotonin reuptake inhibitors might be particularly helpful in depressed patients with a history of childhood trauma. In animal studies researchers further reported that all the HPA-axis and CRH abnormalities returned when treatment stopped, a hint that pharmaceutical therapy in analogous human patients might have to be continued indefinitely to block recurrences of depression.

The data linking child abuse CRH abnormalities raise profound clinical and public health questions. In the U.S. alone in 1995, more than three million children were reportedly abused or neglected, and at least a million of those reports were verified. The findings imply that abuse or neglect may produce permanent changes in the developing brain – changes that chronically boost the output of, and responsiveness to, CRH, and therefore increase the victims' lifelong vulnerability to depression and other illnesses. If that conclusion is correct, investigators will be eager to determine whether noninvasive techniques able to assess the activity of CRH-producing neurons or the number of CRH receptors could identify abused individuals at risk for later health challenges (e.g. depression). In addition, they will want to evaluate whether antidepressants or other interventions, such as psychotherapy, could help prevent depression in children who are shown to be especially susceptible. Researchers will also need to find out whether depressed adults with a history of abuse

need to take antidepressants in perpetuity and whether existing drugs or psychotherapy can restore normal activity in CRH-producing neurons in humans.

The stress-diathesis model does not account for all cases of depression; not everyone who is depressed has been neglected or abused in childhood. But individuals who have both a family history of the condition and a traumatic childhood seem to be unusually prone to the condition. More work on the neurobiology of depression is clearly indicated, but the advances achieved so far are already being translated into ideas for new medications. Several pharmaceutical houses are developing blockers of CRH receptors to test the antidepressant value of such agents. Another promising class of drugs activates specific serotonin receptors; such agents can potentially exert powerful antidepressive effects without stimulating serotonin receptors on neurons that play no part in depression.

IV. Serotonin and Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and is followed by a series of physiological and psychological events. Pain involves a pain-transmission mechanism and a negative feedback loop termed a pain modulation system. Serotoninergic and catecholaminergic neurotransmitter systems of the brain play an important role in the regulation of pain sensitivity. Many studies have more particularly suggested that the serotonergic, noradrenergic and dopaminergic fibers which innervate the dorsal horn of the spinal

cord play an important role in the control of the transmission of the nociceptive messages and are implicated in the mechanisms of analgesia (Kalat 2001).

It is well known that serotonin is a neurotransmitter for inhibitory neurons and is involved in the pain-modulation system. Low blood serotonin levels are found in patients experiencing migraines and with fibromyalgia syndrome. Chronic pain disrupts normal somatic and visceral regulatory processes, altering the level of brain neurotransmitters. Brain serotonin in the area of the dorsal raphe nucleus of the formatio reticularis is depleted, and it is felt that this accounts for chronic pain and the accompanying depression. In one study (Barson & Solomon, 1998) the authors elected to determine if blood serotonin levels are decreased in chronic pain patients. Twenty-six chronic pain patients were below the normal range for blood serotonin (55-250 ng/ml), while seven were above the normal range. The trend was a skewed curve of blood serotonin levels lower than the normal range in chronic pain patients.

Data presented in another study (Alstergren & Kopp 1997) indicates that patients suffering from chronic pain showed a significant difference in blood serotonin levels when compared to controls. While blood serotonin level is not, in and of itself, diagnostic of chronic pain and its associated disabilities (body serotonin levels are influenced by drugs, diet, and metabolic factors), it can give credence to the chronic pain state.

Migraine and Serotonin

Every year, 16 to 18 million Americans experience migraines. Signs include nausea, extreme sensitivity to light and noise, fever, chills, aching, sweating and, most notably, pain. Wolf down some ice cream and the biting head pain you feel almost matches the intensity of migraine pain but it lasts for a fraction of the time. Migraine attacks can continue for days. The presumed cause of the debilitating ailment has changed throughout history as drastically as the treatments. In Hippocrates' antique era of medical practice, the culprit was considered to be an excess of yellow or black bile. Today, the evidence implicates serotonin, changes in blood vessel size, and the activity of nerve fibers that relay sensory signals, among others.

The first substantial lead came in the early 1960s. Studies of migraine sufferers' urine revealed serotonin abnormalities. Additional research suggested that boosting serotonin levels could decrease symptoms. But strangely, the drug methysergide seemed to ward off migraines by blocking serotonin activity. Answers came much later when researchers identified many different families and subtypes of the serotonin receptors, or receiving areas on cells where serotonin acts to produce different actions. It turns out that methysergide blocks the activity of serotonin at one type of receptor while mimicking the effect of serotonin at another type of receptor. Researchers now believe that this last effect makes extended blood vessels tighten and symptoms diminish.

The discovery of the complexity of serotonin receptors led to the synthesis of newer more specific serotonin agonist (triptans like sumatriptan), which causes fewer side effects than methysergide (Conrad 1997). Sumatriptan bypasses the blocking action and activates only the desired receptors.

While the trigger and sequence of events are still unclear, many scientists believe that the migraine attack involves alterations in serotonin-mediated functions. (1) Blood vessels have an intrinsic tone under normal conditions. (2) During a migraine attack, the blood vessels dilate. This "stretching" of the blood vessel walls may produce migraine symptoms. (3) Migraine pain also may stem from the release of peptides from the trigeminal nerve terminals, which project to the blood vessels. The peptides may alter pain thresholds. (4) Many researchers believe that sumatriptan and other related antimigraine drugs under investigation counter one or both of these migraine contributors through their actions on specific serotonin receptors.

Sumatriptan also allowed researchers to test the hypothesis that the trigeminal nerve system is involved in migraine. This system carries information from blood vessels in the head, from the membranes that surround the brain, and from the spinal cord to the brain stem.

Scientists (Conrad 1997) found that sumatriptan targets serotonin receptors located on both the trigeminal nerve and the blood vessels that service the head as well as other parts of the body such as the heart. Some researchers believe that during a migraine attack, the activation of the trigeminal nerve causes the release of protein fragments called peptides which may cause a process that intensifies migraine pain. A drug that selectively targets only the trigeminal nerve receptors to end the peptide release could have fewer potential side effects than sumatriptan, which has widespread effects on blood vessel size. A new compound that has this selective ability inhibited the migraine process in an animal model and is now being tested in humans.

V. Behavioral Aspects, Social Dominance, Stress and Serotonin

Why would a person behave one way rather than another? For years, scientists have agreed that some behavior flaws can arise from environmental influences including how your parents raised you or from a traumatic life crisis such as the death of a loved one. Now a growing body of evidence suggests that chronic stress and/or severe traumatic life experiences (e.g. child abuse) alter the physiology of the CRH and serotonin system. Some scientists believe that low activity of serotonin in the brain can then lead to an underlying inability to handle powerful feelings, which can result in impulsive acts, aggressive behaviors and suicidal tendencies.

Most theories assign a role of general inhibition to serotonin, either behavioral or emotional. Some assign a central role in the states of anxiety to serotonin (Senkowski et al. 2003). One behavioral manifestation in humans and other animals that is believed to be related to levels of a neurotransmitter is aggression. Aggression is specifically thought to be related to levels of serotonin. Although not under the control of serotonin, aggression appears to be greatly influenced by it. In 1973 Luigi Valzelli studied aggressive behavior in mice. Valzelli isolated male mice and then examined the turnover rate of serotonin after four weeks. Turnover is analogous to usage of serotonin; it is the amount that is transmitted across the synapse and re-synthesized to replace the amount of serotonin used. Valzelli found that there was a decrease in serotonin turnover rate as a result of social isolation. The mice were also found to be more aggressive when placed with other males. When Valzelli compared the different genetic strains of mice, he found that the ones that fought the most had the lowest levels of serotonin turnover.

Valzelli also isolated male rats, measured their serotonin turnover rates and placed the rats with mice. The male rats had different reactions to social isolation. Some rats had a decrease in serotonin turnover level, other maintained a constant rate, and some even had increased rates of turnover. When placed with the mice, the rats with the low turnover rates attacked and killed the mice. Those rats with a constant serotonin turnover rate ignored the mice, and those with an increased rate became friendly towards the mice (Valzelli, 1973). In humans, low levels of serotonin are thought to be related to violent behavior, including impulsive homicide and suicide. The depletion of serotonin is believed to disinhibit aggressive behavior (Soubrie, 1986).

In groups of non-depressed people, levels of a serotonin metabolite 5-HIAA, which is thought to correspond to the amount of serotonin transmitted, were found to be positively correlated with socialization, assertiveness and irritability. 5-HIAA levels were negatively correlated with impulsivity (Schalling, 1984). A study by Brown et al. in 1994 shows that the manifestation of aggression can be predicted by the level of serotonin.

Kravitz (1988, 2000) and Katz et al. (1994) have found that the effect of serotonin on a central synapse of crayfishs depends on the social status and the social history of the animal. Like other neuromodulators in many animals, serotonin sets the gain of synapses and circuits in crayfish and, in this way, appears to modify or select those circuits for a greater or lesser role in controlling the behavior of the animal. The modulatory effect of serotonin is itself modulated by the social status and social history of the crayfish, so that in dominant crayfish the synaptic response is transiently increased, in subordinates it is transiently inhibited, and in isolates it is persistently increased.

Although crayfish adopt dominant or subordinate patterns of behavior immediately after their first fight, the changes in the effect of serotonin take much longer to develop. The changes only follow persistent changes in social status and develop more or less linearly over a 2 week period after the change in social status. The slow change in the effect of serotonin may reflect the time it takes to turn the population of serotonin receptors over, but it may also reflect the undesirability of changing the receptor population merely because the animal had a bad day. After the changes in the effects of serotonin are established, they can be reversed if the change in social status is reversed in a persistent manner, such as when a subordinate animal becomes dominant. However, Krawitz and Katz also found that some changes in the modulatory effect of serotonin occur more easily than changes in the reverse direction: changes in the effect of serotonin that follow a subordinate-to-dominant social promotion follow much more quickly than changes that follow a dominant-to-subordinate social demotion.

Serotonin systems have further been implicated in social dominance in nonhuman primates, where social dominance is achieved largely by affiliation (Higley et al. 1996; Raleigh et al 1991; Westergaard et al. 1999). The limited research evidence regarding the role of serotonin in normal adult human social behaviour also associates higher serotonin levels with increased affiliation (Knutson et al. 1998). It has been demonstrated that low levels of serotonin turnover is correlated with aggressive behavior. Higher levels of serotonin are associated with social dominance(Tse & Bond 2002). How are these two factors related? In a normally functioning brain, serotonin may act as a mechanism through which the brain controls states of anxiety, aggression and temperament. An animal (including humans) that has social dominance may have attained status through conflict,

however once the animal is at a high level of status it no longer has to initiate conflicts. The types of conflicts associated with social rank or territorial defense rarely lead to risky physical struggle. These interactions involve ritualized behaviors that signal social status (Ricklefs, 1993). Higher status individuals have less incentive to initiate social conflict. They also have more to lose if social status is called into question. Lower status individuals may exhibit more aggressive behaviors as a sort of pro-active self defense. Tse and Bond (2002) believe that serotonin is related to feelings of security. Those with high levels of serotonin would feel more secure, giving them a cool yet not docile behavior. Those with a lesser sense of security may be more timid, and would also be more prone to striking out as a form of defense. The elevation of serotonin levels by citalopram may give the effects of a perceived higher social status. This may reduce violent tendencies based on anxiety in that individual.

Social Dominance and Allostatic Load.

Sapolsky (1995) studied stress dynamics in a free-ranging baboon population by using one measure of allostatic load namely basal cortisol levels (with lower basal cortisol levels being healthier in terms of long term well-being). And, with a knowledge of the life circumstances of each baboon, he was able to define four factors that lead to variation of allostatic load in the wild.

1. Rank – Higher rank means lower basal cortisol.
2. Social stability and its enforcement – When baboon societies are stable, those in dominant positions have lower basal cortisol levels than they do during periods of instability. When

stability is imposed by high levels of violence and coercion, the non-dominant baboons have higher cortisols than when it is maintained with low levels of violence and coercion.

3. The experience of rank, stability, and enforcement – In periods of social instability when dominant baboons fight for supremacy, some non-dominant baboons will experience decrease in basal cortisol levels if they are left alone. Other low-ranked baboons react with higher levels if they become victim of displaced aggression from the losers in the fight of dominance.
4. Personality and coping styles – Individual characteristics were showed to matter too. The ability to distinguish seriously threatening situations from ruses, to be able to develop friendships and alliances lead to decreased cortisol levels. These individual characteristics were related to supportive upbringing and mentorship.

Elaborate studies in captive Cynomolgus monkeys showed that relative social status of individuals was a major behavioral factor predicting susceptibility to atherosclerosis through activation of the HPA and sympathetic-adrenomedullary systems (Kaplan & Manuck 1999). Dominant male animals housed in reorganized (unstable) social groups developed about twice the coronary atherosclerosis seen among animals in stable environments. This effect was reversible in study males who received propranolol, a ß-adrenoreceptor antagonist that blocks some of the sympathoadrenal activation. Subordinate social status increased atherosclerosis in female monkeys through stress-induced ovarian dysfunction which was reversible when treated with an oral contraceptive.

Social ordering in human societies is associated with gradients of disease. Although the causes of these gradients of health are very complex, they reflect the cumulative burden of coping with limited

resources and negative life events. They also mirror the allostatic load that these burdens place on the physiologic functions of the human body involved in coping and adaptation. Egalitarian communities, states, and countries with income differences that are small tend to be healthier (Wilkinson 1999). Characteristics of social cohesiveness, social trust, active community participation, or in general the quality of social relations correlate with income distribution and influence the overall health status of the community (Kawachi 1999).

VI. Conclusion

The LHPA axis and serotonin systems have important implications for the pathophysiology of stress, mood disorders, suicide, pain, and interpersonal behaviors. This may be one of the mechanisms by which stressful events can precipitate illness episodes in some (genetically) vulnerable individuals and or precipitate aggressive and suicidal behavior. An important therapeutic implication of this model is the prediction that agents that can reduce the stress response, and/or decrease LHPA activation, will be useful in the pharmacological treatment of anxiety, depression and perhaps suicidal behavior. In fact, patients with depression who are resistant to antidepressant treatment, have been reported to improve after receiving steroid suppression agents, like ketoconazole (Murphy et al 1991; Wolkowitz et al 1993). However, these agents have many side effects, and are often difficult for patients to tolerate. In this respect, CRH receptor antagonists, which are currently under development, may provide us with a new therapeutic weapon to treat these patients (De Souza 1995, Chalmers et al., 1996). These compounds could be used in conjunction with antidepressants, as adjuvants or augmenting agents, and may decrease treatment resistance. This agents may also be useful in monotherapy, since preventing hypercortisolemia may be translated into an improvement of

monoaminergic receptor function. The use of modern biochemical and pharmacological tools, coupled with our increased understanding of the neurobiology of depression, should allow us to test these hypotheses, first in animal models and then directly in patients with affective illness.

Finally, biology, physiology, and genetic expression are constantly shaped by environmental factors and their cognitive interpretation. Stress and the experience of trauma and power relations have long term physiological effects that can lead to disease and impaired well-being. Social status disparities, and the way the communities deal with and respond to them – in the form of hierarchical power relations or some forms of egalitarian cooperation – have a huge impact on health. The way individuals, communities, states, and nations handle rank and hierarchy directly reflects the quality of their social relations and health (Williams, Feaganes, & Barefoot 1995; Putnam, Leonradi, & Nanetti 1993; Kawachi, Kennedy, Lochner & Protherow-Smith 1997). Explanations draw on feelings of social anxiety and the accompanying state of physiological arousal – the stress response. The stress or allostatic load of relative poverty or low rank and the affronts to one's dignity it represents may result in violence. The feelings of shame and humiliation that ensue from it are believed to be psychological pathways that are subject to social anxiety and stress. In conclusion processes of harmful social comparisons and psychological perceptions triggered by relative deprivation explain the importance of social status in its effect on health (Kawachi, Kennedy, & Wilkinson 1999).

The experience of hierarchy, social cohesion or lack of social solidarity, violence and conflict resolution have physiological consequences that over time can affect health and well being of

communities. They demonstrate potential biological pathways through which nervous system sensations – such as an individual's response to stress and the social environment – could influence the host defense system and the expression of a number of different diseases.

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