Psychoneuroendocrine Aspects of Temporolimbic Epilepsy

Part I. Brain, Reproductive Steroids, and Emotions

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The temporolimbic structures of the brain that subserve emotional representation are highly epileptogenic and play an important role in the modulation of hormonal secretion and mediation of hormonal feedback. Estrogen is highly epileptogenic and exerts energizing and antidepressant effects. Excessive estrogen influence produces anxiety, agitation, irritability, and lability. It can promote the development of anxiety manifestations (e.g., panic, phobias, and obsessive-compulsive disorder). Progesterone and its metabolites inhibit kindling and seizure activity. They have potent anxiolytic effects, possibly by virtue of their GABAergic activity. Excessive progesterone influence produces sedation and depression. Testosterone has two major metabolites: estradiol, which can exacerbate seizures, and dihydrotestosterone, which blocks NMDA-type glutamate transmission and may be responsible for antiseizure effects. Testosterone has energizing effects and increases sexual desire in both men and women. In excess, however, it may promote aggressive, impulsive, and hypersexual behavior. Hormonal effects tend to be exaggerated or idiosyncratic in the setting of an abnormal or anomalous temporolimbic substrate, especially temporolimbic epilepsy. This may reflect altered neuronal responsivity to hormonal exposure perhaps by virtue of changes in the number of dendritic spines and receptors. (Psychosomatics 1999; 40:95–101)

Temporolimbic structures are highly epileptogenic; serve as important nodes in relating memory, emotion, and motivation to perception, thought, and behavior; and mediate autonomic and endocrine function as well as feedback.[1,2] What follows is an attempt to explore how 1) reciprocal interactions between the temporolimbic system and the hypothalamic-pituitary-gonadal axis may influence emotions and 2) brain-hormone interactions, especially in the setting of an anomalous or abnormal temporolimbic substrate, may participate in the development and manifestations of affective disorders.

NEUROACTIVE AND PSYCHOACTIVE PROPERTIES OF REPRODUCTIVE STEROIDS

Specificity and Range of Actions

Considerable animal experimental and clinical evidence suggests that reproductive steroids exert a wide range of hormone-specific influences on brain function and behavior (Table 1). Estrogen, for example, increases neuronal firing rates and is highly epileptogenic.[3,4] Estrogen exerts energizing and antidepressant effects.[5–9] Depression, in fact, has been related to estrogen deficiency and has been effectively treated in some cases with hormone replacement.[5,6] Even among nondepressed menopausal women, estrogen generally elevates mood,[7–9] whereas the addition of progesterone partially offsets the improvement.[7,9] Although anxiety has also been treated effectively with estrogen in perimenopausal women,[10] excessive estrogen effect can lead to anxiety or exacerbate agitated depression.[11]

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Progesterone, in contrast, inhibits kindling[12] and seizure activity[13–16] and exerts neuroprotective effects against excitotoxic damage.[17] It has anxiolytic actions, possibly by virtue of its gamma-aminobutyric acid (GABA)-ergic activity.[18–20] Withdrawal of progesterone results in GABA A currents insensitive to benzodiazepine modulation in rat CA1 hippocampus [21] and may exacerbate anxiety in animal models.[22] Excessive progesterone influence produces sedation and depression.[16] Testosterone has mixed effects on neuronal excitability, probably depending on the balance of its two major metabolites, which exert opposing influences: estradiol facilitates *N*-methyl-D-aspartate (NMDA)-mediated conductance [23,24] whereas dihydrotestosterone blocks it.[25] Testosterone has energizing effects and is the most important hormonal factor in promoting sexual desire in women as well as men, while estradiol has a more important role in female sexual response.[26,27] Excessive androgenic influence, however, can promote aggressive, impulsive, and hypersexual behavior.[26,27]

Mechanisms of Action

Steroid actions involve a number of mechanisms (Table 1). Steroids exert long-latency and duration (hours to days), genomically mediated effects by binding to specific cytoplasmic receptors, and, after transport to the nucleus, influencing genomic transcription and translation to produce structural and functional proteins.[28] This mechanism is important in the establishment of sexual dimorphism in the structure and function of the developing brain (e.g., larger medial amygdaloid and preoptic nuclei in male than female rodents, and the receptive, lordotic behavior during estrus in female rodents).[28,29]

Steroids can bypass genomic transcription and influence posttranscriptional protein synthesis. This mechanism is operational in neural plasticity (e.g., the continuous reorganization of hippocampal CA1 dendritic spines and excitatory synapse formation, which varies in relation to the estrus cycle and serum steroid levels in particular).[30,31]

Steroids can produce short-latency and duration (seconds to minutes) allostearic effects on ion channel conductance by binding to nonspecific steroid recognition sites near surface membrane excitatory amino acid and inhibitory GABA receptors.[19,20,23,24]

Estrogen

Estrogen increases glucose and oxygen metabolism,[32,33] cerebral blood flow,[34,35] and neural firing rates.[3,4]

TABLE 1. Mechanisms of action and behavioral effects of reproductive steroids

	Estradiol	Progesterone	Testosterone
Specific receptor sites	Primarily hypothalamic, limbic, frontal, raphe, & locus coeruleus	Primarily hypothalamic and limbic	Primarily hypothalamic and limbic
Receptor numbers:			
estradiol	↓ (↑ in neural damage)	↓	—
progesterone	↑	↑	—
Neural plasticity:			
dendritic branches	↑	↓	—
excitatory synapses	↑	↓	↓
CNS-active metabolites	Catechol estrogens	Allopregnanolone	Estradiol (E2) Dihydrotestosterone (DHT) Androstanediol (A)
Neurotransmitter modulation	↑ Glutamate ↓ GABA ↑ Monoamines ↑ Acetyl Choline ↑ Imipramine binding	↑ GABA ↑ Adenosine	E2: ↑ Glutamate ↓ GABA DHT/A: ↓ Glutamate ↑ GABA
EEG	Excitatory	Inhibitory	E2: Excitatory DHT/A: Inhibitory
Emotional behavior	Elation Anxiety Lability	Depression Sedation Stability	Elation or depression Anxiety or sedation Impulsive, aggressive
Other	Anorexia Insomnia	Weight gain Hypnosis	Anabolic Sleep apnea

It potentiates glutamate and blocks GABA-mediated transmission.[23,24] It substantially increases the number of hippocampal CA1 dendritic spines and excitatory synapses over the ovariectomized level in a time-dependent manner.[30,31] The number of spines increase by about 40%.[30,31] It can increase its own receptors in the uterus[36] and, under certain circumstances, in injured neural tissues (e.g., as may occur in the limbic system after excitotoxic damage).[37] Estrogen may exert its antidepressant effects by increasing monoamine levels in the brain (e.g., by the suppression of monoamine oxidase activity,[5,38] by the competition of catechol estrogens with monoamines for sites of metabolism on catechol ortho methyl transferase enzymes,[39] and by the direct action of estrogen on the estradiol receptors that are abundant in the neurons of monoaminergic brainstem nuclei).[40,41] Although it has variable regionally specific effects on serotonin in the brain, estrogen generally increases serotonin synthesis and levels of 5-hydroxy indole acetic acid (5HIAA). It also increases serotonergic postsynaptic responsivity, number of serotonin receptors, and neurotransmitter uptake.[42,43] Estrogen may also exert antidepressant effects by increasing the binding and clinical effects of antidepressant medications.[44,45]

Progesterone

Progesterone has dose-related sedative, hypnotic, antiseizure, and anesthetic effects,[13–16,18] likely as a result of its ready conversion in the brain to highly neuroactive and psychoactive steroid metabolites, most notably allopregnanolone.[19,20,46] These metabolites are comparable to the most potent benzodiazepines in their ability to potentiate GABA transmission.[19,46] Progesterone also potentiates the action of the powerful endogenous inhibitory substance adenosine.[47] Progesterone decreases the number of hippocampal CA1 dendritic spines and excitatory synapses faster than the simple withdrawal of estrogen.[30,31] It binds specific cytoplasmic receptors not only to produce its own characteristic effects but also to lower estrogen receptor numbers and thereby antagonize estrogen actions.[48]

Testosterone

Testosterone acts on specific neural receptors to promote aggression, competition, potency, and libido.[26,27] Dihydrotestosterone, one major testosterone metabolite, blocks glutamate, specifically NMDA, transmission,[25] whereas estradiol, another major testosterone metabolite, potentiates glutamate transmission.[24] Androstanediol, another androgenic metabolite, has a potent augmenting effect on GABA-mediated chloride transport and exerts anxiolytic effects on adult male rat behavior.[49] The net effect of testosterone on neuronal excitability, therefore, may depend on the balance of its conversion to dihydrotestosterone, as well as other neuroactive androgens, and estradiol, which in turn is tissue dependent and varies with the relative local activities of reductase and aromatase enzymes.[50,51]

THE TEMPOROLIMBIC SYSTEM AND EMOTIONS

In 1937, Papez[52] described the limbic system as an entity that subserves emotional representation. Since then, there has been considerable evidence to suggest that affect is broadly represented in the brain in spatially distributed networks and that limbic structures, especially the amygdala, are important nodes that relate emotion and motivation to perception, thought, and behavior.[1,53]

Temporolimbic dysfunction can alter emotion. This can take the form of corticolimbic disconnection that is characterized by deficient emotion and loss of association between perception and emotional and motivational context.[1,54,55] Disconnection results from amygdaloid or temporal cortical/white matter damage. The effects were demonstrated perhaps most dramatically in the original descriptions of the Kluver-Bucy syndrome[56,57] and in a very elegant experiment by Downer[58] who showed in a split-brain (section of the corpus callosum, anterior commissure, and optic chiasm) experiment in the monkey that unilateral amygdaloid damage and patching of the contralateral eye results in a loss of the usually elicited highly aggressive response of the monkey to visual sighting of the investigator. The response is fully expressed, however, with patching of the ipsilateral eye which leaves the contralateral cortico-amygdaloid connections preserved on the side of the visual input. The Kluver-Bucy syndrome occurs in humans as well as in animals. The full-blown clinical syndrome is a common feature of Pick's disease and, occasionally, herpes viral encephalitis. More commonly, however, one encounters milder or partial syndromes after head injuries and in stroke, epilepsy, and Alzheimer's disease.

Temporolimbic dysfunction may also take the form of corticolimbic hyperconnectivity,[59] that is, a heightening of affect and the attachment of exaggerated emotional and motivational context to perception as a result of limbic reorganization leading to the development of epileptiform

activity (with or without overt clinical seizures),[60] or corticolimbic hyperinnervation.[61] Damage to the hippocampus or amygdala leads to structural and biochemical reorganization that can result in the development of abnormal bursting neuronal activity, including epileptiform discharges, occurring spontaneously and in response to external environmental or internal chemical inputs.[60] Anatomical disruption of the cytoarchitectonically organized cortical input to the amygdala leads to reinnervation of the denervated amygdala by sprouting of adjacent cortical afferents leading to overrepresentation of regional cortical input.[61] Temporolimbic hyperconnectivity has been proposed as the basis for some of the interictal personality changes, including deepening of emotions and the development of an unusual degree of philosophical and cosmic interests, which may develop in some individuals with temporolimbic epilepsy (TLE).[62]

Limbic structures show sensitive electrophysiological responses to gonadal steroid exposure.[63] They have high concentrations of glutamate and GABA receptors and have the highest density of reproductive hormone receptors in the cerebral hemispheres.[40,41] Since the amygdala plays an important role in relating perception to emotion and motivation and shows sensitive electrophysiological responses to hormonal influence, there is reason to consider, therefore, that emotions may be affected by the action of hormones on the limbic system.

ROLE OF ANOMALOUS BRAIN SUBSTRATES

Specific features of brain substrates may play a critical role in determining the nature of emotional changes that develop in response to hormonal influence. Chemical effects on the brain depend not only on chemical identity, dosage, and regimen of exposure but also on the specific receptors, transporters, second messengers, and other characteristics of the brain substrates on which chemicals act.

Brain characteristics are determined by genetic and environmental factors. Genetically, for example, twin studies suggest that 40–60% of anxiety-related personality traits are heritable.[64] A polymorphism in the serotonin transporter gene regulatory region has variants that can determine the level of transporter expression, which correlates with both serotonin uptake and scores on questionnaires measuring levels of anxiety.[64] Likewise, mood disorders, especially manic depressive (type I) disorder, have major genetic components, although identification of specific genes has remained elusive.[65]

Genetic factors are also likely to be the basis for the different roles of the left and right hemispheres in emotion. Gainotti,[66] on the basis of lesion studies, suggested that the left hemisphere expresses predominantly positive affect, whereas the right hemisphere expresses predominantly negative affect. Ross et al.,[67] using intracarotid amobarbital (WADA) test data, proposed that the left hemisphere elaborates social emotions whereas the right hemisphere elaborates primary emotions. Flor-Henry[68] found that power spectral EEG changes occur in the right hemispheres of individuals with manic depressive illness, whereas they occur in the left hemispheres of individuals with schizophrenia.

Genetic differences also play an important role in neuroactive steroid sensitivity and biosynthesis. For example, seizures in genetically bred alcohol withdrawal–sensitive rats have been correlated with lower endogenous allopregnanolone levels than in resistant rats.[69]

Genetic and acquired anomalies in brain substrate likely contribute to the development and manifestations of emotional disorders as well as to treatment response and drug resistance. Emotional disorders may show a tendency to occur in individuals with TLE.[62,70,71] Bear and Fedio[62] found manifestations of anxiety and depression to be more common among individuals with TLE than among control subjects. Himmelhoch[72] demonstrated that atypical lithium-resistant rapid cycling mood disorders are significantly associated with paroxysmal EEG disorders. Other neurological disorders including epilepsy, head injury, developmental disorders, and migraine were also overrepresented. Additionally, Hesdorffer[73] has shown that depression is associated with an increased risk of subsequent epilepsy, perhaps due to a common underlying brain pathology or genetic predisposition.

Anomalous limbic substrates, such as mesial temporal sclerosis in TLE,[74,75] may also be responsible for anomalous emotional responses to hormones (e.g., women with premenstrual syndrome show abnormal emotional responses to normal hormonal changes[76]).This notion has been supported by findings that show that markers of anomalous brain substrates are significantly more common among women who have clinically significant agitated depression in relation to menses or menopause than among unaffected control subjects.[77–79] Such markers include paroxysmal EEG abnormalities, neurological and neuropsychometric findings of hemispheric dysfunction, left handedness, and major mood disorders.[77,78] Paroxysmal EEG abnormalities were present in 27% of women with menstrually related agitated depression and in 36% of women with perimenopausal depression; this is a striking overre-

presentation when compared to the expected value of 1–2%. Observations suggest that paroxysmal EEG abnormalities may also be overrepresented among women with anxiety disorders, including generalized anxiety, panic attacks, phobias and possibly obsessive-compulsive disorder (see below).

Hormonal effects tend to be exaggerated or idiosyncratic in the setting of an abnormal or anomalous temporolimbic substrate, especially temporolimbic epilepsy. In this particular setting, hormones can also have a progressive, cumulatively increasing effect on emotional behavior, such that the normal physiological emotional effect of a hormone becomes transformed over days or weeks of continuous unopposed exposure, into a pathological emotional state. This may reflect progressively increasing or kindled neuronal responsivity to continuous hormonal exposure perhaps by virtue of changes in the number of dendritic spines and receptors. Finally, there is reason to believe that repeated episodes of psychosocially triggered emotional stress may utilize the limbic kindling paradigm to promote more spontaneously occurring recurrent mood and anxiety disorders.[80–82] Such a kindling process could also play an important role in the frequent association of reproductive dysfunction with anxiety and mood disorders in both men and women.

Emotional disorders may result when abnormal endocrine states interact with normal brain, when normal endocrine states interact with abnormal brain, and when abnormal endocrine states interact with abnormal brain. An understanding of these relationships and the therapeutic role of reproductive hormones should lead to more effective and comprehensive management of women and men with anxiety and mood disorders.

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