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COMMENTARY

STEROIDS AND BRAIN ACTIVITY

ESSENTIAL DIALOGUE BETWEEN BODY AND MIND

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"Even our destiny is determined by the endocrine glands." Albert Einstein

Steroids as membrane components and general hormones

Steroids are ubiquitously distributed in plasma membranes of eukariotic organisms, where they regulate membrane permeability, maintain cell integrity, and play a crucial role during cell fusion, division and growth [1]. Eukariotic steroid hormones, which are all derived from cholesterol, emerged early in evolution as primitive growth "regulators" and diversified later to sex steroids, gluco- and mineralocorticoids, with remarkable preservation of structure–activity relationships [2].

The functions of steroid hormones as coordinators of cellular activities and regulators of hydro-mineral balance and cell development are essential for survival, since they ensure maintenance of the organism's homeostasis, adaptability to the environment, and reproductive and developmental capabilities. These functions are executed by virtue of two general mechanisms: the interactions of steroids with plasma membranes and with the genome [2]. High lipophilicity of steroids ensures their easy penetration of biological membranes, enabling access to all cells and organs, including the central nervous system (CNS).

Steroid interaction with the CNS produces diversity of both rapid and delayed neuroendocrine and behavioral effects, described in detail elsewhere [3–11]. In recent years, much attention has been devoted to the delayed steroid effects on the CNS. They occur in minutes to hours and are mediated via the interaction with intracellular receptors, triggering alterations of gene expression [8–11]. Delayed steroid actions on the CNS include the induction and the regulation of biosynthesis of various proteins, neurotransmitters, hormones and receptors and are believed to account for several stereotypic behavioral effects, especially those related to sex behavior [7, 10]. These processes also account for the delayed feedback control of the hypothalamo-pituitary-adrenal (HPA) and hypothalamo-pituitary-gonadal axes, via regulation of the synthesis of respective trophic hormones.

Considerably less attention has been focused on the rapid neurotropic effects of steroids, which occur in milliseconds to seconds, such as the alteration of neuronal excitability [4, 6] and rapid feedback control of the release of hypothalamic hormones [12]. In spite of the well described phenomenology of these effects, their molecular nature remains largely obscure, although their rapid time course strongly suggests the involvement of membrane mechanisms.

The principal purpose of this commentary is to generate new interest in rapid neurotropic effects of steroids, which involve modification of neurotransmitter receptors and their effector systems. It is likely that these processes account for multiple physiologic, pathological and behavioral phenomena. Some hypotheses presented here are speculative or provocative. They are not meant to argue with prevalent views but rather to generate new questions and suggest novel avenues of research in this area of neuroendocrinology.

Steroid effects on whole brain excitability

The effects of steroids on neuronal excitability were first recognized by Cashin and Moravek [13], who demonstrated the anesthetic action of intravenously injected cholesterol. Subsequently, in the 1940s, Selye [14, 15] showed rapid and reversible hypnotic actions of certain steroids in the rat. Later studies brought a more complex picture of steroid effects on neuronal activity. While they corroborated that certain steroids, such as progesterone and deoxycorticosterone, have CNS depressant properties, since they decrease brain excitability and increase seizure threshold, they also revealed that 17-hydroxy corticosteroids, such as cortisol and cortisone, have proconvulsant properties, as they increase brain excitability and lower seizure threshold [16–22].

These studies led to the development of a class of steroidal anesthetics, such as hydroxydione (21-hydroxy-5α-pregnane-3,20-dione) (Pfizer) and alphaxalone (3α-hydroxy-5α-pregnane-11,20-dione) (Glaxo) [23–25]. Despite their superior therapeutic properties, such as rapid induction and short duration of anesthesia with minor cardiorespiratory effects and symptom-free awakening, steroidal anesthetics were withdrawn from the market due to their clinical disadvantages. These included the lack of analgesic effects, the existence of some allergic reactions, the occasional precipitation of convulsions, involuntary muscle movement, and toxicity for newborns [24, 25].

The excitatory effects of 17-OH-corticosteroids have been also studied thoroughly in behavioral and

electrophysiological experiments, prompted by clinical observations that cortisol therapy occasionally generated epileptogenic seizures [26, 27] and produced dramatic alterations in electroencephalograms [28]. Both early and recent studies demonstrated predominantly excitatory effects of cortisol and cortisone, injected intravenously, intraventricularly or applied locally, on neurones from various brain regions [29–34; for reviews, see Refs. 4, 6 and 34]. However, inhibitory actions of the glucocorticoid corticosterone in the hippocampus have also been reported [35], as well as bimodal or biphasic effects on the activity of certain diencephalic [31, 36] and motor [4] neurones.

Estrogens have been shown to facilitate neuronal firing in hippocampus [37] and to either increase or inhibit electric activity of hypothalamic neurones in female rats [38]. More detailed studies revealed that the estrogen-induced increase or decrease of neuronal activity is localized to the area that fosters (baso-medial hypothalamus) or inhibits (preoptic area), respectively, female sexual behavior [7]. Testosterone-sulfate, iontophoretically applied to hypothalamic neurones in the preoptic area, facilitated both neuronal firing as well as copulatory behavior in male rats [10]. (It appears that the preoptic area plays an opposite role in expression of male and female sexual behavior, since electrical stimulation of neurones in this area stimulates copulatory behavior in males, but inhibits sexual behavior in females [7, 10]). Although the exact nature of these effects of estrogen and testosterone on neuronal firing is not known, it is likely that they are directly related to the expression of female or male sexual behavior.

Steroid interactions with neurotransmitter receptors

The rapid changes in neuronal excitability following steroid application preclude involvement of genomic mechanisms and suggest interactions with membrane components, such as receptors for neurotransmitters or their effector systems. The interaction of gonadal and adrenal steroid hormones with biogenic amine and opiate receptors in the brain has been described [39–42]. Since the scope of the present article does not allow for a detailed discussion of each of these steroid effects, I will concentrate on our recent findings describing interactions between steroids and the γ-aminobutyric acid (GABA-A) receptor complex and will discuss their physiological and pathological implications.

Steroids and GABA receptors. The GABA-A receptor complex is an oligomeric protein complex, which, when activated by agonists, produces an increase in neuronal membrane conductance to Cl^- ions, resulting in membrane hyperpolarization and reduced neuronal excitability. A number of centrally acting drugs, including convulsants, anticonvulsants, anesthetics and anxiolytics, interact with distinct, but interacting domains of this receptor complex, to modulate Cl^- conductance (for review, see Ref. 43).

Following my original observation that cholesterol increases ligand binding to GABA receptors (Majewska, unpublished observation), we have demonstrated subsequently that several endogenous steroids are potent modulators of the GABA receptor complex. Initially, we have shown that corticosterone and pregnenolone-sulfate modify the binding of muscimol, a GABA-agonist, to synaptosomal membranes from adrenalectomized rats in a biphasic manner, enhancing binding at nanomolar concentrations and reducing it at micromolar concentrations [44]. Autoradiographic analysis revealed a uniform distribution of the interaction between steroids and GABA receptors in several brain regions such as cerebral cortex, hippocampus, thalamus, amygdala and caudate-putamen. An increase of GABA binding by a synthetic steroid anesthetic, alphaxalone, has been also described [45].

Our further studies revealed an intricate nature of steroid modulation of GABA receptors. Some steroids, such as A-ring reduced metabolites of progesterone: 3α-hydroxy-5α-pregnane-20-one (3α-OH-DHP), and of deoxycorticosterone: 5α-pregnane-3α,21-diol-20-one (THDOC), interact with the GABA receptor complex like hypnotic barbiturates. These steroids potentiate both benzodiazepine [46] and muscimol [47] binding, as well as inhibit the binding of the convulsant *t*-butylbicyclophosphorothionate (TBPS) in a manner similar to barbiturates [46]. Furthermore, these steroids stimulate Cl^- uptake into rat brain synaptoneurosomes in a picrotoxin-sensitive manner and potentiate GABA-activated Cl^- conductance in hippocampal neurones [46]. Such actions of reduced metabolites of progesterone and deoxycorticosterone correspond with their reported hypnotic/anesthetic properties [25, 48].

We have also demonstrated that pregnenolone-sulfate (PS), termed a "neurosteroid" due to its apparent central origin [49], at micromolar concentrations interacts with the GABA receptor complex principally as a picrotoxin-like antagonist [50]. PS binds to a "convulsant" picrotoxin-TBPS recognition site at the receptor complex and inhibits pentobarbital-enhanced benzodiazepine binding and GABA agonist-stimulated Cl^- uptake into synaptoneurosomes [50]. The GABA antagonist features of PS are consistent with its excitatory actions in brain [51] and convulsant properties of related 3β-hydroxy steroids [21]. Besides its antagonist actions, *in vitro* PS demonstrates some agonist properties, as it slightly increases muscimol [44] and benzodiazepine [50] binding.

Glucocorticoids interact with the GABA receptor system in a more complex manner. Initially, we demonstrated a biphasic effect of corticosterone on muscimol binding [44], while my later studies revealed that some glucocorticoids, particularly those containing a 17-hydroxy group, interact atypically with the convulsant sites labeled by TBPS. Specifically, cortisol, cortisone and their reduced derivatives, at nanomolar concentrations, enhance TBPS binding and subsequently reduce it at higher concentrations (Majewska, unpublished data). The increment of TBPS binding by 17-OH-glucocorticoids, which is due to an increase in the apparent affinity and density of TBPS recognition sites, is opposite to the action of anesthetic barbiturates and appears to be similar to the effect of the GABA receptor antagonist, bicuculline, on TBPS binding (Majewska, unpublished). The bic-

uculline-like interaction of some synthetic steroids with the GABA receptor complex has been described previously [52–54].

Theoretically, the enhanced apparent affinity and density of "convulsant" binding sites induced by glucocorticoids would be expected to have proconvulsant effects and potentiate neuronal excitability. In fact, this action of glucocorticoids is supported by electrophysiological experiments [4, 6, 29, 30]. Since the steroid PS appears to be a natural ligand for TBPS binding sites [50], 17-OH-glucocorticoids may also enhance its binding and, therefore, amplify its antagonistic actions, thus playing a role of "second order modulators". This concept remains to be experimentally tested, but good correlations between the efficacy of glucocorticoids to potentiate TBPS binding (Majewska, unpublished data) and their ability to lower seizure threshold [17] support the notion that some proconvulsant effects of glucocorticoids may be GABA receptor mediated.

Rapid inhibitory actions of glucocorticoids on neuronal excitability have also been observed [35]. These actions correspond to the enhancement of the GABA agonist binding produced by the glucocorticoid corticosterone [44]. Thus, theoretically, both excitatory and inhibitory effects of glucocorticoids can be GABA receptor mediated, although their exact molecular nature is yet obscure. It is possible that the bidirectional actions of glucocorticoids on neuronal activity, as observed in electrophysiological experiments, may depend on additional cellular and neurochemical factors, for example the availability of PS. The fact that several endogenous steroids heterogenously interact with the GABA receptor system adds to the complexity of the picture, but it also stresses the importance of regulation by steroids of GABAergic neurotransmission.

Mechanisms of steroid interactions with GABA receptors. Our studies have determined stringent structural and stereochemical requirements for interactions of steroids with the GABA receptor complex, both in their expression of barbiturate-like and picrotoxin-like activity [46, 47, 50]. This suggests the existence of specific recognition sites for steroids, located at or near the GABA receptor complex. Indeed, the existence of steroid binding sites in plasma membranes has been demonstrated [55], although the biochemical nature of sites involved in the regulation of the GABA receptor complex is still obscure. Theoretically, these sites could either be associated with the GABA receptor proteins or with membrane phospholipids, as the latter are capable of a high degree of structural and geometrical discrimination in the binding of steroid molecules [56].

Origin of centrally active steroids

In animals, adrenal cortex, gonads and liver are predominant sources of steroids which can eventually reach the CNS. The precursors of "inhibitory" steroids, 3α-OH-DHP and THDOC, are progesterone and deoxycorticosterone, the major steroid hormones released by ovaries and adrenals. These two glands contain enzymes, 5α-steroid reductase and 3α-steroid oxidoreductase, which are capable of forming "anesthetic derivatives" from inactive primary hormones, during a process that remains under strict physiological control [25].

In rodents, ovarian release of 3α-OH-DHP closely follows the phasic release of progesterone during the estrous cycle and is highest at met-oestrus [27, 57]. 3α-OH-DHP secretion is stimulated by the pituitary luteinizing hormone (LH), but not by follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), oxytocin and vasopressin [27]. Although similar experiments in humans have not yet been performed, it is likely that during the menstrual cycle the ovarian secretion of 3α-OH-DHP will also be under the control of LH and will follow the release of progesterone.

During pregnancy in rats, despite high progesterone levels, a fall in the secretion of 3α-OH-DHP has been observed, subsequent to the decrease in the production of hypophyseal LH [58]. However, injections of human chorionic gonadotropin or pregnant mare serum greatly enhance ovarian secretion of 3α-OH-DHP [58]. In male rats progesterone and its reduced metabolites are released by testes [59, 60], but the physiological regulation of this secretion is unknown. The difficulties in extrapolating these data to the human conditions indicate the need for clinical studies to evaluate similar physiological parameters in humans.

Along with classical hormones, such as gluco- and mineralocorticoids, mammalian adrenal cortex secretes steroids with activity that cannot be strictly confined to either of these classes. These include anesthetic steroids, 3α-OH-DHP and THDOC and their precursors [58, 61]. ACTH stimulates the secretion from adrenals not only of major glucocorticoids, but also of mineralocorticoid, deoxycorticosterone (DOC), and its centrally active metabolite, THDOC [61, 62].

Neural tissues and pituitary contain the enzymes, 5α-reductase and 3α-oxidoreductase [63–65], which are capable of converting the inactive precursors, progesterone and deoxycorticosterone, to the anesthetic steroids 3α-OH-DHP and THDOC. The activity of 5α-reductase has a heterogenous regional distribution in the CNS, the highest levels being found in the anterior pituitary, midbrain tegmentum, hypothalamus, medulla and hippocampus [63–65]. In contrast, 3α-oxidoreductase appears to be rather uniformly distributed througout the brain, with the greatest activity found only in the olfactory bulb [66]. Although all brain tissues are capable of producing anesthetic steroids, the greater synthesis of these steroids (determined by the distribution of synthesizing enzymes) in areas such as the olfactory bulb, anterior pituitary, midbrain tegmentum, medulla, hypothalamus and other limbic structures suggests a physiological role of these steroids in the regulation of the sexual behavior, emotions, postural control sleep and wakefulness, and other vital activities.

The brain contains substantial amounts of the steroid precursors, cholesterol and its sulfate [67], and appears to be able to synthesize *de novo* 3β-hydroxysteroids such as pregnenolone, dehydroepiandrosterone and their sulfate derivatives [49], apparently in the glial compartment [68]. The relatively large

amounts of these steroids in the CNS, their fast turnover, and alterations during various physiological states imply their role in CNS function. Some studies suggest their involvement in the regulation of sexual behavior [68], and our observations imply that PS may function as an endogenous antagonist of the GABA receptor complex [50]. Furthermore, since the metabolic conversion of pregnenolone to progesterone also occurs in brain [68, 69], it is likely that the brain is capable of limited *de novo* synthesis of both GABA-agonistic and -antagonistic steroids.

Physiologic and pathological roles of GABA receptor-steroid interactions

Sexual functions. Neuroendocrine and behavioral studies suggest a facilitatory role of GABA in the induction of sexual receptivity in female rats [70]. Since both progesterone and deoxycorticosterone, as well as their reduced metabolites, promote lordosis in female rats [71], it is tempting to speculate that these steroids act, at least in part, through a potentiation of GABAergic inhibition of neurones involved in expression of this behavior. The pyrogenic nature of 5β-reduced progestins, also occurring naturally [64], may be responsible for elevation of the body temperature, characteristic for the early luteal phase of the menstrual cycle, when the progesterone level is high [24]. The role of PS in the expression of male sexual behavior is suggested by the fact that, upon heterosexual exposure, the amount of this steroid is reduced in the olfactory bulb, but increased in the olfactory tubercule and amygdala in rats [68]. Since PS has GABA-antagonistic properties, this may lead to alterations of neuronal firing in brain regions that control male sexual behavior.

Stress. Stress represents a chain of the organism's integrated adaptive reactions evoked by aversive stimuli of physiologic or psychologic nature. The stress reactions, termed by Selye as a "general adaptation syndrome", develop in stages: alarm reactions, stage of resistance, and stage of exhaustion [72]. They are associated with the intense psychologic changes and integrated neuroendocrine and somatic reactions resulting in a variety of behaviors. Stress is always associated with the activation of the sympathetic nervous system and the HPA axis, concomitant with the inhibition of functions not essential for preservation of life during emergency, such as reproductive and developmental functions.

During stress, the hypothalamus releases corticotropin-releasing factor (CRF) into the hypophyseal portal circulation, which stimulates the secretion of ACTH from the anterior pituitary. Subsequently, ACTH activates the release from the adrenals into the circulation of several steroids, which perform multiple peripheral functions important for survival during the state of emergency. These include: stimulation of hepatic gluconeogenesis, lipolysis, proteolysis, suppression of immune reactions, inhibition of peripheral glucose uptake, and conservation of electrolytes.

Alterations in neuronal activity may be also important for survival during stress. Corticosteroids released in stress, cortisol and THDOC, are modulators of the GABA receptor complex [44, 46]. Furthermore, experimental data suggest that in stress the brain content of PS also increases [68]. Although information concerning stress-related alterations of the brain content of specific steroids is unavailable, physiologic and behavioral observations invite the speculation that elevated brain PS levels may suppress GABAergic inhibitory activity, thereby contributing to the arousal associated with early stages of stress. The 17-OH-glucocorticoids could augment these actions of PS. Teleologically, the facilitation of neuronal firing by excitatory steroids may be essential for prolonged maintenance of alertness during "fight or flight" reactions.

However, ACTH also stimulates the release of THDOC from the adrenals. This steroid, which has both anxiolytic and anesthetic properties [24, 25, 73], may then protect neurones from overstimulation during stress. It is likely that this steroid comes into play during the stage of "resistance" and is responsible for the restoration of CNS homeostasis during stress. Thus, one can hypothesize that the activity of the CNS during stress may be shaped by an interplay between the excitatory and inhibitory steroids, since we have shown that they modulate each other's actions [50]. The diversity of individual reactions to stressors may depend, to some degree, on the type of steroid predominating in stress (determined by the enzymatic activity of steroidogenic tissues and the CNS). Furthermore, it is predictable that stress behavioral reactions will be modified by physiological states such as pregnancy, phases of the menstrual cycle, puberty or menopause, likely to be associated with altered plasma and CNS levels of inhibitory and/or excitatory steroids (see Fig. 1).

Feedback control of steroid release. It has been documented that GABA inhibits the activity of the HPA axis, thereby modulating the adrenocortical response to stress. Injected intracerebroventricularly, GABA suppresses the stress-induced released of ACTH in rats [74] and, applied *in vitro* to the bathing medium, GABA inhibits acetylcholine- and serotonin-stimulated release of CRF from the hypothalamus in a picrotoxin-dependent manner [75]. It is tempting to predict that "inhibitory" steroids, such as reduced metabolites of progesterone and deoxycorticosterone, could participate directly in the negative steroid feedback mechanism by potentiation of the inhibitory actions of GABA. This question still remains to be tested experimentally, although the existing data do not necessarily support this prediction. First, Kraulis and collaborators [48] reported that administration of THDOC did not inhibit the adrenal response to stress. Second, the structural requirements for fast and delayed feedback of corticosteroids [76] are different from those for expression of their barbiturate-like activity [47]. Third, the pattern of interaction between GABA receptors and corticosteroids in the hypothalamus appears to be distinct from that observed in other brain regions, since the steroid-induced enhancement of muscimol binding in the hypothalamus is absent [44]. Finally, pentobarbital, which potentiates the activity of the GABA receptor complex, does not depress the acute stress-induced elevation of plasma corticosterone, nor its circadian rhythm, although it does inhibit the rise in corti-

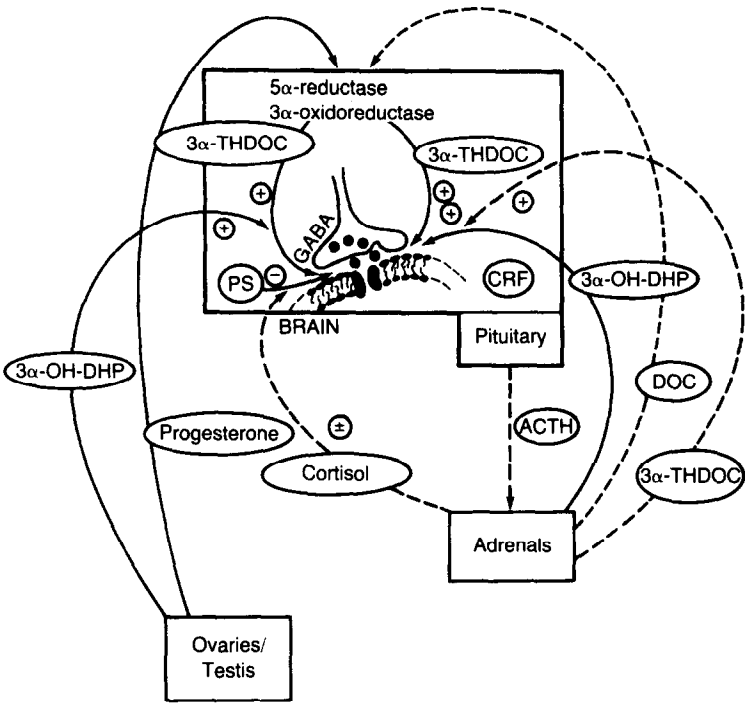

Fig. 1. Pathways of regulation of the brain GABA receptor by steroids. This figure presents theoretical routes of regulation by steroids of the central GABA receptor complex. Ellipsoidal lines enclose names of steroids: 3α-OH-DHP (3α-OH-dihydroprogesterone, 3α-OH-5α-pregnane-20-one), 3α-THDOC (3α-tetrahydrodeoxycorticosterone, 5α-pregnane-3α, 21-diol-20-one), DOC (deoxycorticosterone), and PS (pregnenolone-sulfate). Dashed lines represent stress-induced release from the adrenal cortex of "GABAergic" steroids: cortisol, deoxycorticosterone and 3α-THDOC. Signs (+) or (−) denote steroids that potentiate or inhibit GABA receptor function, respectively. *Inhibitory steroids* (+) can be synthesized peripherally in the gonads or adrenals or can be produced in the CNS from inactive precursors: progesterone and deoxycorticosterone. These steroids have hypnotic and anxiolytic effects and probably play a role during physiological states such as sleep, stress, pregnancy and various phases of ovarian cycle. *Excitatory steroid* (−), PS, originates *in situ* in the CNS, most likely in the oligodendroglia [68]. This steroid may be a "local" modulator synthesized and released from glia during stress, sexual functions, and possibly other physiological states. By restriction of inhibitory function of GABA, PS may contribute to the arousal and play a role of an endogenous analeptic. *Cortisol* and other glucocorticoids (±) probably have bimodal or biphasic modulatory effects on function of the GABA receptor complex.

costerone levels induced by fasting or prefeeding time [77, 78]. This suggests the existence of heterogenous physiological mechanisms for activation of the HPA axis. It is likely, however, that THDOC secreted during stress could reduce the HPA activity through the inhibition of afferent stimuli from extrahypothalamic limbic structures.

Depression and anxiety. The important role of GABA in the modulation of behavior and emotions as well as in the etiology of some affective disorders has been recognized recently [79–81]. GABA function in depressive disorders is suggested by the following observations: (a) GABA levels are low in cerebrospinal fluid (CSF) of depressed patients; (b) GABA agonists inhibit depression; (c) intrahippocampal injections of the GABA antagonist, bicuculline, produce "helpless" behavior in naive rats and injections of GABA to this region immediately reverse helplessness [79–81]. (Learned helplessness is a behavior widely utilized as an animal model of depression, as its psychological and psychomotor profile resembles several symptoms of human depression [82]). A GABAergic theory of depression is also supported by the findings that tricyclic antidepressants inhibit GABA uptake and stimulate its release, and that the antidepressant effect of MAO inhibitors can be blocked by bicuculline [80]. The fact that GABA-mimetics enhance noradrenergic transmission, like classical antidepressants, provides a link between the older aminergic and the more recent GABAergic theory of depression. Finally, clinical observations point to a close relationship between depression and anxiety disorders, recognized as resulting from deficiences in GABAergic transmission [79, 83].

Involvement of steroids in the regulation of GABA receptors suggests their pivotal role in mood disorders. Indeed, the hyperactivity of the HPA axis and hypersecretion of 17-OH-corticosteroids are commonly linked to depression [84, 85], and the resistance to feedback inhibition (escape from dexamethasone suppression) has been proposed as a biological marker of depression [86]. Moreover, emotional disturbances, ranging from depression to

euphoria, are frequent features of both hyper- or hypocorticolism [87, 88].

With respect to overactivity of the HPA axis, as well as to other biological and psychological symptoms, depression closely resembles the chronic stress syndrome in animal models [89]. Thus, it is possible that some forms of human depression constitute a state of a chronic stress that has reached its final stage of "exhaustion", according to Selye's stress terminology [72]. At this stage, high levels of circulating glucocorticoids may curtail fast negative feedback [90], and one may speculate that via their apparent GABA receptor antagonistic actions they may promote anxiety, irritability and fatigue, the typical syndrome of depression. Regardless of the cause of chronic pituitary-adrenal disinhibition (organic or psychoenvironmental), the prolonged exposure to 17-OH-corticosteroids may increase neuronal excitability, thus leading to psychological exhaustion. However, the acute exposure to these steroids may have an analeptic or euphoric effect due to a transient reduction of inhibitory actions of GABA.

Antidepressants can control the corticosteroid hypersecretion by increasing noradrenergic transmission, which tonically inhibits the HPA axis by a suppression of CRF release [75]. Inhibition of the HPA axis through the enhancement of GABAergic transmission represents an alternative method of treatment of depression [91]. Since we have demonstrated that steroid THDOC has anxiolytic properties in animal models of anxiety [73], one can suggest that inhibitory steroids of similar structures may be useful for treatment of depression. One can speculate even further that some forms of human depression are associated with deficiencies in the peripheral or central synthesis of anxiolytic steroids, generating an imbalance between agonistic and antagonistic modulators of the GABA receptor complex.

Premenstrual tension (PMS) and post-partum depression (PPD). These two disorders are characterized by similar symptoms, such as increased tension, irritability and exhaustion, commonly observed in depression, and their occurrence coincides with the fall in circulating progesterone levels [92]. If high progesterone levels in the early luteal phase and in pregnancy are associated with elevated levels of 3α-OH-DHP (inhibitory steroid), this may lead to the development of "auto-dependency" on this natural anxiolytic. Hence, it is likely that a sudden physiological drop in the level of this steroid may evoke a "withdrawal syndrome", as well as anxiety and depressive symptoms. This hypothesis is in agreement with Dalton's concept that a low progesterone level is responsible for PMS [93] and is supported by the fact that progesterone is frequently efficacious in the treatment of PMS [92]. Future studies should address the question, whether PMS and PPD are linked to lower-than-normal plasma or CNS levels of anxiolytic progesterone metabolites, as this may suggest more specific methods of treatment of these disorders.

Seizures. Impairment of GABAergic transmission is believed to be associated with some seizure disorders [94–96]. The frequency of seizures is altered in physiological states typically associated with changes in steroid hormone secretion, such as stress or pregnancy [97, 98]. Since anesthetic steroids increase seizure threshold and convulsant steroids lower it [17], it is possible that the profile of circulating steroids affects the occurrence of seizures. The fact that the anesthetic steroid althesin [99] and medroxyprogesterone [100] improve experimentally-induced seizures suggests that certain steroids may be useful as anticonvulsants.

Blood pressure regulation. Involvement of "inhibitory steroids" in the regulation of cardiovascular function is suggested by a correlation between hypertension and reduced adrenal secretion of 3α-OH-DHP [58]. The presumed hypotensive effect of this steroid may be of a mixed central and peripheral nature, through the potentiation of GABAergic transmission in central [101] and in vascular [102] tissues, which are involved in the regulation of heart rate and blood pressure.

Brain trauma. Steroids have been used to treat brain trauma and edema with variable results, ranging from improvement to deterioration [103]. Commonly used therapeutic steroids, glucocorticoids, have been shown recently to potentiate injury to neurones [104, 105]. The mechanism of these actions is not clear, but it is possible that it may partially result from GABA antagonistic effects of glucocorticoids, leading to clinically undesirable increased neuronal excitability. Since we have demonstrated that barbiturates protect brain against anoxic damage [106, 107] and others have shown their beneficial effects in the treatment of brain edema [108], one can predict that the anesthetic steroids should also have therapeutic action. Theoretically, they should even surpass barbiturates in the treatment of brain trauma, for they selectively reduce neuronal activity (glucose and oxygen consumption) in forebrain with lesser effects on hindbrain, thus better preserving basic physiological functions [109].

Defects in steroidogenesis. Since various steroids exert bidirectional effects on neuronal excitability, the abnormalities in steroid metabolism can undermine their fine physiological balance and contribute to the development of several CNS disorders. For example, Cushing's syndrome, a disease characterized by oversecretion of adrenal steroids, is associated with severe neuropsychiatric manifestations, resembling depressive disorders [87, 110]. Also, adrenal insufficiency, Addison's disease, is accompanied by psychiatric disturbances [111]. Besides gross defects in the levels of circulating steroids, the subtle physiological balance of plasma steroids can be also disturbed by errors in adrenal enzymes, called adrenal hyperplasia [112], contributing to a variety of mental disorders. The latter can also arise from errors in brain activity of steroid-metabolizing enzymes.

Conclusions

Regardless of their origin, steroids influence the activity of the CNS generally in processes associated with adaptive or sexual functions. Steroid actions on the CNS can be categorized into slow, genomic, and rapid effects, mediated through the plasma membrane. The latter category involves steroid

interactions with neurotransmitter receptors, which may result in alterations of interneuronal communication. Heterogenous regulation by various steroids of GABA receptor function, resulting in altered neuronal excitability, may represent an important means of communication between the body and the brain, essential for the organism's integrated responses to external stimuli or internal physiological or pathological signals. It is possible that a disturbance in the synthesis of centrally active steroids contributes to the defects in neurotransmission, which underlie a variety of neuronal and affective disorders, and that normal levels of these steroids are essential for maintenance of CNS homeostasis, emotional stability and mental health.

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