Steroid secretion. Newly Discovered Functions in the Brain. Fundamental and Clinical considerations.

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Abstract

While the relationships between endocrines and psychiatry have long been established, the implications of neurosteroid (NS) hormones, identified in the early 1980s for psychopathology, started to be recognized in the nineties.

Tetrahydro metabolites of progesterone (ATHP) and deoxycorticosterone (ATHDOC) act as positive allosteric modulators of neurotransmitter receptors such as GABAA. Other NSs, i.e., androsterone, pregnenolone, dehydroepiandrosterone (DHEA), their sulfates and lipid derivatives modulate glycine-activated chloride channels, neural nicotinic acetylcholine receptors constituted in Xenopus laevis oocytes, and voltage-activated calcium channels. Sigma receptors, as pharmacologically defined by their effect on N-methyl-D-aspartate (NMDA) activity, have been studied in rat hippocampal preparations: here DHEAS acts as a sigma receptor agonist, differently from pregnenolone which appears as a sigma inverse agonist and progesterone which behaves as an antagonist. All of them were identified as NSs.

Neuroactive steroids rapidly change CNS excitability and produce behavioral effects within seconds to minutes following administration to both laboratory animals and man. These fast actions probably indicate membrane mediated effects. This notwithstanding, Rupprecht et al. showed that after oxidation, ring A reduced pregnanes can regulate gene expression via the progesterone intracellular receptor. The necessary enzymes for the metabolism of primary adrenal and gonadal steroids, a peripheral source for NSs, exist in the brain in a compartmentalized way. The 5 a reductase is present in both neurons and glial cells. The 3 a hydroxysteroid dehydrogenase (3HSD) is particularly concentrated in type I astrocytes.

The effects of different NSs on depression syndromes, anxiety, stress responses to different stimuli, as well as memory processes and related phenomena such as long term potentiation are critically evaluated. The importance of context for the interpretation of behavioral effects of hormones as well as for hormonal levels in body fluids is reemphasized. Finally, the possibility that NSs may act in a paracrine manner to modulate neural processes involved in learning, memory and depression is presented.

Introduction

In 1913, during the opening address of the Phipps Psychiatric Clinic, Cushing presented his concept of an interaction between emotions and endocrine secretions. He agreed with the notion that "psychic conditions profoundly influence the discharges from the glands of internal secretion." But, he added, "we are on a much less secure footing when we come to the reverse, namely, the effect on the psyche and nervous system of chronic states of glandular overactivity and under activity" (38).

Cushing postulated that each glandular disorder would induce a typical psychopathology, "its peculiar symptom-complex and its more or less characteristic mental deviations." He concluded by pointing out a problem still very much alive in neuroendocrinology, "the present difficulty in determining which was the primary factor - the psychic instability or the disturbance of endocrine secretion" (38).

In 1932, Cushing noted that in patients with adrenal hyperactivity the presence of "sleeplessness, inability to concentrate, visual disturbances" and "fits of unnatural irritability alternated with periods of depression" (39). These findings were repeatedly corroborated, and, although not the exclusive manifestation of Cushing's disorders (syndrome and disease), depression is the most frequent behavioral disturbance observed in patients with these disorders (36, 60, 63,93,98,128,138,147).

The incidence of depression in Cushing's disorders is significantly higher than in any other endocrine disorders (36). Within this context, it is of great interest that the correction of hormonal pathology (193) in Cushing's alleviates the depression syndrome even in cases where classical psychopharmacological treatment, tricyclic antidepressants, was not effective (147,228). These results led Cohen (36) to suggest that, "the simplest explanation for these various observations is that where Cushing's syndrome develops it commonly causes depressive illness."

So much are adrenocortical hormones, specifically glucocorticoids (GC), considered to play a role in the pathophysiology of depression (34,60,98,302) that inhibition of their secretion (98,128,147, 222,228) or blocking of their effects (14,222) have been proposed, and are being used for the treatment of depression syndromes.

The spectrum of affective and cognitive symptoms in Cushing's disorders greatly overlaps with those described in the DSM IV to diagnose depressions. Starkman and Schteingart's (259) study reported that increase in fatigue and a loss of energy were present, respectively, 100% and 97% of the time, in 35 patients with Cushing's syndrome. Impaired memory was reported by 83% of the same subjects. Dysphoric mood (i.e. depressed) and irritability were present in 86% and 77% respectively of the patients . Sleep disturbances and decreased libido were reported by 69% of these patients. Diminished ability to think or concentrate was reported by 66% of the patients. Increase and/or decrease in appetite, sense of hopelessness, social withdrawal and anxiety were also significantly present in patients with Cushing's disorders.

In normal subjects, approximately 20% of sleep is spent in stages 3 and 4, also known as the delta stage (118). In patients with Cushing's disease, as well as in those with depression syndromes, there is an absence of, or marked reduction, in stages 3 and 4 (149,150). Also, a shorter rapid eye movement (REM) sleep latency can be observed in both groups of patients (150).

The presence of adrenal steroids, however, is not an essential prerequisite for depression to occur. Some patients with Cushing's disorders can present with mania (35,277), and, on the other hand, Addison's patients can show depressions (35,57. Also, in experimental animals, the induction of learned helplessness, a recognized model of depression (63), is enhanced by adrenalectomy (73).

Besides, neither in Cushing's nor in depression syndromes does the intensity of psychopathology correlate with cortisol levels (260,277). This is not surprising as the adrenal glands produce a plethora of hormones. Already in 1985 Holzbauer et al. (122) wrote: "the extent to which this gland contributes hormones not confined to so-called gluco and mineralocorticoid activities is much less considered and deserves attention.

These include steroids commonly associated with the ovary such as progesterone or pregnenolone as well as other steroids devoid of gonadal or corticoid activity which may, nevertheless, have a biological role such as the ones related to their anesthetic action." Most likely, then, other hormones besides cortisol (162) and imbalances between counteracting sets of hormones acting on the CNS (74) or produced in situ (12), lead to steroid induced psychopathology (60,61). Within them, neurosteroids (11,12,62) play fundamental roles.

Neurosteroid Hormones

The term "neurosteroid" (NS) was introduced by Baulieu in 1981 (11,12) to name a steroid hormone, dehydroepiandrosterone sulfate (DHEAS), that was found at high levels in the brain and plasma long after gonadectomy and adrenalectomy. Later, androsterone, pregnenolone, their sulfates (12,169,256), and lipid derivatives as well as tetrahydro metabolites of progesterone (P) (32) and deoxycorticosterone (DOC) were identified as neurosteroids (11). More recently some estrogen derivatives (304) have also been classified as NSs (241).

Enzymes that catalyze conversion of these pregnanes, P and DOC, at ring A sites are fundamental components of this process. 5 a reductase, mainly concentrated in white matter (31,133,186,264), is the rate-limiting enzyme for pregnane steroids metabolism (186). With 3 a hydroxy steroid dehydrogenase, acting after 5 a reductase, they produce from P and DOC allotetrahydro P (ATHP) and allotetrahydro DOC (ATHDOC) (32,190), both powerful GABAA agonists (110,111,169,188,198).

There are stringent structure-function relationships for these reduced pregnanes, e.g., an OH group in the a position at C3 is essential for them to act as positive allosteric modulators of the GABAA receptor complex. An OH group in b position instead of a at C3 in tetrahydroprogesterone, e.g., transforms the NS into a functional antagonist of GABAA (241).

Neurosteroids bind and modulate different types of receptors . The GABA and Sigma receptor complexes are the most extensively studied (2,224,225,227,230252, 254,255,281,282) while glycine activated chloride channels (223), nicotinic acetylcholine receptors constituted in Xenopus laevis oocytes (11) and voltage-activated calcium channels (77,126,127), although less explored, are also very much involved with NS's actions.

Some neurosteroids, ATHP and ATDOC, positively modulate GABAA receptors in a manner similar to benzodiazepines and barbiturates but seem to act at a site distinct from that of benzodiazepines (241). In favor of this view is the fact that coadministration of the benzodiazepine antagonist, flumazenil, does not diminish the anxiolytic effect of allopregnanolone (30).

In studies on brain slices, at nanomolar concentrations, ATHP and ATHDOC, potentiate GABAA-induced chloride influx through the ion-channel by prolonging the duration of opening and increasing opening frequency leading to increased duration of the resulting inhibitory postsynaptic potential (311). At micromolar concentrations these neurosteroids induce inward currents even in the absence of GABA (170,311). Gender and brain region influence NS's modulation of gaba complex responses (297).

Behaviorally, ATHP and ATHDOC have been shown to have anxiolytic (22,23,37,106,213,296), hypnotic (40,151) anti-aggressive, (137,241) and anticonvulsive effects (15,152).

Significant regional heterogeneities in the affinity of THDOC for its binding sites have been reported, e.g., the neurosteroid inhibits (35S) t-butylbicyclophosphorothionate (TBSP) binding in the prefrontal cortex but not in the spinal cord (104). In prefrontal regions it also decreases dopamine levels (104).

After entering the cell, ATHP and ATHDOC can be oxidated to 5a dihydro P (DH P) and 5a-dihydro DOC (DOC) which then bind to the cytosolic P receptor, and subsequently influences gene expression (239). In this way these NSs can modulate GABAA receptor complex subunit composition , which, in turn, determines sensitivity to neurosteroids and benzodiazepines . Levels of ATHP vary with gender, age and endocrine status (91).

Withdrawal from P in pseudopregnancy models, (i.e. animals with artificially induced high plasma P levels) which simulates the rapid decrease of P as it occurs both during PreMenstrual Dysphoric Disorder (PMDD) and during the postpartum period (20,95,196,254), results in a decrease in brain content of ATHP with subsequent increase in the expression of the GABAA-receptor alpha-4 subunit (107,108,255).

Presence of the alpha-4 subunit has been shown to be essential for the occurrence of P withdrawl effects, i.e., increase of anxiety and seizures; decreased sensitivity to positive allosteric GABAA-receptor modulators, ATHDOC and ATHP, benzodiazepines and ethanol, and increased sensitivity to negative allosteric GABAA-receptor modulators, DHEAS (86,95,108).

Steroids, Neurosteroids and Memory

Since the classical work of Papez (208), the hippocampal formatio (HF) has been recognized as an essential neural component of emotional behavior, a notion later remphasized by MacLean in his triune brain theory (5,64). But it was soon discovered that as important as its involvement in emotional behavior, the HF is also essential for cognitive activities (192,258). Hippocampal lesions severely interfere with memory processes, lying down and retrieval, as well as learning, both in humans (258) and experimental animals (258).

Not surprisingly, the hippocampus is also involved in attentional processes. In turn, there is a great deal of interaction between memory and attention (243,244). Attention determines the content of memory, and retrieved memories serve as the basis of expectations and direct attention. Thus, a change in memory would be expected to result in a change in attention and expectations, and vice versa, and it is not surprising, then, to find NS's abnormalities in attention deficit hyperactivity disorder (261).

Memory disturbances are also almost a constant feature of depression syndromes (163,164,165). Lishman considers that they play a primary role in their pathogenesis and maintenance (163,164). Weingartner and Silberman (294) showed that depressed patients use weak or incomplete encoding strategies to organize and transform events to be remembered. In patients with depressive syndromes, memory also undergoes qualitative changes; it turns toward negative, self-deprecating aspects of their lives.

Lishman et al (163,164,165) showed that with increased levels of depression accessibility of negative memories increased. This was evaluated by the higher frequency of recall of unpleasant words, as well as by short latency to identify negative connotated words. Also, in depressed patients, response biases were altered, so that unpleasant material was handled in a preferential way to neutral or pleasant material in a signal detection analysis study (72). The fact that congruence between affective state and tone of material recalled interact during retrieval is well documented (29,243,275).

The internal milieu, of which steroids are a component, is one of the determinants of the complex net of autonomic, biochemical and emotional-cognitive factors that establishes mood at the moment of a particular experience. The reinstatement or persistance of this environment may then help to recreate or maintain one type of a very powerful source of context effect in memory: mood (29,275).

It is conceivable, too, that memories with different contents, i.e., sad or happy, may correspond with different biochemical mediators and/or different neuronal circuits (59,60), activated by different internal milieus (62) or behaving in different modes (59). The latter proposal was already made by Von Monakow (289) (see also 243).

The possibility that neural processes related with remembering can be biased toward positive or negative views in relation to the composition of the internal milieu is consistent with cognitive conceptualizations of depression (13). In them, negative thinking is seen not as a symptom, as classically regarded in psychiatry, but as causally related to the syndromes (13,274). Therapists then, focus their efforts on the destructive elements of thinking that affect patients the most (13).

Results of different experiments on the effects of GC on memory functions have shown inconsistencies. One reason for this is that investigators do not systematically take into consideration if the GC's doses employed in their studies, occupy just Type I, MC receptors (215) or both Type I and II GR receptors and the different effects that this will have on memory related activities (46,48,217), as has been shown to be the case in sleep behavior (28). Based mostly on animal experimental studies, Roozendaal (235) has proposed that GCs enhanced memory consolidation, in contrast, when circulating at high levels, the same hormone group impairs memory retrieval processes . Working with humans, Lupien et al. (166) found that working memory is more sensitive than declarative memory to the acute effects of GCs hormones.

Overall, short term, semantic and space memories were negatively affected by high doses of GCs (48,53). However, baseline, minimal circulating levels of GCs were found to be essential for normal performance of cognitive tasks (167) as well as for keeping intact the structural integrity of the dentate gyrus (DG) (253).

It would be expected that the effects of a GABAA positive allosteric modulator NS like ATHP will be detrimental on memory functions on account of its benzodiazepine-like actions (151,198). Mayo et al (181) reported that injection of 2 ng of ATHP in the nucleus basalis magnocellularis of rats disrupted performance in a two-trial recognition task when injected before an acqusition trial. No effects were observed if injections were effected after acquisition trials, suggesting that they interfere with learning process during the acquisition phase.

In turn, Johannson et al (130) showed that ATHP inhibited learning in the Morris water maze. In contrast, data of Frye and Sturgis (87) showed that both ATHP and DHEAS have pronounced activational effects on spatial/reference, working, and long-term memory. These effects were independent of motor activity. The similarity of actions of these NSs were unexpected due to the opposite effects that ATHP and DHEAS have on the GABAA receptor complex: while ATHP has positive allosteric agonistic modulatory actions (227), DHEAS acts as a negative allosteric modulator (170).

ATHP has been reported to enhance dopamine release (142,237) a fact that may account for some of its stimulant effects.

Memory enhancing effects of DHEAS in aging mice were described early after the identification of the hormone as a NS (82,83). Later, DHEAS was also shown to decrease impairments in memory produced by dizocilpine, a non-competitive NMDA receptor antagonist, and by scopolamine, a muscarinic acetylcholine receptor antagonist (283,312). In elderly human populations, the effects of the NS vary: enhancing memory but decreasing attentions span, after exposure to laboratory stress (300,301).

These effects were explained by the agonist effects of DHEAS on the sigma 1 receptor (30). The following results support this explanation: Memory tasks are impaired by dizocipine and scopolamine (283,312). Treatment with DHEAS improves performance in animals treated with these drugs. However, treatment with NE-100, a sigma I receptor antagonist inhibit the improvement in

performance of memory tasks impaired by dizocilpine and scopolamine, that DHEAS produce (283,312), probably via signal receptors.

A caveat to the generalization of the effects of DHEAS as a cognitive enhancer is that studies in humans could not replicate results in animals (125,299, but see 18).

At sigma receptor sites, DHEAS acts as a sigma receptor agonist, different from pregnenolone which behaves as a sigma inverse agonist and then acts as an antagonist (195). DHEAS does not interact with cortisol receptors and although a DHEAS receptor or binding site(s) for the hormone has been identified in murine T cells (185), this is not the case in the central nervous system.

Neurosteroids and Long Term Potentiation (LTP)

LTP is a prolonged enhancement of synaptic transmission first described in the rabbit hippocampus (131), a structure essential for the temporary storage of long-term and for the establishment of declarative memories (258). LTP is a widely accepted electrophysiological model for associative type memories (24,43,136).

Several reasons underlie the importance of LTP expression in the hippocampus. First, the phenomena can be elicited from its pathways from entorhinal cortex via the perforant path to the DG, from the mossy fibers and from the Shaffer collaterals. By travelling through the hippocampal circuit, this structure can modulate sensory signals that were first processed in cortical regions (136).

A second reason for the importance of LTP expression in the hippocampus is that the phenomena can be rapidly induced, a single electrical tetanus can double the strength of a synaptic connection, i.e., the amplitude of the response to the same test stimulus can be twice the baseline (24). A third reason is that once induced, LTP is stable for one or more hours, even days. And a fourth one, is that besides being the neural site from where LTP can be more easily elicited (24), the hippocampus is an important mediator for the behavioral effects of corticoadrenal steroids (47,69,79,80,129), and a site where they regulate amine receptors (173).

In rats, CS injected at doses sufficient to occupy Type II glucocorticoid receptors (GR) produces a decrement of LTP (68,214) but also a depotentiation of priorly induced LTP (216). One mechanism by which CS may interfere with LTP generation is thought to be the inhibition of the GABAB mediated late component of the IPSP. Davies et al. (44) showed that GABA release mediated through GABAB receptors is required for induction of LTP. In the CA1 region of the hippocampus GABAB receptors opening K+ channels mediate the late (ca. 120 ms) component of the inhibitory post synaptic potential (IPSP).

Relations between CS levels and LTP, however, are not linear. Bennet et al. (16) reported an inverted-U relationship between CS and prime burst (PB) potentiation, a modified form of LTP (54). Behavioral stress, by producing high levels of CS in plasma, facilitates the induction of long term depression (LTD) (304), a putative mechanism for forgetting (306). Besides GCs, oxytocine (OT), a hormone that impairs memory processes (71), also induces LTD (71).

Interestingly, the OT receptor has been identified as the first G protein coupled receptor for which steroids can be ligands (241).

In contrast to CS, the NS dehydroepiandrosterone sulfate (DHEAS) increases LTP in a dose-related manner (309). The enhancement may relate to the negative modulatory effects that DHEA and DHEAS exert at GABAA receptor sites (51,169), GABA is known to block the induction of LTP (309).

Harlen-Meyer and Gruol (109) showed that DHEAS increased neural excitability of hippocampal slices. They explained this effect by the facts (a), that DHEAS inhibited a fast inhibitory post-synaptic potential (IPSP) component of the evoked synaptic response and, (b), DHEAS produced a direct enhancement of the excitatory post-synaptic potentials (EPSPs). When DHEAS was simultaneously injected with CS, a depressogenic type hormone (68), the NS can counteract the decremental effects of CS on hippocampal LTP (135), a phenomena that suggested the potential use of the hormone as an antidepressant (61).

Two other androgenic NS hormones, androsterone sulfate (AS) (285) and androstenedione (248), have also been shown to enhance LTP, although with different characteristics than DHEAS. While DHEAS (309) enhanced both DG components of the evoked responses elicited by perforant path stimulation, EPSP and PS, androstenedione (248) and AS (285) enhanced only the PS. This is in keeping with the fact that mechanisms for EPSPs and spike generation can be independently affected (24,131).

One possibility that could account, in part at least, for the increase in PSs, but not EPSPs is that androstenedione and AS may exert part of their effects by acting near the site of impulse generation, axon hillock, by counteracting the effects of inhibitory inputs on the initial segment. The velocity at which membrane potential changes during the application of an excitatory stimulus affects the threshold voltage at which an action potential is triggered. The more slowly the stimulus depolarizes the membrane, the greater the depolarization required to initiate an action potential (285).

Even a minor increase in the pEPSP slope may be translated in a faster depolarization of the initial segment and, hence, in a lower threshold for spike triggering. Together these events could lead to a recruitment of new action potentials and, as a result, an increase of the PS amplitude with the NSs androstenedione and AS. As androstenedione and AS also modulate glutamate receptor (62) and voltage gated CA2+ channels (77) and Ca 2+ influx is essential for LTP induction (136), these NSs can affect LTP generation through their effects on these mechanisms (77,126,127).

In different experiments, Stewart and Reid (263) examined the effects of the SSRI antidepressant fluoxetine, and repeated electroconvulsive shock (rECS) on hippocampal LTP. Both procedures produced a decrease in LTP evaluated after normalization of the data. Spatial learning was unaffected by fluoxetine treatment but significantly impaired following rECS. Evoked responses (ER) from the dentate gyrus after either treatment, rECS or fluoxetine, were statistically larger than in control animals (neither rECT nor fluoxetine treatments). The commonality of effects of rECS and fluoxetine on LTP and their dissociation on space tasks led Stewart and Reid to speculate that at least one mechanism

related to the antidepressant actions of rECS and fluoxetine involves an increase in neuronal connectivity as manifested by increased baseline amplitude values of the ERs even in the presence of a diminished LTP.

Watanabe et al. (291) showed that the tricyclic antidepressants imipramine, desipramine and amitriptyline blocked the induction of LTP in a concentration-dependent manner. Recent studies with trimipramine produced similar results (153,179).

Recently we shoed that ATHP and ATHDOC produced a significant decrement of hippocampal LTP, both at 0.1 mg/kg and at 0.5 mg/kg doses (Dubrovsky et al., submitted).

These NSs behave like the SSRI fluoxetine (263) and TCAs (153,179,291), i.e., they depress LTP in the hippocampus. But CS, a depressogenic hormone, when given in doses to occupy GC or Type II R, also induces a decrement in LTP. These commonality of effects on LTP cannot be considered to be specifically related with mechanisms causally related with antidepressant effects.

Hence, it appears more appropriate that correlations between ATHP and ATHDOC levels should be carried out with salient symptoms present in depression, i.e., anxiety, sleep and memory disturbances, rather than the syndrome itself.

Neurosteroids and Stress

A mild stressful situation for rodents, e.g., exposing them to a brief swim in ambient temperature water, produces an increase in plasma ATHP and ATHDOC (9,199,226).

In turn, these NSs inhibit the release of CRH and AVP from the hypothalamus. As ATHP and ATHDOC are ACTH secretagogs, inhibition of their release inhibits that activation of the pituitary adrenal axis. Patchev et al. (211,212) also showed that ATHP attenuates CRH release in stress responses. The uncovering of these facts led to the hypothesis that ATHP and ATHDOC are part of a negative local feedback regulatory system (56,190) that prevents allostatic load of the HPAA axis (183).

This hypothesis is supported by other experimental data. In adult male rats, subcutaneous administration of ATHP, decreases CS release in response to air puffs (a stress test), and decrease gene transcription of AVP, a secretagogue of CRH and a putative depressogenic hormone in the hypothalamus (113,114). Treatment with ATHDOC also attenuated the long HPA axis-related alterations associated with maternal separation in infant male rats. Thus, administration of ATHDOC to male rat pups before separation from their mothers counteracted the exaggerated adrenocortical responses, i.e., increased CS production produced by the separation (213). Animals treated with ATHDOC also show a decreased responsiveness to the suppressive action of dexamethasone, and the diminished numbers of glucocorticoid receptor-encoding transcripts in the hippocampus in response to a mild stress (205,213).

Do-Rego et al. (56) demonstrated that activation of the GABAA receptors inhibit the activity of the neurosteroidogenic enzymes; 5 a reductase and 3 a

hydroxysteroid Thus, as GABA agonists, ATHP and ATHDOC are part of an ultra-short loop in which they regulate their own biosynthesis.

Recent studies (62,146,207) confirmed and extended Mason's (176,177,178) pioneering work showing that the hormonal profile response elicited by different stress stimuli depend greatly on how individual subjects evaluate or appraise the stimuli (160). For Ursin (286), the "coping filter" is "the best understood and best developed concept in the stress literature....."; later he adds, "the psychological filtering mechanism of defence is only identified in humans".

Consistent with the specificity of hormonal mediators according to the nature of the stressor, ACTH secretagogs, i.e., CRH, AVP, oxytocin (OT) and catecholamines, vary depending on the stressor (hypoglycemia, hypotension, hemorrhage, burn, etc) (207). Thus, during chronic inflammation, e.g., there is a shift from a primarily CRH driven to an AVP driven HPAA (62).

Once more, these data highlight the notion that the behavioral effects of hormonal levels in body fluids can only be properly ascertained within the context: biochemical, environmental and historical, of the organism being studied. In turn, the clinical and/or behavioral significance of hormone levels also depend on the context in which they are measured. For example, similar increases in plasma levels of a cortisol can be observed under very different behavioral circumstances: i.e., a pleasant one, watching a film comedy (124), or an unpleasant one, being exposed to a fearful stimuli (143).

But, if instead of a single hormone, a hormonal profile is obtained, e.g., hypothalamic activating peptides, pituitary trophic hormones, and hormones from their target glands: adrenals, thyroid, etc., in response to various stimuli at different times, then the situation changes. The hormonal spectrum so obtained for each stimulus can be reliably reproduced if conditions during elicitation remain stable.

In the particular case of the HPAA, activation "occur in many different laboratory and life situations involving a wide variety of stimuli, because emotional reactions (which elicit adrenocortical responses) occur commonly in a wide variety of situations in which animals or humans are subjected to physical stress. This 'non-specific' response is of a primarily behavioral nature" (177), and involves NSs (62,95,249).

Although the term neurosteroid suggests that the biology of these hormones are circumscribed to nervous systems, this is not the case. Thus, e.g., ATHP is also produced in lymphocytes (154), while androgen neurosteroids modulate muscular growth (307).

Pregnanes like DOC (65,148), P (8,152) and their Ring A reduced metabolites (8,19,22,23,65, 79,151,189,200,231) decrease nervous system excitability. For CS, the effects can vary, i.e., excitatory for the parent compound (CS) (66) and depressant for their Ring A reduced metabolites in the same neuronal population (67,70). In the case of P and DOC, both of them decrease CNS excitability. However their respective tetrahydro metabolites are significantly more powerful, 30-40 fold higher than their parent compounds (65,152).

There is great interest in the potential use of NSs such as ATHP and ATHDOC as medications (240), and as anesthetic agents (121), especially for short-lasting procedures, due to their short half life. Early trials from the pharmaceutical industry (33) showed that some manufactured steroids, e.g., Alphaxalone, Althesin, were effective anesthetics (121). As with other anesthetics, e.g. lidocaine (70), the effects of these steroids can be bimodal. Myoclonic seizures were also elicited by slow doses of them (78) Solvents for anesthetic steroids were liable to induce phlebitis and/or anaphilactic shock in humans. For these reasons, they were withdrawn for use in humans.

Alphaxalone is still available for veterinary use. As natural body products, these steroids are more easily eliminated than synthetic anesthetics, a feaure of great importance in patients with liver or kidney problems (121).

NS and Anxiety

Le Doux (155) defined anxiety as an "aroused state of mind initiated and maintained by emotional processing". It is clear, however, that cognitive processes such as anticipation of uncertain events and/or recollections of previous anxious states, can also generate anxiety. Considering these facts, a broader view of anxiety as an affective-cognitive phenomena will be more in keeping with currents views of emotion-cognitive interactions (5,64).

An increased level of arousal, although necessary, is not sufficient for the experience of anxiety (155). Norepinephrine release induces activation and EEG arousal which manifests as a synchronization of EEG fast rhythms (ca 40 Hz) (262).

Besides conventional synaptic contacts, there exists in the cerebral cortex, a large number of monoaminergic and cholinergic nerve fibers that end as terminal varicosities in the extracellular space (262), not in neural or glial cells. They have been recognized as part of volume conduction systems (1,55) and proposed to play an important role in arousal phenomena (262).

The main source of the cortical catecholamine afferents comes from fibers whose neuronal bodies are in the mesencephalic and pontine reticular formation (84).

Corticosterone (CS) increases the discharge rates of tonically firing neurons in these regions (66) which, in turn, increase norepinephrine release at cortical regions contributing to the development of anxiety (194). When activated via classical specific sensory paths, cortically responding neurons exert, in turn, descending activating effects on the brain stem reticular formation thus creating a corticoreticular positive feedback which further activates the reticulocortical activating system, thus increasing arousal (262) .
On the other hand, at membrane levels (111,123,293), CS (6,66) also stimulates brain stem neurons of the raphe nucleus (7), a mainly indolamine projecting system to diencephalic regions associated with, among other behaviors, sedation (7). However, clinically, hypercortisolemia is generally accompanied by anxiety as indicated by patients with Cushing's and depression syndromes (259).

Contrasting with the mainly excitatory effects of CS at pontine and mesencephalic regions of the reticular formatio (66,70). Ring A metabolites of CS

(66,70) and DOC (65) as well as from DOC per se (65,70,231), exert depressant effects on the same neuronal population.

Behaviorally, the anxiolytic effects of ATHDOC and ATHP have been consistently demonstrated. The work of Akwa et al. (3) and Ferrara et al (76) indicate that anxiolytic like effects of ATHP are mediated via the amygdala and are accompanied by an increase in neuropeptide Y. In in vitro brain alices, DHEA and DHEAS have bimodal effects on GABAA receptors: positive allosteric modulation at low, nanomolar concentrations, and negative at high, micromolar concentrations (169). These effects are mirrored at behavioral level. Thus mice receiving low doses of DHEA or DHEAS in the anxiogenic plus-mode model test, manifest lower levels of anxiety than control, non-treated animals (187). Besides direct effects on the GABA receptor, the anxiolytic properties of DHEA and its sulfated form (4) may also be the result of the metabolization of these hormones to androsterone and 3 a diol which behave as positive GABAA receptor modulators at low concentrations (88). In the mirror chamber test, DHEAS can also block the anxiolytic actions of dizocilpine, an NMDA receptor antagonist. This implies that DHEA and DHEAS effects on anxiety might also be mediated through GABA independent mechanisms (229).

The anxiogenic effects of DHEAS at high doses, has been shown in mice undergoing the mirror chamber behavioral test The excitatory effects of DHEA manifest at high plasma level concentrations of the hormone. Seizures have been reported in patients with adrenal adenomas presenting with elevated DHEA plasma levels (116). In turn, Heuser's studies showed that IV or IP injections of DHEA in the 100 mg/kg range, induced seizures in cebus monkeys (116).

On the other hand, other androgenic NSs, e,g, androsterone sulfate (AS) and androstenedione (88,252), are, like testosterone itself (89), endowed with antiseizure capacity.

Testosterone, as well as androgen NSs, like DHEAS, AS and androstenedione, are widely used by body builders, a habit that entails serious dangers (218,238,307,308). Among them, e.g., manic states have been reported with doses of 150 mg/daily of DHEA (172).

As many NSs act as modulators of the GABA receptor complex, it should be expected to find abnormalities in the circulating levels of NSs in patients suffering from different forms of panic disorders (158, 267,268). However, recent studies in humans did not reveal statistical differences in normal baseline plasma levels of ATHP between patients with generalized anxiety disorder (158,250), generalized social phobia (158), panic disorders (158) and those challenged with the panicogenic agent pentagastrin (272) compared with control subjects. However, pentagastrin challenge produced an increase of DHEA plasma levels (272).

Rather surprisingly, Ströhle et al. (269) found that levels of the anxiolytic NS ATHP are higher than normal in patients with panic disorder. In contrast, the same group showed that panic attacks induced by sodium lactate and cholecystokinin tetrapeptide in patients suffering from panic disorder were accompanied by pronounced decreases in the concentration ATHP and 3a, 5b-THP and a concomitant increase in the concentrations of the functional

antagonistic isomer 3b,5a,-THP, findings that are compatible with a decreased GABA-ergic tone (269).

Heydari and Le Mellédo found that patients with generalized anxiety disorder or generalized social phobia, but not with panic disorder, had lower plasma levels of pregnenolone sulfate (PREGS) than healthy volunteers (117).

The NS PREGS is a negative allosteric modulator of the GABAA receptor complex and a positive allosteric modulator at the level of the N-methyl-D-aspartate (NMDA) excitatory amino acid receptor, i.e., it augments glutamate induced depolarization (305). Contrary results have been reported for the actions of PREGS on CA2+ mobility. While for Irwin et al. (126) PREGS significantly increases NMDA receptor mediated elevations in intracellular free CA2+, for Spence et al. (256), the NS blocks CA2+ currents.

For Heydari and LeMélledo, lower production of PREGS in the context of pathological anxiety, could be interpreted as a homeostatic attempt of the organism to decrease anxiogenic activity through a lesser negative modulation of the GABAA receptor and a lesser positive modulation of the NMDA receptor (117).

The increased levels of plasma ATHP reported by Ströhle et al (269) in patients with panic disorders, could also be considered as an increased production of the NS in order to return the organism to normality. In male patients with combat-related posttraumatic stress disorders, Spivak et al. (257) found that plasma levels of DHEA and DHEAS were higher than baseline values.

Neuroprotective and Neurogenesis Effects by DHEA and ATHP

Some NSs have been shown to be endowed with neuroprotective properties and to exert selective effects on neurogenesis (168, 233,247,310).

In acute models of both spinal cord and cerebral ischemia, DHEA reduces both neuronal and glial injury (310). When administered before or concurrent with the ischemic insult, DHEA has been shown to decrease hippocampal injury. DHEA has also been shown to protect hippocampal neuronal cultures against glutamate-mediated neuro-toxicity. In addition, the GABAA antagonist, bicuculline, abolished the neuroprotective effect of DHEAS in a model of reversible spinal cord ischemia, suggesting a role for GABA receptors in neuroprotection (310).

Allopregnanolone reduces glutamate-induced irreversible changes in intracellular Ca2+ concentrations in models of hippocampal neurotoxicity (85). These results suggest that neurosteroids serve as endogenous neuroprotectants against acute or chronic neuro-toxocity, acting in concert through several mechanisms to delay and/or protect neurons from cell death (85,171).

It is of interest, then, that in rat hippocampus and cerebral cortex treatment with antidepressants, tricyclics (TCA) (234) and selective serotonin reuptake inhibitors (SSRIs) (287,288) as well as lithium (Li) (234), induce an increase of ATHP. It is possible, then, that one mechanism, by no means the only one (171), by which some ADs and Li have neuroprotective effects is via their augmentation of ATHP levels in CNSs.

In relation to neurogenesis control, DHEA promotes axonal growth (132) and morphological indices of synaptic contacts, whereas DHEAS promotes dendritic growth and branching. Local DHEA to DHEAS ratios might regulate specific neurite outgrowth in the neocortex, thereby shaping protections and synapses during embryogenesis (310).

In turn, ATHP induces axonal regression in the developing hippocampus, suggesting that neurosteroid produced de novo in the nervous system function in concert to promote, guide and refine axonal growth and synaptic connections in the developing brain.

Neurosteroids and Depression

The relation between depression and the HPAA has long been established (38,39,46,96,97,119,120,220). In turn, the abnormalities of NSs levels in depressive syndromes were unmasked shortly after the discovery of NSs in the early 1980s (11).

In patients suffering from major depression, ATHP concentrations in plasma and cerebrospinal fluid are significantly lower than those measured in control subjects (287,288). In contrast, in the same clinical populations, ATHDOC is found at significantly higher concentrations in plasma in relation to control (healthy) subjects (241)

Although with a different time course, concentrations of both of these hormones return to normal baseline levels with successful treatment of the syndrome either with tricyclics (TCA), or with selective serotonin reuptake inhibitors (SSRIs) antidepressants (AD) (265,266). While ATHP levels normalize rapidly with successful treatment with either SSRIs or TCA (265), ATHDOC returns to baseline levels only after (ca) 50 days of fluoxetine treatment (265,266). The question then emerged, are the changes in ATHP concentrations correlative or causally related to the depression syndromes? Attempts have been made to answer this question both in animal experiments and clinical studies.

The Porsolt forced swim test (219) has been proposed, and is used in rodents as an experimental model of depression. In the test, arrest or immobility in the water pool is interpreted as a state of despair in which rats or mice have learned that escape is impossible and resign themselves to the experimental conditions. Studies (141) in which ATHP was given to animals subjected to the test revealed that, like various AD medications (219), the NS extended the time of swimming prior to immobility in treated animals. The results support the proposal that ATHP can be considered an AD (141).

The caveat of this conclusion is that AD drugs are also successfully used to treat syndromes like obsessive-compulsive, panic and PMDD, thus the effects of these medications are not restricted to treat one type of syndrome, i.e., depression. On the other hand, some support for the idea that ATHP can exert antidepressant effects comes from data showing that ATHP and ATHDOC, probably by activation of GABAA receptors in neurons of the parvocellular nucleus of the hypothalamus decrease both gene expression as well as release of corticotropin release

hormone (CRH) and arginine vasopressin (AVP), both of them considered depressogenic hormones (112,113,114).

Consistent with this notion is the fact that GABA levels have been shown to be lower than normal in the CSF of depressed patients (92,99).

Indirect support for the notion that ATHP may act as AD comes also from studies showing that administration of the SSRI's ADs fluoxetine and paroxetine increase brain content of the NS in rodents and humans (140,287). The enhancement occurred only in certain zones of nervous systems: cerebral cortex and hippocampus, but not mesencephalon.

While experimental, clinical and psychopharmacological data supports the concept that serotonin plays a role in the physiopathology of affective disorders, its role(s) is clearly neither simple nor exclusive (7,105,106,182).

The fact that an increase in ATHP production by fluoxetine occurs independent of the effects of the drug on serotonin, that fluoxetine stimulates glycogenolysis in astrocytes showing 5HT (IC) agonist properties (62), as well as the fact that drugs such as Tianeptine (105) have therapeutic effects on depression, as do the SSRIs, but with opposite effects on serotonin, i.e., it enhances its reuptake, while other ADs, such as bupropion, affect dopamine and noradrenaline, but not serotonin, emphasizes the need for further exploration on the therapeutic effects of SSRIs and tricyclic antidepressants (62,105,106).

However, in contrast to what occurs in humans, long-term administration of fluoxetine to rats produced a decrease in plasma and brain levels of ATHP (251).

Neither the concentrations of P nor those of allopregnane-diol, a metabolite of ATHP vary in patients either before or after treatment with ADs (234,241). These results suggest that the decreased allopregnanolone concentrations in depressed patients are due to changes in the activities of the enzymes that are involved in the conversion of P into ATHP.

Griffin and Mellon (103) found that SSRIs increased the affinity of 3a HSOR, the enzyme that catalyses the reduction of the dihydrometabolites of P and DOC, for their substrates. This process, shifting conversion toward the tetrahydrometabolies of P and DOC results in an increase in ATHP and ATHDOC, and hence an enhanced GABAergic tone which, in turn, can also account for the anticonvulsant effect of fluoxetine (94,210) Another SSRI examined, Sertraline, decreases the conversion of ATHP to 5a DHP by decreasing the affinity of 3a HSOR for ATHP. In support of this SSRIs induced, serotonergic independent increase in ATHP brain content, is the normalization of the decreased ATHP brain content in socially isolated mice after administration of fluoxetine independent of its action on brain serotonin reuptake as shown by Matsumoto et al. (180).

Can other methods of depression therapy, normalize neurosteroid levels as some AD's medications do? Two have been examined, but neither partial sleep deprivation (PSD) (246), one of them, nor repetitive transcranial magnetic stimulation (rTMS) (206), the other method investigated, affected NSs plasma concentrations in responders and non-responders to treatment. It can be

surmised from these results that normalization of plasma NSs levels is not a necessary condition for recovery from depression.

Increases in ATHP and ATHDOC content in the brain are not restricted to antidepressant drugs. Drugs with no obvious serotonergic properties like carbamazepine or lithium (234) and the newer antipsychotics clozapine and olanzapine (10,174,175) increase brain ATHP and ATHDOC content. Haldol, a first generation antipsychotic, is inactive in this context (10).

The incidence of extra pyramidal (EP) unwanted effects produced by typical antipsychotics like Haldol, is significantly lower when atypical ones, e.g., clozapine and olanzapine are used (175). The unwanted EP effects of the typical antipsychotics have been linked to a dysfunction of central gamma aminobutyric acid (GABA) mediated neurotransmission (175). Rats treated with atypical antipsychotics, clozapine, olanzapine, show significant increases of brain concentration of ATHP. The positive allosteric effects of these atypicals on GABA could account for the decrease in unwanted EP effects by them.

It is well established that DHEA counteracts glucocorticoid actions, i.e,. inhibition of GC enzyme activity (134), inhibition of dexamethasone-induced suppression of lymphocytes and thymic involution, inhibition of the decremental effects of CS on LTP (135) as well as impairment of contextual fear conditioning (81) and neurotoxic effects of GCs (139,144).

DHEA has been shown to decrease plasma cortisol levels also (299,303). Like ATHP and some ADs, administration of DHEAS also ameliorates effects in the Porsolt et al. test model of depression (230,284). Based on some of these data, the hypothesis that the hormone can be used in the treatment of depressive syndromes, in particular those presenting with hypercortisolemia was put forward (61). Clinical studies validated this hypothesis. Thus, in open label as well as double-blind, randomized, placebo-controlled studies (303), oral administration of DHEA decreased depression symptoms in patients with major forms of the syndrome as well as with dysthymia (25).

Besides its antiglucocorticoid effects, other mechanisms may be involved in the antidepressant actions of DHEA (298,300,301) One is the agonistic action of DHEA on Sigma 1 receptors (2,280,282,284). Enhancement of noradrenaline (49) and serotonin (50) neurotransmission have anti-depressant effects, and in vitro data suggest that sigma ligands inhibit noradrenaline presynaptic uptake in brain synaptosomes (145) and increase noradrenaline release (195). Noradrenaline release is also stimulated by activation of GABAA receptors on noradrenergic nerve terminals (26,27). Furthermore, treatment with DHEAS increases the number of NMDA receptors (295) and potentiates NMDA-evoked noradrenaline release via sigma receptors (195).

The evaluation of basal concentration levels of hormonal sets not just data from challenge neuroendocrine tests, with thorough clinical history-taking, will add precision to diagnosis and guide treatment of affective disorders. Ratios between potentially counteractive hormones provide more reliable correlations between corticoadrenal hormones and behavior (47,201).

In the presence of normal cortisol levels, a low DHEA level could result in functional hypercortisolemia (90). As there is a wide interindividual variability in the plasma DHEAS levels (203,204), cortisol/DHEA(S) ratios are more informative than DHEA(S) values alone (115). Indeed, some studies in depressed patients found significantly higher cortisol/DHEA(S) ratios compared to controls (197) while other studies found lower ones (75) and still others failed to find abnormal ratios (157).

The ratio of cortisol/18-OH-DOC has been shown to be a more reliable index of depresssive states than the Dexamethasone Suppression Test (DST) (52). 18-OH-DOC (21), one of the main hormones secreted by the human adrenal, has been shown to modulate CNS excitability, exerting decremental effects on evoked responses in the CNS as well as in the establishment and develpment of LTP (58,80).

Reported values of plasma DHEA(S) levels in depression differed widely (191,279). When considering data about DHEA, DHEA(S) levels in depressed patients other factors must be taken into account , age differences (203), DHEA(S) concentration declines with increasing age (202), concurrent somatic or psychiatric diseases (242,273) and differences in the time of day samples are obtained. While DHEAS does not have a circadian rhythm measured in saliva, DHEA has one (209), and this rhythm is lost in a subset of depressed patients (100).

As of now, different peripheral circulating levels of DHEA have not been shown to correspond with, or indicate, any specific psychopathological condition (278). Weber et al. (292) reported an increase in androgenic steroids, testosterone, dihydrotestosterone and the NS androstenedione, in women with major depression. However, in the absence of levels of potential counteractive hormones, it is difficult to ascertain the value of these data. This raises the problem of hormone-receptor interactions for the whole spectrum of endocrines.

Peripheral circulating levels of hormones are just one aspect in the determination of their effects: the messenger hormone does not specify the message (62). This became specified after interacting with the receptor apparatus and context where the interaction occurs.

Typological, essentialist thinking, contrary to evolutionary, population thinking (102,161), led to the false notion that particular, e.g., MC-Type I receptor complex or GC-Type II receptor complex-hormone interactions, work in monolithic ways in different body tisues (45).

An example of the difficulties encountered in interpreting the significance of isolated values of plasma hormonal levels, comes from a clinical neuroendocrine study of women suffering from PMDD where NSs disregulation have been repeatedly reported in the disorder (20,86,95, 270,290). The study showed that in women with PMDD, the occurence of symptoms appear in the presence of normal changes in hormonal levels during the cycle. Schmidt et al. (245) showed that in patients with PMDD and with total suppression of ovarian steroids secretion via Leuprolide; minimal, below normal, doses of exogenous ovarian steroids elicited symptoms of the syndrome. In contrast, women not affected by PMDD, with similar treatment did not show psychopathological symptoms. The

results implicate either defects in brain steroid receptors as underlying the syndrome (47), or possible imbalances in the ratio of counteractive hormones and/or NSs.

Commentary

Evolution of steroid hormones, as of other endocrines (41,159,236) occurred mostly at peripheral target organs, e.g. the nasal glands, an acquistion of marine birds and marine reptiles (17) that allow these groups of animals to excrete fluids with higher salt concentration than either blood plasma or urine, under steroid control, 18 HODOC (21).
"Endocrine evolution", Medawar asserted, "is not an evolution of hormones, but an evolution of the uses to which they are put" ... "is the evolution of new reactivities and tissue competences not of chemical formulae" (184).

A characteristic of biological evolution throughout life history is the conservation of some genes concerned with the ordering of the parts of an organism from one end to the other, the modularity homeo box genes (102). They can be observed in humans, insects, worms, and even plants. Homeobox genes turn on or off various types of cellular activities (161).

Steroids are already present in prokariotes (159) and their chemical formulae do not change significantly through the evolutionary process (60). However, not being proteins, it is difficult to establish if the analogies in the chemical structures among steroids and NSs in different species are homologies (107, 161,236). Neurosteroid compounds have been identified and studied in ancestral species (156). Recent work (42) also revealed that in mammalian brain, steroid production is affected by factors such as sodium consumption. These results lead to the suggestion that "these locally generated adrenal steroids may act in a paracrine manner to modulate a potentially diverse range of characteristics, blood pressure, learning abilities, memory, or, under chronic stress, depressive behavior" (42).

Majewska (169) proposed that ATHP and ATHDOC derived from P and DOC from peripheral glands, i.e., adrenals and ovaries, also be considered NS. We believe this accepted notion could be further extended in the context of what is known about evolution of endocrine systems (41,159,184,236). We suggest that, as precursors of ATHP and ATHDOC, the most powerful endogenous GABA agonists, P and DOC should be considered prohormones. Besides their classical, recognized functions in reproduction and electrolite balance, P and DOC, when metabolized to their tetrahydro derivatives at specific neural sites in CNSs, exert powerful and important actions in the control of neural excitability. These actions, the result of "new competences" (184) which evolved in peripheral targets of the parent hormones, allow for localized and space limited effects of the powerful NSs.

This data is yet another evidence that organisms reaction to stimuli are always characterized by concerted neuroendocrine responses.

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