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Pro- and Anticonvulsant Effects of Stress: The Role of Neuroactive Steroids

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MYSLOBODSKY, M. S. *Pro- and anticonvulsant effects of stress: The role of neuroactive steroids.* NEUROSCI BIOBEHAV REV 17(2) 129-139, 1993.—The present review deals with findings related to the contribution of pro- and anticonvulsant effects of "neuroactive" steroids and the role of the γ-aminobutyric acid (GABA) receptor as a physiological target for naturally occuring steroids. Ways are discussed via which GABAergic neurotransmission can be enhanced or reduced following maneuvers that inflict stress. The duality of stress effects is emphasized in conjunction with different types of epileptogenesis (e.g., grand mal vs petit mal) that undergo dissimilar evolution. Among the issues covered are steroid-induced sedation and epileptogenicity, excitatory steroids, stress and epilepsy, GABA and respiratory functions, asymmetric brain injury, and psychopathology and stress.

Epilepsy Stress GABA Neuroactive steroids Sedative and excitatory steroids Respiratory functions

IT has long been recognized that gonadal and adrenal steroids modulate brain excitability, and cause both pro- and anticonvulsant effects in experimental animals (42,46,120,139,149-151). Also, there are numerous examples of cyclic exacerbations of adverse emotional disturbances, somatic discomfort, and seizures in females (catamenial epilepsy) (101,102). In contrast, the status of stress-related epilepsy, and thus the effects of glucocorticoids were always uncertain. Ever since Kraepelin (57), convulsive phenomena were believed to be only rarely affected by emotional factors. The "emotional upsets" were expected to precipitate mood disorders, frenzied motor excitement, and twilight states that were not recognized as epileptogenic. Kraepelin's authority apart, attention to the role of emotions in triggering epilepsy was also diminished due to the fact that the concept of stress is often elusively abstract when applied to human conditions. The problems that are encountered in attempts to define the intensity of stress are too well appreciated to be discussed here. As Yuwiler (156) put it: "It is not what happens to man that is important, but rather what he thinks happens to him." However, it is recognized that stressful events change the excitatory/inhibitory balance of the CNS, causing both facilitation and reduction of seizures. Stress can be convincingly implicated in epilepsy when administered to sensitive subjects, such as timid ("withdrawn") cats (1), or gerbils which respond with seizures to handling (70). Some contradictory reports in this area were briefly illustrated elsewhere (97). Yet, until very recently, no firm conclusion could be drawn regarding the nature of these effects.

The renewed interest in the role of emotional stress is associated with the discovery that γ-aminobutyric acid (GABA) receptor is a physiological target for naturally occurring steroids (8,34,35,73,75,105). Yet, the roots of the present trend are in the discovery of corticoid receptors in the brain, notably their predominance in the hippocampus (82), and findings that excessive glucocorticoids could attack hippocampal neurons, ultimately causing cellular damage with repeated stress (81,82,119). Based on this evidence, it was shown that there exists an unambiguous biochemical, molecular biological and electrophysiological framework applicable to the clinical experience with which the central effects of steroids could be more easily understood. In this paper we shall discuss findings chiefly related to the understanding of pro- and anticonvulsant effects of neuroactive steroids. The term "neuroactive" was introduced by Paul and Purdy (105) to emphasize the robust and fast central effects of certain peripheral steroids and their metabolites.

GABA AND NEUROACTIVE STEROIDS

The contribution of GABA in the central effects of steroids was long perceived as plausible. Bilateral adrenalectomy was shown to produce increased [^{3}H]GABA binding sites, whereas corticosterone treatment opposed this change (54). GABA content in the amygdala and septum was decreased following castration of rats, and such changes were antagonized by testosterone or estradiol (26). GABA antagonists (bicuculline, picrotoxin) administered intracerebroventricularly appear to

stimulate adrenocorticotropic hormone (ACTH) release in rats with deafferented medio-basal hypothalami. The effect was antagonized by a coadministration of GABA (79). Some ACTH-analogues, or corticosterone, were shown to decrease brain GABA content in rats and mice (66,116). There were numerous other examples indicating that GABA-steroid interactions accompany us literally ab ovo. The ovaries even have a high affinity uptake system for GABA, (29) and the oviduct in the rat has a GABA level twice as high as that of the brain (23). These and other findings point to a profound involvement of GABA in neuroendocrine regulation (21,22). Yet, the nature of this coupling remained obscure, perhaps because the research efforts were focused on the effect of GABA and GABAergic substances on different hormones and/or hormonally dependent mechanisms, rather than on hormonal effects on the system of GABAergic neurotransmission.

The first tangible clue to the mystery of the GABA-steroid coupling was provided when a potent sedative pregnane steroid, alphaxalone (3α-hydroxy-5α-pregnane-11,20-dione), was observed to augment effects of GABA and its agonists in the preparation of the rat cuneate nucleus (42). It was shown that ring-A reduced metabolites of progesterone and deoxycorticosterone (allopregnanolone; 3α-hydrox-5α-pregnan-20-one and allotetrahydroDOC; 3α, 21-dihydroxy-5β-pregnan-20-one (THDOC)) potentiated benzodiazepine and muscimol binding (75). These findings, seen in the context of GABAergic effects of benzodiazepines and barbiturates, helped to unveil the nature of the hypnotic potency of steroids, established over 50 years ago by Selye (122).

In the context of epilepsy, the potentiation of GABA-related neurotransmission is conceived to be a therapeutically desirable goal because GABAergic compounds are viewed as potential anticonvulsants (84). In fact, sedative steroids often exhibit significant antiepileptic activity in a number of epilepsy models. Progesterone, and especially some of its reduced metabolites (3α-hydroxy-5α- and 5β-pregnan-20-one), appear to be active in controlling penicillin-induced focal spiking in the cat cerebral cortex (65). Surprisingly, allopregnanolone was found to be effective against metrazol-, bicuculline-, and pictrotoxin-induced generalized convulsions, but not against tonic-clonic seizures elicited by maximal electroshock (8). The hypnotic and antiepileptic effects do not have an obligatory coupling (8). As will be discussed later, the hypnotic potency of a steroid does not guarantee ipso facto its anticonvulsant action (33).

Excitatory Steroids

Despite the proliferation of experimental models, there is still little understanding of how the continuous operation of silent, but susceptible neurons would eventually unite into aggregates generating epileptic spikes. The discovery of the fact that pregnenolone sulphate like other 3β-hydroxy-Δ5-steroid, dehydroepiandrosterone is a novel class of compounds synthesized de novo in the brain, (i.e., "neurosteroids") (6,7) seems to aid in the understanding of how this process may be set in motion. Using fresh crude synaptosomal preparation of the rat forebrain, Majewska and Schwartz (77) established that pregnenolone sulphate at low micromolar concentrations interacts with $GABA_A$ receptor in a picrotoxin-like fashion. It binds competitively to convulsant, (*t*-[^{35}S]-butyl bicyclophosphoronthionate) ([^{35}S]TBPS) recognition site, and inhibits GABA-activated Cl^- transport in synaptoneurosomes. The sulphate of dihydroepiandrosterone also showed GABA-antagonistic potency (77). However, [^{3}H]pregnenalone sulfate binding was inhibited by dihydroepiandrosterone sulphate, whereas [^{35}S]TBPS was not, thereby suggesting that the two may not interact at the same receptor site.

Unlike pregnenolone sulfate, glucocorticoids and their metabolites might also reduce seizure thresholds, but by allosterically increasing the affinity of GABA-antagonistic type ligands for TBPS binding sites. Thus, cortisol, tetrahydrocortisol (3α, 11β, 17,21-tetrahydroxy-5β-pregnan-20-one) and tetrahydrocortisone (3α,17,21-trihydroxy-5β-pregnane-11,20-dione) at nanomolar concentrations potentiated [^{35}S]TBPS binding at 50% over control values (72). Corticosterone, cortisone, as well as tetrahydrocorticosterone (3α, 11β,21-trihydroxy-5β-pregnane-20-one) appeared to be much weaker, augmenting [^{35}S]TBPS binding at the level of 20% above control values. By comparison, bicuculline increased [^{35}S]TBPS binding in synaptosomes by 150% above control (72). Similar to glucocorticoids and bicuculline, the addition of 3α-hydroxy-16-imino,5β-17-azaandrostan-11-one (RU5135) to rat brain P_2 membranes augments specific [^{35}S]TBPS binding by 10–20% (129).

A synthetic steroid, RU5135, described a decade ago (48), is another interesting example of a compound that could have been misperceived for a sedative with epileptogenic properties. RU5135 is a uniquely potent $GABA_A$ receptor antagonist with an affinity for $GABA_A$ receptor about 500 times greater than a reference GABA-receptor antagonist, bicuculline (48). RU5135 is even more potent as an antagonist at the glycine receptor (20, 48). And yet, in a preclinical study in mice, RU5135 showed a depressant-hypnotic action (12). Based on that effect, and our previous finding of behavioral sedation accompanied by wave-spikes after the systemic administration of another $GABA_A$ antagonist, picrotoxin (100), we expected that RU5135 would cause a similar hypersynchronization. However, we observed that within a period of 5–30 min, RU5135 administered to waking Wistar rats with implanted electrodes caused reduced motility and ataxic gait that was followed by and coexisted with a lasting period of epileptic spikes (98). The reduced motility and/or ataxia must have been interpreted as an hypnotic effect, inasmuch as epileptiform motor manifestations following RU5135 administration are meager (98).

The Duality of RU5135 Effects and Cortical Injury

The effect caused by RU5135 appears intriguing in that "all-or-none" interictal spikes, although activated by a systemically administered drug, are very similar to interictal discharges caused by topically applied convulsants, or other maneuvers associated with neocortical injury. Given that brain surgery in small rodents is unavoidably accompanied by brain injury, does it mean that RU5135 also induces epileptic spikes as a result of cortical damage unwittingly inflicted by surgery? The answer to this question appeared to be in the affirmative (99). Even a "zero damage" by the criteria of light microscopy was still associated with a few low-threshold cases of spiking, suggesting that the injury might have been more subtle. Similar spikes were obtained in rabbits. In the latter animal, it was possible to implant an electrode with little, if any, signs of crude cortical lesion. However, even in the latter case, the blood-brain barrier (BBB) was invariably breached consequent to surgery (99). As soon as we implanted electrodes that did not penetrate the inner table of the cranium, it appeared that a higher dose of the drug had to be administered to cause spiking under the nontraumatic (intraosteal) electrode (99). Mintz and Myslobodsky (89), replicated the duality of RU5135 effects in a group of rats prepared for the analysis of

visual-evoked potentials (VEP). The predrug pattern of VEP in rats with implanted penetrating and nonpenetrating electrodes proved to be roughly similar. The striking difference in VEP configuration emerged in response to RU5135. At doses of 0.5 mg/kg, in six out of fourteen animals examined in the study, a clear facilitation of sensory wave-spike after-discharges was obtained only under the intraosteal electrodes. Apparently, the stage of wave-spikes could have been masked in the injured cortex due to the swift development of triggered focal spikes. The coexistence of focal and generalized discharges in the same preparation with the same drug could be explained, assuming that these events represent two different stages of epileptogenesis.

Steroid-Induced Sedation and Epileptogenicity

The resting "brain steroid tone" associated with the cycle of gonadal steroids, seems to represent another factor of the biochemical machinery that channels the focal activity into either wave-spike hypersynchrony, or grand mal-type afterdischarges. This suggestion may be illustrated by the effects of progesterone. The latter was shown to exert a weak potentiating action on the $GABA_A$ receptor. Its 3α-hydroxy-5α and 5β-metabolites are far more potent compounds in this regard, and they exert pronounced antiepileptic and hypnotic effects (152). 5α-pregnane-3α-ol-20-one is present in the brain in a concentration about 100 times higher than in plasma (4). The concentration of progesterone in the cortex is higher than in any other brain area with the exception of the hypothalamus (11). Thus, progesterone and its metabolites could potently increase the "GABAergic tone" of the brain, thereby normally promoting hypnotic effects. They have long been known to cause lasting EEG synchronization in rats, rabbits, and cats (10,52,60,69). The special state of mind characterized by reduced concern, relaxation, sleepiness, and "bizarre dream-like fantasies" that is frequently experienced by pregnant women (14,68) may also be attributed to progesterone potentiation of GABA. So may be the increased resistance to grand mal seizures that was occasionally noticed during pregnancy ever since Collier (18).

The same enhanced background GABA tone is also recognized as a favorable one for the activation of wave-spike discharges (93). In laboratory animals, experimental wave-spike discharges were shown to be facilitated by enhanced GABAergic neurotransmission (95). In keeping with this, Backstrom et al. (4) observed that in four of their patients with petit mal, attacks were more frequent during the luteal phase, and reduced in frequency during menstruation. The synchronizing effect of steroids may be a reflection of a normal mechanism that operates in controlling drives, and mediating the state of drive-reduction that occasionally culminates in epileptogenicity with wave-spike discharges in vulnerable individuals. The synchronous bursting in EEG is associated with a variety of drive-reducing events, such as ingestion of sucrose (in rats), or milk (in cats), escape from painful stimuli, postcoital states, etc. Collectively, these periods of enhanced synchronicity of brain electrical activity were termed "pleasure waves" (93). It was suggested that the pleasure waves may serve as precursors of wave-spike discharges in experimental animals and man.

Neurophysiologically defined, wave-spike hypersynchrony is believed to require two major conditions for its development: 1) a reliable activity of the system of recurrent inhibition, and 2) the excitatory barrage of sufficient intensity (93). To generalize from Eccles (27), provided that the inhibitory synaptic action generated by each burst of action potentials is distributed sufficiently widely in the thalamic neurons, there is no need to postulate any phasic device that causes wave-spike discharges other than rhythmically generated inhibitory postsynaptic potentials (IPSPs) and the background excitatory synaptic activity. In keeping with this dictum, the development of wave-spikes could be expected to occur when the balance between sedative and excitatory steroids is shifted, and estrogens would continue to remain active at a time of sufficiently high progesterone plasma levels. Thus, absences might be expected to predominate in the luteal, or "progesterone" stage of cycle. Alternatively, endogenous GABA antagonists (e.g., sulphated pregnenolone) and/or estrogens (125) would provide sufficient excitatory background to trigger IPSPs, whereas progesterone and its metabolites would facilitate inhibitory postsynaptic action beyond the magnitude required for regulating drives and drive-reduction responses.

Recent studies discovered a more elegant mechanism, whereby excitatory synaptic drive might be effective on a background of IPSPs potentiated by progesterone. It appeared that apart from the "tonic" mode of discharges of the depolarized membrane, there is the transient hyperpolarization that deinactivates a low-threshold voltage-dependent Ca^{2+} current (T-current). The latter assumes a form of a slow, triangular-shaped depolarizing event, termed the low threshold spike (LTS) (134). The LTS underlies a burst of Na^+-dependent action potentials that ride on its crest. Thus, a train of GABA-mediated IPSPs would be a sufficient condition for triggering LTSs (i.e., the "rebound" discharges) when the background excitatory barrage represents a potentiating, but not an obligatory condition as was postualted elsewhere (93).

Even if the process of facilitation of GABA-related inhibitory mechanisms were to be de-emphasized, there still would be a way for progesterone to reduce the excitability of the CNS. Using voltage-clamped neurons, Wu et al. (152) showed that progesterone is capable of reversibly antagonizing glycine-induced Cl^--mediated currents through a site that is distinct from the strychnine and glycine-binding sites. This puzzling effect suggests that progesterone may conceivably cause sedative and antiepileptic effects through glycine-modulated *N*-methyl-D-asparte (NMDA)-receptor functions. The suppression by progesterone of excitatory epileptogenesis is consistent with its attenuation of responses to quisqualate, kainate, and NMDA (126). According to Wu et al. (152), the range of progesterone concentrations in rat plasma is close enough to their EC_{50} values for progesterone to affect glycine-related responses. Therefore, it cannot be ruled out that in vivo, progesterone could contribute to EEG synchronization, and cause sedative effects both through direct, $GABA_A$-receptor related and "indirect" (i.e., glycine-receptor) mediated actions.

This scenario is expected to have exemptions since synchronized discharges based on EPSP-IPSP sequences may be a precursor of epileptic discharges (93), thereby suggesting that sedative steroids may, in certain conditions, show signs of frank epileptogenicity. It is of interest that a potent sedative steroid, alphaxalone, administered either IV or IP in a dose of 4 mg/kg "paradoxically" appeared to potentiate myoclonic seizures in mice with a significant dose-related increase in the duration of the myoclonus. Similar phenomena were noted after the administration of 5β-epimer of alphaxalone and pregnenolone by File and Simmonds (33). Although small doses (0.1–0.25 mg/kg) of pregnenolone and its 3α-epimer caused synchronous EEG patterns in cats, these steroids also caused focal spiking when given in higher doses (2.5 mg/kg) (60). These effects were rather expected if recalled that muscimol,

a specific GABA receptor agonist, produces myoclonic jerks in mice in a dose 2 mg/kg (IP) (86).

Based on the fact that estrogen increases neuronal responses to excitatory amino acids (125), one might expect that reduced progesterone, and/or increased estrogen level could contribute to depolarization of neuronal elements, and the exacerbation of "non-petit mal" forms of epilepsy. The fact that female rats may respond with seizures to a dose of picrotoxin, which is subthreshold for male rats (109), could be associated with such periods of fluctuations of the GABAergic brain tone. It is known that women with partial epilepsy have two peaks of generalized seizure potentiation; the first is coincident with a reduced progesterone blood level during menstruation, whereas the second follows the preovulatory rise of estrogen. During the luteal phase the number of seizures is minimal (4). Clearly, different steroids may have dissimilar effects on these two classes of ictal mechanisms.

Seizures and the Circadian Cycle

There is a certain commonality between the machinery of rapid eye movement (REM)-sleep and the mechanisms of generalized epileptic attacks of grand mal type (28). It is, therefore, understandable that seizures in some way may substitute for REM (17). After electroconvulsive shocks, REM deprived cats exhibited a reduced compensatory REM rebound (16,17). Likewise, in depressed patients on electroconvulsive therapy (ECT), REM-sleep was reduced, and there was no compensatory REM rebound after the end of therapy (157). Neuroactive steroids may well contribute to the coupling, however imprecise, between epileptic seizures and REM-sleep. Estrogens, which are known to increase CNS excitability, would be surmised to act akin to convulsions, or ECT in that they should reduce REM-sleep time. Indeed, a reduction of time spent in REM-sleep was reported during estrogen-induced behavioral estros in spayed rats (154) and guinea pigs (80). Excessive response to cortisol in patients with Cushing's syndrome is associated with a robust reduction of slow-wave sleep stages III and IV (58,59); the effect is still seen a year after surgery (58). It has long been recognized that glucocorticoids lower seizure thresholds in experimental animals (149), and nocturnal grand mal seizures might be expected to be facilitated under conditions of reduced slow-wave sleep. The role of neurosteroids in these effects have yet to be elucidated. It is of interest that pregnenalone sulphate injected cerebroventricularly or even IP to pentabarbital-anesthetized Fisher-344 rats, significantly shortened the sleep time (76).

STRESS AND EPILEPSY

The contribution of neuroactive steroids in mediating either of these effects of stress is being actively examined by several groups. Purdy et al. (112) reported that allopregnenolone and allotetrahydroDOC rise in the cerebral cortex to high levels (3–6 ng/ml, 10–20 nM) 10 min after swim stress compared to nonstressed male rats (< 1 ng/g). This level of these steroids appears to be sufficient to affect GABA-mediated inhibition. Allopregnanolone levels peaked in the cortex to the maximal levels 30–60 min prior to its peak levels in the plasma. This time difference is suggestive of its being formed in situ, apparently from progesterone; the latency of the effect is sufficient for the latter to be converted to its metabolites. Unlike allotetrahydroDOC, allopregnanolone was still measurable in the cerebral cortex of adrenalectomized rats (112). Allopregnanolone, at nanomolar concentrations, appears to potentiate the binding of muscimol and benzodiazepines to the $GABA_A$ receptor, and allosterically inhibits the binding of the convulsant TBPS (74). Observations on voltage-clamped bovine adrenomedullary chromaffin cells in culture showed that allopregnanolone is capable of enhancing GABA responses when administered in the concentration range of 10–30 nM (64). Steroids elicited during stress may be beneficial in that an animal confronted by mortal danger is given a chance to escape rather than develop a panic attack and/or convulsions. As an example, immersion stress administered to the El mice, an inbred mutant strain susceptible to convulsion, caused a complete control of seizures in 38% of animals immediately after stress; the effect being detectable 24 h thereafter. In 41% of them, seizure reduction was obtained following the immobilization procedure (91). Soubrie et al. (128) showed that swim-stress decreased convulsant potency of picrotoxin and pentetrazol, and enhanced cortical binding of [^{3}H]flunitrazepam.

The above effect of stress may vary in different species, and even in different strains of rodents (113), or to different stressors. Also, it may not work well with repeated stressors which could gradually desensitize GABA receptor-gated Cl-channel. Weizman et al. (146) demonstrated this possibility on the example of the in vivo binding of [^{3}H]Ro 15-1788 in conditions of repeated swim stress in mice. It appeared that seven consecutive days of daily swim sessions for only 2 and 10 min were sufficient to cause a regionally selective decrease in benzodiazepine receptor occupancy. The effect was especially robust in the cerebral cortex and hippocampus, but was also detected in the midbrain, striatum, and hypothalamus. In parallel with the reduction of [^{3}H]Ro 15-1788 binding, the anticonvulsant clonazepam appeared to be less effective in protecting stressed animals against a challenging dose of pentylenetetrazol. It is of interest that the effect of reduced [^{3}H]Ro 15-1788 binding to hippocampal membranes in vivo was not obtained in adrenalectomized animals suggesting that peripheral corticosteroids play a role in the regulation of GABA/benzodiazepine receptor synthesis and expression (147).

It is conceivable that the reduction of seizure thresholds in stress may be associated with an increase in the levels of GABA-antagonistic neurosteroid, pregnenolone sulphate (7). The latter enhances NMDA-gated currents in spinal cord neurons, acting at the same time as an antagonist at both GABA and glycine receptors. Although being synthesized in the brain in minute amounts, this agent may conceivably cause a potent local epileptogenic event (153). Why pregnenolone sulphate is being released during stress when protective GABAergic neurotransmission is also being enhanced, is ill understood. There are several equally plausible mechanisms that can serve as a foundation for exploring the relationship between pregnenolone sulphate and stress. The first assumes that the neurosteroid may act as endogenous analeptic maintaining the enhanced state of vigilance (73). Consistent with the effects of flumazenil (63) it may cause anxiety, and, thus, facilitate exploratory behavior and learning. The second possibility might conceive its release, by analogy with effects of GABA antagonists in rats (79,109), as a part of the back-up system, or feedforward circuit further elevating plasma cortisol level. Another class of explanations may derive from the fact that seizures cause a rapid postictal increase of cortical benzodiazepine receptors (106), so that convulsant properties of pregnenolone sulphate may be essential for the proliferation of GABA receptors that counteract the process of their gradual desensitization.

Futher studies will have to elucidate what determines when

excitatory or inhibitory component of steroid action dominate. Among other factors, the type of stress (24), sex, and age (13,25,26,82,111), as well as individual differences in the regulation of pituitary-adrenal functions (82), seem to be relevant to the ways in which the excitatory/inhibitory ratio is being established in the brain.

GABA and Respiratory Functions

One might wonder whether analeptic properties of sulfated pregnenolone are primarily needed to facilitate respiratory functions during emotional and/or physical stress. The increase in ventilation is a common physiological response to acute stress, much as is the cardiac acceleration. In anxious individuals, notably with thoracic respiratory pattern, this normal response may evolve into the hyperventialtion syndrome (78). The syndrome is comprised of impaired sleep, fatigue, depression, and palpitation. In some children, it may be associated with seizures (78,45).

Brain regions involved in respiratory control have a high concentration of GABA, notably in the newborn (44). GABA is recognized as a neurotransmitter that inhibits brainstem respiratory neurons. Applied to the preparation of the isolated spinal cord of the neonatal rat in a dose of 0.1–0.5 mM it causes a dose-dependent reduction in the spontaneous burst frequency (127). Administered intracerebroventricularly, GABA causes respiratory depression in immature animals, the effect being antagonized by bicuculline (44). Much higher doses of bicuculline are needed to stimulate the phrenic nerve activity in hypoxic than in normoxic condition (103). The brainstem reticular formation might be the primary target for sulphated pregnenolone because a neurosteroid with analeptic action may be useful in the early stages of ontogeny when it may accelerate pulmonary maturation, and antagonize GABA-related anoxia in the neonate. Asphyxia is known to cause increased levels of GABA by reducing the circulation of α-ketoglutarate, inhibition of GABA-transaminase, and increasing the intracellular acidity that favors the activity of glutamic decarboxylaze (103). Surprisingly, however, progesterone tend to increase alveolar ventilation in pregnancy as well as during the luteal phase of menstruation, and medroxyprogesterone acetate was found to be effective in the obesity hyperventilation syndrome (133). That might be the reason why women have somewhat higher respiratory rate [and lower hypoxic ventilatory response (148)] than do men.

Pulmonary Surfactant, and Brain Damage Leading to Seizures

The lung has important metabolic functions. It is known that fetal lung is capable of locally converting corticosterone to cortisol (158) with the pace that is increased with advancing gestational age. It contains 2- to 5-fold greater concentration of receptor sites for glucocorticoids than many other fetal tissues, including the brain (5,140). These receptors are believed to facilitate ventilatory drive by acting directly on lung parenchyma (121). The other synthetic lung function is the production of pulmonary surfactant, a substance comprised of lipids, proteins, and carbohydrates that line the surface of lung alveoli and respiratory bronchioles. Its major role is to lower the surface tension of the alveolar lining fluid. The importance of this function is illustrated by the fact that sufactant deficiency—typically associated with lung immaturity—leads to maladaptation and hypoxia, which may culminate in a formidable condition known as the neonatal respiratory distress syndrome (RDS). Numerous studies indicate that endogenous corticosteroids control the rate of surfactant synthesis, and that natural and synthetic corticosteroids accelerate maturation, enhance stability, compliance, and maximal volume of lungs in preterm animals (56,92,135). These findings are of special interest in view of the fact that at the same gestational age, male infants are at greater risk of developing respiratory distress than female infants (141). Predictably, male rabbit fetuses appear to show a lesser response to glucocorticoids than female fetuses (56). The presence of male littermates delays lung maturation in the female fetuses. Similar effects were obtained after daily injection of dihydrotestosterone to pregnant rabbits from day 12 of gestation (141). Given that secretion of surfactant by fetal type II cells should be well synchronized with other maturational processes so as to anticipate delivery, it is not clear why the system preparing fetal lung for postnatal air breathing is less perfectly tuned to delivery in males than in females. It is possible that this puzzling disadvantage of males makes them particularly vulnerable to hypoxia and seizures. This possibility is of interest in view of a higher incidence of temporal lobe epilepsy in human. The preponderance of males with temporal lobe epilepsy was noticed in almost every age group with the male/female ratio within 1.35/1 (138), and often as impressive as 1.7/1 (13). This excess was more clearly seen in childhood (61,138). However, there is a preponderance of females over males among patients characterized by absence seizures. Hauser et al. (43) suggest that females are more sensistive to hormonal changes within the hypothalamic-pituitary-gonadal axis.

Psychopathology, Epilepsy, and Stress

According to Stevens (130), atrophic brain changes in limbic structures of schizophrenic patients are the end result of focal "microseizures" akin to discharges noticed in the septum and anterior striatum in actively hallucinating patients (47). Schizophrenic-like symptoms were described as appearing interictally in patients with temporal lobe epilepsy (123). The kindling model of epilepsy is believed to reproduce various aspects of psychopathology (2). A number of morphometric studies—some of them conducted in the context of CT and/or MRI assessement of the disorder—have been extremely productive, indeed, in elucidating indices of limbic-prefrontal pathology (131). It is of interest that lasting treatment with ACTH and dexamethasone of therapy-resistant petit mal epileptics caused a severe enlargement of ventricles, dilated sulci, and cisterns (62). It should be added that the reduction of seizures was achieved at a price of decreased vigilance and spontaneity, and reduced cognitive functions bordering on pseudodementia.

In both schizophrenia, and epilepsy, the "AAA factor" (Activation, Adaptation, and Atrophy) of McEwen et al. (82) seems to operate in early stages of ontogeny. Among monozygotic twins discordant for schizophrenia, the twin who later became psychotic was more likely to have perinatal complications (110). Schizophrenic males are more likely to have a history of obstetric complications and structural brain abnormalities than are females (107). Similar to schizophrenia, infantile stress in the form of emotional and physical isolation is implicated in epilepsy where parental separation and neglect are occasionally reported as important factors of social background (137, for review and discussion). In laboratory experiments, isolated mice were suggested, in the past, as model subjects for schizophrenia in the past (22). Isolated animals are highly excitable, and known to be excessively aggressive when socially stimulated (22). In contrast, handled (postna-

tally stressed) animals appear to show resistance to stress in adulthood, and reduced susceptibility to seizures elicited by electro-convulsive shock (67). Although an excessive production of glucocorticoids in stress might provide the missing link in the chain of events leading to structural brain damage in both psychopathology and epilepsy, the problem of how intrinsic brain vulnerability, infantile stress, and epileptogenic lesion are put together over time has hardly begun to be approached. Weinberger (145) put forward a few broad speculative suggestions that demonstrate the contribution of stress in schizophrenia conceived in the continuum of aberiant behaviors ranging from attention disorders to Alzheimer's dementia. More recently, the idea of such a continuum was suggested in a somewhat different perspective by Feldon and Weiner (31) who considered Sapolsky's arguments (119) for Alzheimer's dementia as applicable to *dementia praecox*. The problem with this speculation is that it assumes a 12-week exposure to glucocorticoids for hippocampal damage (119). This is a long period of stress, considering the life-span of a rat. Assuming that limbic injury in schizophrenia is attributable to excessive glucocorticoids exposure of comparable length, one might be bothered by the lack of symptoms of hyperadrenocorticism. For example, the neonatal exposure to glucocorticoids due to emotional and/or physical neglect and isolation might be expected to result in the retardation of developmental processes ranging from delayed formation of dendritic spines to EEG slowing (53), and the short stature, such as the "deprivation dwarfism" syndrome which is attributed to emotional neglect (142). For example, the greater vulnerability of males to stress may be seen in an excess of small-grown boys among epileptics (138). In contrast, schizophrenic patients often tend to be taller than controls (108). Another difficulty is posed by the fact that schizophreniform signs seldom if ever are described among symptoms of hypercortisolism (15).

Asymmetric Brain Injury and Stress

Pre- or perinatal stress is especially harmful to neurons in conjunction with the coincidental injury, hypoxia, infections, and/or opportunistic seizures that could cause a massive exodus of excitatory amino acids, and a loss of Ca^{2+} homeostasis. Human infants are exposed to varying degree of hypoxia in a number of clinical conditions (e.g., perinatal asphyxia, respiratory arrest, near-miss suddent infant death syndrome, etc.). Because hippocampal corticoid receptors and hippocampal cells are major victims in events initiated or modulated by glucocorticoids (71,117–119), it might be important to examine why and when a generalized effect of this type should cause injury to a single hemisphere. For example, Ammon's Horn sclerosis is commonly found in the brain of epileptics is frequently unilateral (30). Given that there is no a priori reason to suspect that hippocampal cells of one hemisphere are able to resist excitatory amino acid neurotoxicity, or are better equipped with growth factors, the explanation of unilateral foci may be looked for in such vaiables as the imbalanced neurotransmitter systems, sex-related heterochronicity of the rate of maturation of cerebral hemispheres, stress-related modulation of transmitter asymmetries, brain perfusion imbalances, etc. Among more mechanistic concepts, one might recall that McLardy (83), experimenting with epilepsy in guinea-pigs, attributed the lateralized foci to the postural imbalance of an animal recovering after seizures. He mentioned a tendency for the sclerosis to appear in the underlying rather than in the overlying hemisphere. To maximize the bilateral symmetry, he had to alternate the side on which the animal lay postictally during successive seizures. Asymmetric hippocampal lesions in baboons with experimentally induced generalized seizures, also appear to occur on the side the animals were observed lying postictally (85). It is likely that the underlying side might have been less perfused, and the cumulative effect of hypoxia must have caused a massive release of excitatory amino acids contributing to the lateralized damage. It should be recalled that there is a tendency of head-turning in healthy infants (36). This preference may be frozen in the more persistent motor imbalance ("position of comfort") with tilting of the pelvis and lateral curvature of the trunk. In the weak and/or preterm babies, this position along with reduced motility leads to some degree of skull molding, often in the form known as plagiocephaly (38,51,114). It is of interest that male infants appear to be predominant in developing coronal craniostenosis, which is the major cause of plagiocephaly (49). This hypothesis of McLardy (83) is nice in its symplicity, and it could be easily explored whether infants with cranial deformities are at a higher risk for development of unilateral temporal lobe impairment after occasional febrile convulsions.

However, the situation must be more complex as evidenced by the facts of interactions among pre and perinatal damage, laterality and gender-dependent risk factors (see, 138, for review). It is of interest that prenatal irradiation damage occasionally causes circling behavior in adult rats (94). It was recently shown that radiation-induced damage to the hippocampus is associated with spontaneous turns in long, slow bouts without reversals (88), which is indicative of lateralized or asymmetric damage. Also, there are observations that rat pups separated from their mothers, and reared in conditions of stress in the form of artificial feeding, tend to show left-biased eye opening (124). Undisturbed pups manifest no bias, thereby suggesting that eye opening in isolated pups was associated with a preferable pattern of stress-induced lateralization of the brain (124). In view of this imbalance, it is of interest that diazepam binding inhibitor (DBI), an endogenous ligand of benzodiazepine receptors, appear to be asymmetrically distributed in the hippocampus (L > R) (32).

The Diazepam Binding Inhibitor

The DBI is a negative allosteric modulator of GABAergic transmission (19) that can act directly at $GABA_A$ receptor, and affect it indirectly through the formation of neuroactive steroids by activating the mitochondrial benzodiazepine receptor (MBR) on glial mitochondria. Although DBI might contribute to epilepsy owing to its facilitation of anxiogenic reactions in experimental animals (32,39), its more direct role in changing of brain reactivity might be conceived as that of a trigger of synthesis of neurosteroids. By increasing the formation of sulfated pregnenalone and dihydroepiandrosterone, DBI may cause negative modulation of the responsiveness of $GABA_A$ receptors to GABA. Also, DBI appear to trigger the ACTH-induced steroidogenesis in the adrenal gland (9). In this capacity, it is conceived of as a possible factor in the pathogenesis of hepatic encephalopathy (39). So far, the role for GABA in the latter condition was not compelling (95a,96).

CONCLUDING REMARKS

Stressful events are never solely pro or anticonvulsant because they may both facilitate and inhibit epileptic discharges. Also, they may affect differentially grand mal-type and pe-

tit mal-type epileptogenesis (97). Clearly, an increment of GABAergic tone caused by neuroactive steroids could be of a benefit to patients with excessively depolarized foci of neurons. Yet, excessive GABA may cause untoward effects by reducing the activity of the pontine-medullary circuitry controlling respiration and arousal. This alone would enhance the likelihood of EEG synchronisation, and predispose to epileptogenicity. In addition, the facilitation of IPSP, and reduced arousal caused by excessive GABA might augment cellular bursting (134,143). The latter process is an important, and perhaps more realistic, alternative to the enhanced recurrent excitation postulated to account for robust bursts of postinhibitory spikes, and facilitated responsiveness to flickering light in experimental wave-spike discharges and petit mal epilepsy with photosensitivity (93). The reduced activity of brainstem mechanisms responsible for vigilance and respiration, (i.e., "centrasthenic effect") (93) may be conceived as responsible for the reduced frequency of IPSP-EPSP sequences that brings the neocortical rhythmicity down to the classical 3 cps. Thus, for females with petit mal epilepsy, notably in the luteal phase of the menstrual cycle, the enhanced GABAergic activity may be a mixed blessing.

The epileptogenesis may be conceived as a continuum where wave-spike discharges represent a mild form of pathology, whereas discharges of the focal type (with underlying paroxysmal depolarization) represent its more severe end (37,93). The magnitude of neuronal impairment might actually determine which epileptogenic response (grand mal- or petit mal-type) will occur in response to the neuroactive steroid. The hyperdepolarizing effects of stress are probabaly more likely to occur in the presence of pre or perinatal deficit of limbic neurons, or local brain damage and breached blood brain-barrier when steroids would tend to augment the effect of spilling of excitatory neuroactive substances such as glutamate into the interstitial space from depolarized neurons, and the NMDA-induced flux of Ca^{2+} across the membrane of hippocampal neurons. Certain steroids appear to aggravate glutamate "excitotoxicity". The glucocorticoid pretreatment prior to kainic acid administration, potentiated injury to the hippocampal neurons (71,117). Hall (40) draws attention to an important study by Kerr, Campbell, Hao et al. (55) which showed that corticosteroids augment intracellular free Ca^{2+} concentration in hippocampal neurons. In such circumstances, the ACTH-stimulated DBI might tend to further tip the pendulum of epileptogenicity in the direction of increased vigilance and anxiety by negative modulation of the responsiveness of $GABA_A$ receptors to GABA. By promoting the synthesis of excitatory neurosteroids, DBI may also reduce the strength of GABAergic inhibition. In this context it would be also important to keep in mind the contribution of androsterosteneidione (D4-A) that is secreted along with glucocorticoids during adrenal activation. Although its role in epilepsy has yet to be elucidated, it is mentioned here in view of its association with emotional stress, and acting out, chiefly in boys (132). Judging by studies conducted by Adamec and associates (1,2), the threshold of seizure afterdischarges in the limbic system appears to vary inversely with the propensity for aggression, and degee of withdrawal in cats. Also, prenatally stressed rats tend to be more withdrawn in that they spend more time in defensive freezing than control animals; they take longer time to adapt to the test situation, and to imitate contacts and play with other rats (136). Prenatal history is recognized as an important variable in epileptogenesis. The present review selected respiratory problems of a neonate as relevant for understanding why males are more likely to manifest exacerbated cerebral injury due to increased metabolic debt along with lactic acidosis following inadequate oxygenetation. The preponderance of males with temporal lobe epilepsy was noticed in almost every age group (12a,138) especially in childhood (61,138).

With the advantage of hindsight, one could recognize that the duality of response to stress is faithfully reproduced by high-frequency stimulation of the cerebellum and brainstem reticular formation that modifies focal and self-sustained discharges (93,144). It would be an oversimplification to attribute all such brain excitability changes solely to neuroactive steroids acting at the GABAergic neurotransmission (e.g., 115). For example, GABAergic facilitation may occur consequent to a well concerted action of norepinephrine at GABA receptors. Also, it should be kept in mind that corticosteroids may act indirectly via numerous participating neurotransmitter systems implicated in epilepsy. As an example, arousal-related suppression of wave-spike discharges could be attributed to either corticoid influence on the biosynthesis of catecholamine (3), and/or their impairment of norepinephrine activation through blocking of its extraneuronal uptake (50). The GABA-mediated inhibition of Purkinje cells was shown to be potentiated by norepinephrine (90). It is of interest that proconvulsant effect of muscimol mentioned earlier also requires norepinephrine and serotonin in the production of that response (86). This is an interesting phenomenon in view of the well recognized role of norepinephrine in stress activation, and the possible role glucocorticoids may have in blunting their effects (82). In general, the story of GABA-steroid interaction is only a small part of the picture currently being grasped. Viewing it from that side is akin to a deliberate surrender to the principle which O'Brien (104) called the "academic scotomata." Although GABA is uniquely fit to do the job of commutation of the neuronal flow from a number of systems controling brain reactivity, it hardly does it alone. Only a few possible contributors were mentioned here. This omission is not due to a lack of appreciation of these potential others to the pathophysiology of epilepsy. Simply, very little is known about exact connections of GABA-steroid machinery with that of another set of "stress hormones," such as endogenous opiates are, as well as of aspartate-glutamate systems, histamine, prostaglandin, melatonin that, too, are implicated in epilepsy. We know even less of how different components of this broader system interact in vivo when genomic and nongenomic mechanisms cooperate. These may be themes for a different story.

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