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Antiepileptic Drugs

Hormones and Epilepsy

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Despite rapid advances in our knowledge of CNS-endocrine interactions, the role of hormones in epilepsy is still poorly understood and the applications of hormonal therapy in this disease remain elusive. The CNS regulation of hormonal production and secretion has attracted widespread attention for several years, and our understanding of these CNS-endocrine relations has increased dramatically. In contrast, the reciprocal information on the physiologic effects of hormones on the CNS in general, and on epileptic states in particular, is less well known. Yet, accumulating evidence points to specific CNS sites and mechanisms of action of several hormones on the brain. The potent effects of some hormones, such as thyroxine and glucocorticoids, on certain aspects of normal and abnormal brain function are well recognized; equally promising are the growing indications that hormones can influence either the development of convulsive disorders or the incidence and severity of epileptic seizures once the CNS is fully developed.

For a summary of earlier studies on the above topics, the reader is referred to previous reviews (34,35,50). Focusing on more recent research, we will consider here hormonal influences on CNS development, hormone-specific receptors in the brain, convulsant and anticonvulsant effects of hormones, interrelations between hormones and conventional anticonvulsant drugs, and new avenues of potential hormonal therapy.

HORMONAL INFLUENCES ON CNS DEVELOPMENT

Various hormones control the differentiation of the hypothalamus, in terms of its pituitary-gonadal regulation, and also influence many other aspects of general neural maturation. The impact of these organizational actions of hormones can best be appreciated when one recognizes that hormonal deficiency or excess does not need to be operative for a prolonged period of time to produce long-lasting effects; hormonal imbalances of a transitory nature occurring during critical periods of development lead to immediate or delayed alterations of CNS structure and function, including seizure disorders. Several hormones, particularly gonadal and adrenocortical steroids and thyroid hormones, are known to affect brain development. For brevity, we will consider here only the effects of thyroid hormones as an illustrative example; the neuronal actions of the other hormones will be discussed in another section.

A deficiency of thyroid hormones induced

at an early age slows neuronal growth in terms of cell size and dendritic and axonal development, reduces synaptogenesis and neurotransmitter competence, delays myelinogenesis, impairs overall synthesis of proteins and nucleic acids and of specific enzymes involved in neurotransmitter metabolism or electrolyte transport, and depresses general brain tissue respiration and glucose metabolism; see (14) for comprehensive reviews on these effects of hypothyroidism. These morphological and biochemical changes are associated with marked neurophysiologic defects (retarded development of brain spontaneous and evoked electrical activity) and severe behavioral disturbances (cretinism in humans), and these functional effects persist throughout life unless replacement therapy is initiated before or at the critical age when the action of thyroid hormones is crucial for promoting optimal brain maturation. The critical period for this hormone is species dependent. For example, the most important time for thyroid hormone effects on brain maturation is around 10 to 12 days after birth for rats (see 14) and during the last fetal trimester and early postnatal period in humans (see 47).

Closely related to the ontogenesis of seizures is the observation that in rats made hypothyroid at birth, the pattern of electroshock convulsions is markedly different from that of euthyroid controls, with a lowering of seizure threshold, shortening of tonic flexion, lengthening of tonic extension, and prolongation of postictal recovery time (33). Such developmental changes in electroconvulsive responses, as well as the increased susceptibility to audiogenic seizures (57) have been interpreted as manifestations of increased brain excitability resulting from delayed and impaired maturation of cortical inhibitory centers or imbalances between inhibitory and excitatory circuits. If we relate the increased CNS excitability of the young hypothyroid animal to recent electron microscope visualization of more numerous but shorter (immature?) synapses in the cerebral cortex of these animals (Table 1), it may be possible to hypothesize that hormonal insufficiency during early development may predispose the affected animal to seizure activity by interfering with normal synaptic formation at the critical time of active cortical synaptogenesis. The importance of thyroid hormones in development and subsequent function of synapses is further demonstrated by observations of retarded proliferation of the dendritic tree, increased density of dendritic spines and synapses in the cerebel-

TABLE 1. *Effects of neonatal hypothyroidism on number and length of synapses in cerebral cortex of 13- and 37-day-old rats*

Age and treatment	Synapses/micrograph[a]	Difference	Length/post-synaptic density (nm)	Difference
13 days				
Control	4.60 ± 0.2[b]		239.4 ± 7.3	
Hypothyroid	4.25 ± 0.31	−8% (p = ns)	207.8 ± 8.2	−13% ($p < 0.001$)
37 days				
Control	5.60 ± 0.32		258.5 ± 8.8	
Hypothyroid	7.30 ± 0.38	+30% ($p < 0.05$)	236.8 ± 6.4	−8% ($p < 0.05$)

[a] Each micrograph represents a tissue area of 34.6 μm^2; a total of 80 micrographs and 115–230 synapses were studied for each age group.

[b] Numbers represent the means ±SE for 4 animals per group. Animals were perfused with 4% glutaldehyde and formaldehyde, and a section from the frontal cerebral cortex was fixed in 2% osmium tetroxide in cacodylate buffer, embedded in araldite resin, and stained with uranyl acetate–lead citrate for electron microscopy (for details of techniques and results, see 16).

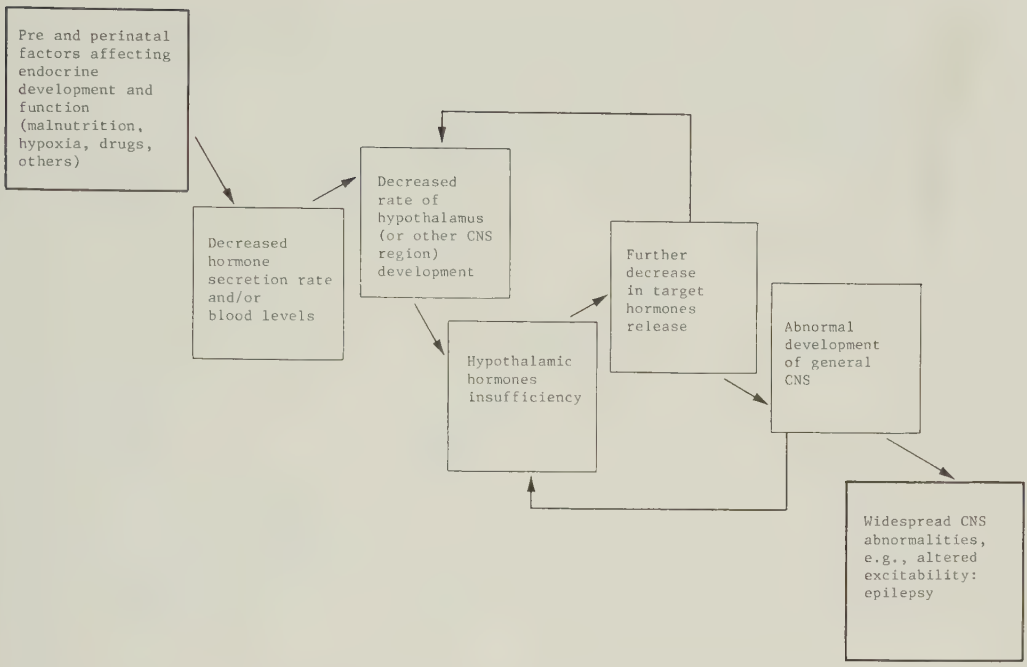

FIG. 1. Proposed brain-endocrine interactions during normal and abnormal development.

lum (24); and these morphologic alterations are associated with disturbances in cholinergic (55), monoaminergic (54), and GABA (10,39) systems after neonatal hypothyroidism. In most cases, replacement therapy at the critical age will restore normal synaptogenesis in hypothyroid animals. Conversely, hyperthyroidism usually accelerates synaptogenesis; but, under some circumstances, this acceleration is only transitory and may indeed revert to a final deficit in synaptic formation (11,24). Thus proper levels of thyroid hormones are necessary for maintaining normal rates of many aspects of brain maturation and for coordinating optimal development of excitability.

Hormonal deficiencies in the fetus are relatively rare inasmuch as maternal or placental hormones usually supply adequate replacement. In the newborn, such deficiencies are probably more frequent (especially thyroid deficiency) but are difficult to detect unless they are extremely severe. Yet, accumulating evidence indicates that a variety of adverse conditions (e.g., nutritional deprivation, hypoxia and atmospheric pollution, drugs) may lead to developmental alterations of endocrine functions and consequent alteration of brain maturation (Fig. 1). Failure to recognize and correct defective hormonal secretion during late fetal and early postnatal life can result in irreversible brain damage; reciprocally, an improved understanding of the mechanisms of hormonal effects on brain development and CNS function may lead to hormonal therapy able to prevent the development of convulsive disorders or to control the incidence and magnitude of epileptic seizures after CNS maturation has been achieved.

HORMONE-SPECIFIC RECEPTORS IN THE CNS

The selective effects of individual hormones on the development of the CNS and on its functions in mature animals imply the existence of distinct hormone-specific receptors in neural cells. Hormones that alter excitability

of central neurons may do so by activating their receptors either pre- or post-synaptically and thereby influencing the efficiency of synaptic neurotransmission. Further knowledge of the locations and functions of the hormone-specific receptors in the brain will eventually improve our understanding of the effects of hormones on central neurotransmission and epilepsy.

Specific receptors for several hormones have been identified in various regions of the adult brain, and their distribution is summarized in Table 2. Of the hormones that are known to have specific receptors in the brain, two have particularly distinct effects on adult brain excitability. As pointed out in early experiments (32,34,35,50) and again demonstrated in recent studies, estrogens increase cortical excitability (18), lower convulsive thresholds, and are clearly associated with certain cases of petit mal epilepsy. Glucocorticoids decrease septal-hippocampal excitability (40), elevate convulsive thresholds of these limbic structures, and have an anticonvulsant effect, at least in infantile myoclonic seizures. It is not yet clear whether the effects of these two hormones on seizure susceptibility directly involve interaction of the hormone with the intracellular receptors.

The developing brain also has hormone-specific receptors. Activation of these receptors at critical stages during maturation can alter the excitability of cortical and subcortical regions after maturation. One of our working hypotheses is that hormone-specific receptors may be most abundant or most sensitive to the hormone during the "critical" period of brain development, and the absence of that hormone during this time leaves the receptors in a continued state of hypersensitivity or abundance. Subsequent exposure to the hormone would overactivate neurons carrying these sensitive receptors and induce seizure activity. The specific binding of estradiol to cerebral cortex is highest during maturation and very low in the adult brain (4,30). This difference cannot be attributed entirely to changes in the penetration of estradiol in the brain after maturation, but, rather, could be due to an age-related decrease in either the number of estrogen receptors or the ability of these receptors to bind estrogen. In either case, the mature cerebral cortex would be relatively insensitive to estrogen when compared to the immature brain. The proconvulsant activity of estrogens is more evident in young than in mature animals, suggesting that the ability of estrogens to increase cortical excitability is directly related to the availability (or sensitivity) of estrogen receptors in the cortex. If animals were deprived of estrogen at some critical time during cortical development, the sensitivity of estrogen receptors in the cortex might remain high during the rest of the developmental period and thereafter. When tested as adults, these animals could then be ex-

TABLE 2. *Relative abundance of hormone-specific binding proteins in various regions of adult rat brain*[a]

Brain area	Estrogen	Androgen	Corticosteroid	Thyroid hormone
Hypothalamus	—	—	—	Low
Preoptic	Moderate	Low	Low	
Other	Moderate	Moderate	Low	
Limbic	—	—	—	Unknown
Hippocampus	Low	Low	High	
Septum	Low	Low	Moderate	
Amygdala	Moderate	Low	Low	
Cerebral cortex	Low	Low	Low	High

[a] Data compiled from refs. 6, 7, 30, 31, and 56.

TABLE 3. *Effects of age and hypothyroidism on the binding of triiodothyronine (T_3) to cerebral nuclei*

Age (days) and treatment	T_3 binding sites (10^{-17} moles/μg DNA)	Equilibrium dissociation constant (10^{-10} moles/liter)
Control		
1	212 ± 28 (5)[a]	3.9 ± 0.80
6	190 ± 20 (2)	6.1 ± 0.01
8	97 ± 6 (2) $p < 0.01$	5.7 ± 0.19
13	115 ± 7 (6) $p = 0.02$	4.2 ± 0.41
33	106 ± 18 (5) $p = 0.05$	3.6 ± 0.77
Adult	120 ± 9 (10) $p < 0.01$	2.31 ± 0.37 $p = 0.05$
Hypothyroid		
13	167 ± 8 (4) $p = 0.05$	3.7 ± 0.52
33–35	154 ± 19 (3) $p = 0.05$	2.2 ± 0.11
Adult	170 (1)	1.5

[a] Numbers represent the means ±SE from number of determinations shown in parentheses. Probability value indicates significance of differences between 1-day-old and subsequent ages in controls, and between control and hypothyroid animals of the same age.

Animals were radiothyroidectomized at birth, the cerebral hemispheres were dissected and homogenized, the purity of the nuclear pellet verified by phase and electron microscopy, and the binding of T_3 to nuclei measured by standard techniques (for details see 7, 56).

tremely sensitive to the proconvulsant effects of estrogens.

Thyroid hormone receptors have been identified in cell nuclei not only of thyroid hormone-responsive organs such as the liver, pituitary, and kidney, but also in the cerebral hemispheres of newborn and adult animals where they are found in high density (6,7,46). In the cerebral hemispheres of newborn animals, both thyroid hormone uptake (51) and receptor density are highest during the first postnatal week when brain maturation, particularly synaptogenesis, is critically dependent on these hormones (Table 3). Furthermore, the number of receptors appears to be dependent on thyroid states, being greater in the hypothyroid animals than in controls at all ages. These data suggest that thyroid hormones may regulate receptor function (*in vivo* and *in vitro*) by producing a compensatory increase in receptor density when thyroid hormone levels are low (44,46,56). That hormones influence the number and state of their own receptors is also known for estrogens (3). The regional distribution of hormone receptors in the brain, their age dependence, and their regulation by hormonal levels indicate not only their importance in brain development and function but also their potential for altering normal function. Thus even a moderate and transient degree of hypothyroidism during early development may increase the number and/or sensitivity of brain thyroid hormone receptors. If subsequently thyroid hormone is administered or its endogenous production increases, overstimulation of supersensitive or superabundant thyroid hormone receptors may lead to alterations in neural function, such as changes in convulsibility. On the other hand, it is conceivable that metabolites of thyroid hormones, or the administration of appropriate hormone analogues, may attenuate hormone-induced convulsions by competing for the receptor and thus provide a basis for therapy.

HORMONAL CYCLICITY

The presence of hormone receptors in selected brain areas, their changes in number and binding capacity with age and with the hormonal state, and their possible functional association with other neuronal receptors—particularly those associated with neuro-

transmitters—may help to re-evaluate some aspects of the complex neuroendocrine interrelationships regulating cyclicity of several functions. With respect to epilepsy, one of the relations most extensively studied is the increase in seizures in some epileptic women and in some laboratory animals at specific times during the menstrual or estral cycles. The affected patients usually demonstrate mixed seizure types, including complex partial seizures. The mechanisms of this so-called "catamenial" epilepsy are unknown. Water retention and electrolyte changes in the brain, perhaps reflecting systemic alterations occurring during the menstrual cycle, have been implicated in the etiopathogenesis of these seizures (see 34,35), even though recent studies seem to discount the physiologic basis of many of the physical and psychologic symptoms associated with menstrual cyclicity (43). On the other hand, acetazolamide (DIAMOX), a carbonic anhydrase inhibitor and diuretic, is successful in the treatment of many cases of these seizures (42), and in refractory cases progestational agents are effective (59).

In addition to indirect actions on systemic metabolism, ovarian hormones display direct actions on CNS excitability which differ with the type of hormone; estrogens increase and progesterone decreases cortical excitability

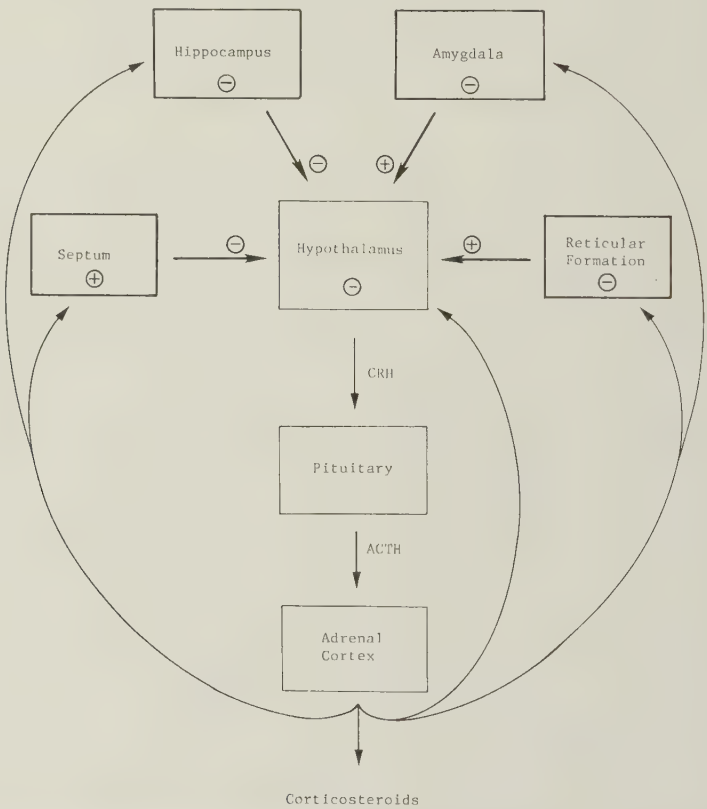

FIG. 2. Neural-hormonal control of adrenocorticotropic hormone (ACTH) secretion. Corticosteroids directly stimulate (+) or inhibit (−) the brain regions indicated in the diagram; concomitantly, neurons in the corticosteroid-sensitive brain regions either stimulate or inhibit the hypothalamus. Thus the hypothalamic secretion of corticotropin releasing hormone (CRH) is modulated directly by circulating corticosteroid levels and indirectly by the regulatory actions of these hormones on limbic and midbrain reticular structures. Although not indicated here, the limbic structures and the reticular formation are also interrelated neuronally and exert complex controls on hypothalamic endocrine function. Finally, both endocrine and neural mechanisms underlying CRH and ACTH secretion respond to endogenous cyclicity and to exogenous stimuli.

(see 32,50). Earlier reports in experimental animals have been confirmed more recently by direct measurements of estrogen and progesterone levels in women in whom epileptic seizures were more severe and frequent during the estrogen-dominated preovulatory phase of the menstrual cycle than in the progesterone-dominated postovulatory phase (1). Progesterone and estrogen levels are lowest during menstruation and progesterone values drop more precipitously than those of estrogens prior to the onset of menses. Enhancement of seizure activity might result from increased excitability consequent to increasing levels of estrogens, or progesterone withdrawal or disregulation in relative or absolute levels of one or both hormones.

Cyclicity in sex hormone secretion has been related to cyclicity in the electrical activity of the hippocampus and the amygdala, two brain areas associated with sexual behavior and control of hypothalamic-pituitary-gonadal function (see 32). The threshold for electrically induced seizures in the dorsal hippocampus and medial amygdala of the rat is lowest during proestrus and part of estrus (at the time of higher estrogen levels) and then increases to a maximum during diestrus (at the time of lowest estrogen levels); the reverse is true for the lateral amygdala. In each brain region, these changes in seizure threshold show a continuing rhythmicity parallel to the hormonal cyclicity of the gonads (see 32,50). Similarly, the circadian rhythmicity of adrenocortical steroids seems to be influenced by hippocampal and amygdaloid inputs (see 32). In seeking the mechanisms of this hormonal and neural cyclicity, it is of interest to note that the hippocampus has the lowest seizure threshold of any structure in the brain: it has been postulated that electrically induced seizures probably originate in the hippocampus, gradually involve other portions of the limbic system, and finally spread to the cortex. The discovery that glucocorticoids are selectively bound by neuronal receptors in the hippocampus in amounts greater than in any other region of the brain suggests that variations in the levels of these hormones, either alone or in association with other CNS drugs, in this seizure-susceptible area may be expected to alter seizure activity (Fig. 2). Data in support of this possibility are still few and therapeutic applicability still remote.

HORMONAL EFFECTS ON SEIZURE MECHANISMS

The clearest effects of hormones on seizure susceptibility are those involving alterations of the threshold or pattern of electroshock seizures in experimental animals (34,50). Many of the hormones which affect electroconvulsive parameters in the laboratory also influence epilepsy in humans. Some hormones for which distinct receptors have not been discovered in the brain may exert marked indirect effects on epilepsy; hyperinsulinemia may precipitate seizures due to hypoglycemia, and hypoparathyroidism may do so by lowering blood and brain concentrations of calcium. Also, ACTH may trigger epileptic convulsions by increasing intracellular sodium concentration throughout the body (35), although direct effects of this hormone on central neuronal function might be even more important to its proconvulsant activity. Other hormones appear to affect clinical seizures by direct CNS actions. Of those hormones for which specific receptors have been identified in the brain, estrogens and thyroid hormone can exacerbate seizures in various types of epilepsy (26), and corticosteroids may have either anticonvulsant activity as indicated by exacerbation of seizures in hypoadrenalism, or proconvulsant effects judging from their ability to induce status epilepticus (2). Progesterone can effectively reduce the frequency and severity of intractable seizures associated with menstruation (59), even though progesterone does not appear to have specific receptors in the brain. Progesterone inhibits corticosteroid binding and subsequent nuclear transfer of corticosteroid in hippocampal neurons (12,31). It is possible that progesterone might also antagonize binding of estradiol to its target neurons and

thereby attenuate the proconvulsant effects of estrogens.

Several studies on the electrophysiological mechanisms of epilepsy have contributed to our knowledge of hormonal effects on seizure phenomena. From the overly simple view that increased brain excitability is an integral part of epileptic processes, it would seem that several hormones may influence epilepsy by altering excitability of cortical or limbic regions. For example, progesterone is able to first decrease and then increase the cortical arousal threshold for electrical stimulation of the reticular activating system (19). Progesterone also apparently suppresses neuronal activity in the hippocampus and amygdala (20). Each of these actions could limit seizure development in epileptic patients. In contrast, estrogens probably increase excitability of the hippocampus and amygdala (20) and are capable of inducing epileptiform electrical activity when applied directly to the intact cerebral cortex (18,29), to various regions of the thalamus, or to chronically isolated cortical slabs (23). In view of these effects, the ability of estrogens to promote seizures, particularly in cases of absence and complex partial seizures, is not surprising.

With respect to thyroid hormones, their actions on neurotransmission, important during early development, may represent their principal and perhaps only role in adulthood. Until quite recently it was difficult to reconcile the continuing behavioral and neurologic consequences of hypo- and hyperthyroidism in the adult individual with the apparent refractoriness of the brain to thyroid hormones, at least as measured by specific biochemical endpoints such as oxygen consumption. The high levels of thyroid hormone receptors in the adult brain without general metabolic effects suggest that these receptors may regulate a different set of gene products depending on whether the brain is still developing or has achieved maturity (7). It has been shown in recent experiments that thyroid hormones do influence both levels and synthesis of the different monoamines in specific areas of the adult brain (17). For example, dopamine and 5-hydroxytryptamine, but not norepinephrine, levels in the cerebral hemispheres are decreased in hypothyroid and increased in hyperthyroid animals; simultaneously, synthesis of these neurotransmitters is correspondingly decreased or increased in the hindbrain where monoamine cell bodies are located. It has been proposed and supported through studies involving drug interactions (8) that thyroid hormones may affect monoamine metabolism by altering receptor sensitivity. In hypothyroidism, a decrease in monoamine receptor sensitivity would lead to a decrease in the postsynaptic response to the appropriate monoamine neurotransmitter; this decreased postsynaptic effect would, in turn, stimulate turnover of the involved monoamine through a negative feedback action on the presynaptic synthesizing enzymes for the monoamine (e.g., tyrosine hydroxylase for the catecholamines). The relevance of these concepts to epilepsy is of interest and worthy of continuing exploration within the important context of hormones, neurotransmission, and convulsibility.

The ability of hormones to influence neurotransmission in the brain is further substantiated by the power of glucocorticoids to enhance the activity of tyrosine and tryptophan hydroxylases, the two rate-limiting enzymes in the synthesis of monoamines (41,48), and the dose-dependent stimulatory or inhibitory actions of these steroid hormones on monoamine catabolic enzymes (36,38). While the pathophysiology of infantile myoclonic seizures is still incompletely understood, the effectiveness of ACTH and glucocorticoids in the treatment of this condition is well demonstrated. It is possible that the anticonvulsant effects of these adrenocortical hormones in the affected children derive from normalization of central neurotransmitter development or function (11), for example, by induction or stimulation of tyrosine hydroxylase (37,52). Indeed, the stimulatory action of stress on monoaminergic synthesizing enzymes could be

partly or mainly due to intervening adrenocortical hyperfunction (52). Perhaps, more directly related to epilepsy, glucocorticoids participate in ethanol-withdrawal seizures by promoting induction of tryptophan hydroxylase and thereby enhancing serotonin turnover in the brain (49).

Several other studies indicate that the effects of ACTH and other hormones and of certain brain peptides on behavior are mediated by alteration of central neurotransmitters (5). Among endogenous peptides, the opiate-like β-endorphins are currently the subject of active investigation in several laboratories. Not only are these peptides found in the brain and secreted by the anterior pituitary simultaneously with ACTH (15), but they have also been shown to induce powerful physiologic (pleasure activation) and pharmacologic (analgesic) effects in several laboratory animals, perhaps through their selective action on monoaminergic neurotransmission (27).

Considering the markedly proconvulsant effects of estrogens, it is surprising that the differential effects of sex hormones on central neurotransmitter mechanisms have been only sparingly investigated. Sex-related differences in activity of many synthetic and catabolic enzymes for the monoamines and acetylcholine occur in the rat: in general, the female has a higher level of activity of brain monoamine enzymes (52,53). In ovariectomized rats, estradiol decreases monoamine oxidase activity and increases choline acetyltransferase activity in various brain regions (28,29). The ability of estrogens to alter the turnover rates of dopamine and norepinephrine in the brain (9) is a clear example of the capacity of hormones to influence fundamental processes of CNS neurotransmission and may relate to the proconvulsant action of estrogens in catamenial epilepsy. Indeed, sex-related differences in brain monoamines may underlie differences in male and female responses to several drugs. Awareness of such differences may prove extremely useful in planning optimal therapeutic regimens for anticonvulsant drugs and may be particularly important in adjusting type and dose of drug therapy in specific conditions associated with an endogenous increase (e.g., pregnancy; 22,45) or decrease (e.g., menopause) or the prolonged administration (e.g., use of contraceptive steroids) of specific sex hormones.

The effects of hormones on GABAergic neurons in the brain also have not been carefully examined as yet. This is unfortunate because of the known effects of hormones on seizure susceptibility and the suspected relationship between GABAergic hypofunction and epilepsy. It is interesting that among many other effects, hypothyroidism in perinatal animals has striking suppressant effects on GABA metabolism (39) and also causes a persistent lowering of electroconvulsive threshold (33). One must wonder whether hyperthyroidism, which increases seizure susceptibility in adult humans, also suppresses GABAergic function in the brain.

HORMONAL EFFECTS OF ANTICONVULSANT DRUGS

Inasmuch as several different hormones have pronounced effects on brain excitability and seizure liability, the mechanisms of action of various anticonvulsant drugs theoretically could involve drug-induced hormonal alterations. So far, the only antiepileptic drug with distinct effects on hormonal release or action is phenytoin; this drug increases the rate of release of glucocorticoids from the adrenal cortex (58), causes hyperglycemia by inhibiting insulin secretion (21,25), and appears to antagonize or counteract the effects of parathyroid hormone on plasma calcium concentration, thereby causing hypocalcemia (13). In short, the known hormonal effects of phenytoin would tend to counteract the anticonvulsant actions of the drug on the CNS; however, the effects of phenytoin, as well as other anticonvulsants, on gonadal and thyroid hormones have not been thoroughly investigated, and the possibility that hormonal actions con-

tribute to the therapeutic effects of anticonvulsant drugs invites scientific examination.

CONCLUSIONS

Endocrine-epilepsy relationships may be viewed as manifestations of the overall regulatory actions of hormones on CNS structure, function, and chemistry. Seizure activity is sensitive to the hormonal state of the individual and is influenced by the balance between the hormones that increase convulsibility (estrogen, cortisol, thyroid hormone) and those that decrease it (corticosterone, progesterone). Hormones are physiologic modulators of cellular activity and exert particularly strong effects on neural tissue; during development, they can induce the differentiation of discrete brain regions, such as the amygdala, hippocampus, hypothalamus, and cerebral cortex, and also influence the differentiation of specific neuronal and glial components directly involved in synaptogenesis and myelinogenesis.

In light of current evidence on the relationship between various hormonal states and epilepsy, further research is needed to determine which hormones are most influential in governing seizure susceptibility, the neurochemical mechanisms of action of proconvulsant and anticonvulsant hormones, and the importance of specific hormonal imbalances during development in the genesis of convulsive disorders.

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