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Neurosteroids, neuroactive steroids, and symptoms of affective disorders

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Abstract

Neurosteroids (NS) are steroids synthesized by the brain. Neuroactive steroids (NAS) refers to steroids that, independent of their origin, are capable of modifying neural activities. NAS bind and modulate different types of membrane receptors. The gamma amino butyric acid (GABA) and sigma receptor complexes have been the most extensively studied. Oxidized ring A reduced pregnanes, tetrahydroprogesterone (THP), and tetrahydrodeoxycorticosterone (THDOC) bind to the progesterone intracellular receptor (PR), and in this way can also regulate gene expression. Animal experimentation showed that salient symptoms of depression, viz., anxiety, sleep disturbances, and memory and sexual dysfunctions, are modulated by NAS. In turn, psychotropic drugs modulate NS and NAS levels. NS levels as well as NAS plasma concentrations change in patients with depression syndromes, the levels return to normal baseline with recovery, but normalization is not necessary for successful therapy.

Results from current studies on the evolution of nervous systems, including evolutionary developmental biology as well as anatomical and physiological findings, almost preclude a categorical classification of the psychiatric ailments the human brain succumbs to. The persistence in maintaining such essentialist classifications may help to explain why up to now the search for biological markers in psychiatry has been an unrewarding effort. It is proposed that it would be more fruitful to focus on relationships between NAS and symptoms of psychiatric disorders, rather than with typologically defined disorders.

Keywords: Neurosteroids; Neuroactive steroids; Depression; Panic disorders; Anxiety; Glia; 5α-reductase; Tetrahydroprogesterone; Tetrahydrodeoxycorticosterone; Dehydroepiandrosterone

1. Introduction

The amine theory of affective disorders fostered and extended research programs that continue until now. Delay in the initiation of therapeutic effects, high proportion of non-responding patients, persistence of unwanted effects of the drugs, and better understanding of the neurobiology of the disorder are factors that lead to current attempts to develop new antidepressant (AD) compounds. Besides indol and catecholamines, dysregulation of peptides (Gurwitz and Weizman, 2005), steroid hormones (Dubrovsky, 2005a; Pisu and Serra, 2004), and other neurotransmitter systems also play significant roles in depression syndromes (Harris and Oreland, 2001).

Most AD target a limited number of biological systems out of the much larger number affected in depressive syndromes. Hence, shortcomings of current AD treatments are to be expected. Among others, two reasons conspiring against a successful and scientific solution to the problem of depression treatment are lack of an adequate animal model of the disorder, and difficulties with current classifications of psychiatric disorders.

This paper addresses the problem of the relationships between neurosteroids and neuroactive steroids and psychopathology, with emphasis on salient symptoms of depression syndromes.

2. Neurosteroids and neuroactive steroids

The term "neurosteroid" (NS), introduced by Baulieu in 1981 (Baulieu, 1998), names a steroid hormone, dehydroepiandrosterone sulfate (DHEAS), found at high levels in the brain long after

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gonadectomy and adrenalectomy, and later shown to be synthesized by the brain. Later, androstenedione, pregnenolone, their sulfates (Baulieu, 1998; Majewska, 1992) and lipid derivatives, as well as tetrahydrometabolites of progesterone (P) (Cheny et al., 1995) and deoxycorticosterone (DOC) were identified as neurosteroids (Baulieu, 1998). Production of ring A metabolites from P is not restricted to nervous systems (Leb et al., 1997).

There are differences between steroid synthesis in the brain and in the adrenals. Corticosteroid synthesis involves converting DOC to either aldosterone by aldosterone synthase or to corticosterone by 11β-hydroxylase. In the adrenals the enzymes are never expressed in the same cell. But in the brain, the enzymes coexpress not only in the same region, but even within the same cell, therefore aldosterone synthase and 11β-hydroxylase must compete for DOC (Greener, 2003). In the brain, the pregnanes are metabolized in sequence by the enzymes 5α-reductase and 3α hydroxysteroid dehydrogenase (HSD). Progesterone (P) to tetrahydroprogesterone (THP), deoxycorticosterone (DOC) to tetrahydrodeoxycorticosterone (THDOC) and testosterone to androstanediol. While the 5α-reduction process is unidirectional, the 3α reduction is bidirectional. Thus 5α-reduction is the rate-limiting step in the production of NAS and NS. Maayan et al. (2004), showed that 17β estradiol decreased THP formation by reduction of LTP.

Working "in vitro" in the frog hypothalamus, Do-Rego et al. (2000) showed that activation of $GABA_A$ receptors inhibits the activity of the 5α-reductase and 3α HSD enzymes in neurons and glia cells. As THP and THDOC are strong positive allosteric modulators at $GABA_A$ sites, NS themselves are part of an ultra short feedback loop that regulates their own rate of biosynthesis.

There are stringent structure–activity relationships for ring A reduced pregnanes. An OH group in the α position at C3 is essential for positive allosteric modulator activity at the $GABA_A$ receptor complex. An OH group in the β position at C3 converts α THP into a functional antagonist at the $GABA_A$ receptor complex (Dubrovsky, 2005b).

NAS bind and modulate different types of membrane receptors. The GABA and sigma receptor complexes have been the most extensively studied (Akunne et al., 2001; Reddy et al., 1998; Simoncini and Genazzi, 2003; Smith, 2002; Ukai et al., 1998). Glycine-activated chloride channels (Prince and Simmonds, 1992), nicotinic acetylcholine receptors constituted in xenopus laevis oocytes (Valera et al., 1992), and mouse striatal and thalamic synaptosomes (Bullock et al., 1997), and voltage-activated calcium channels, although less explored, are also modulated by NAS (Irwin et al., 1994).

Within the glutamate receptor family, *N*-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, and kainate receptors have also been demonstrated to be a target for steroid modulation (Wulf et al., 1991; Weaver et al., 1997).

Pregnanolone sulfate and 11β estradiol are negative modulators of the NMDA receptors. Pregnenolone sulfate (PS) and DHEA are positive modulators of the NMDA receptor (Mellon and Griffith, 2002). In the AMPA and kainate receptor PS acts as negative modulator (Mellon and Griffith, 2002).

Sensitivity of $GABA_A$ receptors to NAS depends on their previous exposure to chemicals, e.g. alcohol (Finn et al., 2004), to other endocrines, or to hormonal withdrawal, e.g., P in termination of pseudo pregnancy, Premenstrual Dysphoric Behavior Disorder (PMDD) or during the postpartum period (Biggio et al., 2001; Bitran and Smith, 2005). P withdrawal results in a decrease in brain content of THP and a subsequent increase in the expression of the $GABA_A$-receptor alpha-4 subunit (Smith, 2002). It has been proposed that the presence of the alpha-4 subunit is essential for the occurrence of P withdrawal effects, viz., increase of anxiety and seizures, decreased sensitivity to positive allosteric $GABA_A$-receptor modulators THDOC and THP, benzodiazepines and ethanol (Khisti et al., 2002), and increased sensitivity to negative allosteric $GABA_A$-receptor modulators like dehydroepiandrosterone sulfate (DHEAS) (Finn et al., 2004; Smith et al., 2005).

Brussard and Koksma (2003) have advanced an alternative explanation to account for sensitivity changes in the $GABA_A$ receptor complex. In addition to their allosteric interaction with $GABA_A$ receptors, neurosteroids play a role in translocation of particular phospho-kinase C (PKC) isomers toward the membrane which, in turn, would affect the neurosteroid sensitivity of $GABA_A$ receptors being expressed. For them, available evidence argues in favor of a simple model as being the most parsimonious one: neurosteroid sensitivity affects $GABA_A$ receptors in a bidirectional manner, being dependent on, but also affecting, the metabotropic modulation of $GABA_A$ receptors. Brussard and Koksma (2003) question receptor subunit specificity and argue that their model presents a general concept that (a) also occurs in other brain areas and (b) one which neurosteroids and other allosteric modulators might have in common. Their studies show that THP not only potentiates $GABA_A$ receptor function but also prevents its suppression by PKC, and propose that neurosteroid sensitivity of the $GABA_A$ receptor complex itself is dependent on the balance between endogenous phosphatase and PKC activity and not, as previously suggested, on subunit composition changes of the $GABA_A$ receptor. These data imply that native $GABA_A$ receptors are only sensitive to 3α DHP if there is endogenous phosphatase activity. In contrast, when due to endogenous release of oxytocin in the hypothalamus (Koksma et al., 2003), the intracellular balance is shifted from high phosphatase activity toward a higher level of PKC-dependent phosphorylation, this leads to 3α-OH-DHP-insensitivity of the $GABA_A$ receptors.

In classical models of steroid hormone action, pregnenes from the adrenals and gonads, e.g., mineralocorticoids (MC), glucocorticoids (GC), and gonad hormones, bind to cytosolic receptors. Subsequently, these receptors change their conformation by dissociation from chaperone molecules, the heat shock protein, and translocate to the nucleus where they bind as homodimers or heterodimers to the respective response elements that are located in the regulator regions of target promoters. Alternatively, these ligand-activated receptors can influence transactivation through protein–protein interaction with other transcription factors, thus acting as transcription factors in the regulation of gene expression.

There is strong evidence that steroids transcriptional and non-genomic actions behave as a coordinated system. From an evolutionary perspective, Csaba (1980) has argued that the "primordial receptor development (for environmental signals, e.g., hormones),

took place on the surface of contact. Further, cytosol receptors (could) arise by internalization of membrane receptors."

Allera and Wildt (1992) and Danfeldt et al. (2003) have identified a membrane-initiated steroid signaling (MISS) protein that transfers steroids such as corticosterone, cortisol, and particular gestagens and estrogens, into the nuclei of rat and human liver cells. In vitro and in vivo studies suggest that MISS mediates rapid, nongenomic responses to steroids, as well as genomic steroid action, the process they call membrane-initiated steroid signaling (Stocco, 2000).

3. Behavioral effects of NAS

The NAS THDOC and THP exert anxiolytic (Bitran et al., 2000; Guidotti and Costa, 1998; Jain et al., 2005), hypnotic (Damianisch et al., 2001; Lancel et al., 1997), anti aggressive (Kavaliers, 1988) anticonvulsant effects (Belelli et al., 1989; Landgren et al., 1987), improve performance in the forced swim stress test (Khisti et al., 2000) and decreases CNS excitability (Dubrovsky et al., 1982, 1990, 1993).

The work of Akwa et al. (1999), single intraventricular or intra-amygdala injections of THP, suggests that the anxiolytic-like effects of THP may be mediated via the amygdala and are accompanied by an increase in neuropeptide Y.

However, although until now THP has been associated with anti-anxiety and sedative effects, Spalletta et al. (2005) report that elevated THP plasma levels can also be associated with increased aggressiveness and hostility, as seen in some schizophrenic patients. Contrary to THDOC which exerts uniform decremental effects on hippocampal long-term potentiation (LTP), (Dubrovsky et al., 2004c), THP has bimodal effects, it first lowers and then enhances LTP (Dubrovsky, unpublished). Fish et al. (2001) reported that in mice, THP can also induce aggressive behavior. In women undergoing Hormonal Replacement Treatment (HRT), Andreen et al. (2005) reported significantly more negative mood symptoms in subjects showing high levels of THP serum concentrations.

3.1. Panic disorders

Since many NAS act as modulators of the $GABA_A$ receptor complex, abnormalities in the circulating levels of NAS in patients experiencing different types of anxiety disorders are to be expected. One particular NAS, DHEA, and its sulfated form DHEAS, have been investigated more extensively due to their anxiogenic properties at large doses.

In in vitro brain slices, DHEA and DHEAS have bimodal effects on $GABA_A$ receptors: positive allosteric modulation at low, nanomolar concentrations, and negative modulation at high, micromolar concentrations (Majewska, 1992). Behavioral studies (Prasad et al., 1997) show similar concentration dependent effects. Mice receiving low doses of DHEA or DHEAS in the anxiogenic plus model test, manifest lower levels of anxiety than control, non-treated animals (Melchior and Ritzmann, 1994). Besides direct effects on the $GABA_A$ receptor, the anxiolytic properties of DHEA and its sulfated form may also relate to the effects of its metabolites, androsterone and androstanediol. At low doses, these NAS behave as positive $GABA_A$ receptor modulators (Frye and Reed, 1998; Edinger and Frye, 2004). DHEA also induces a reduction in brain concentration of pregnenolone sulfate (PS), a negative $GABA_A$ receptor modulator; this could also play a role in the anxiolytic effects of DHEA (Young et al., 1991). In the plus maze test, PS shows a biphasic response, but no effect in the defense-burying test (Rodgers and Johnson, 1998).

In the mirror chamber test, DHEAS can block the anxiolytic actions of dizocilpine, an NMDA receptor antagonist, suggesting that DHEA and DHEAS effects on anxiety might also be mediated through $GABA_A$ independent mechanisms (Reddy and Kulkarni, 1997). In the plus maze, DHEA exerts anxiolytic effects (Melchior and Ritzmann, 1994). At high plasma levels, DHEAS is anxiogenic as has been shown in the mirror chamber behavioral test in mice.

Results from studies of NAS levels in panic attacks were somewhat disappointing. They did not reveal significant differences between normal baseline plasma levels of THP in patients with generalized anxiety disorder (Le Melledo and Baker, 2002), generalized social phobia or panic disorders (Le Melledo and Baker, 2002) and those challenged with the panicogenic agent pentagastrin (Tait et al., 2002).

Surprisingly, Strohle et al. (2003) found that levels of the anxiolytic NAS THP were higher than normal in patients with panic disorder. In contrast, the same group of researchers showed that panic attacks induced by sodium lactate and cholecystokinin tetrapeptide (CCK4) in patients suffering from panic disorder were accompanied by pronounced decreases in the concentration of THP and 3α5β-THP, and a concomitant increase in the concentrations of 3β5α-THP, a functional antagonistic isomer of THP, a finding compatible with a decreased GABA-ergic tone (Strohle et al., 2003).

Zwanzger et al. (2004) reported that in healthy volunteers, NAS are not affected by panic induced with 50 μg of cholecystokinin tetrapeptide 4 (CCK4). However, in a later study, the same group (Eser et al., 2005) found an increase in the anxiolytic NAS THDOC with CCK4 treatment.

Strohle et al. (2003) reported increased levels of plasma THP in patients with panic disorders. They interpreted these finding as an "attempt" by the organism to return plasma NAS to normal, baseline levels. Brambilla et al. (2003) found high levels of P, THP, THDOC and pregnenolone in female patients with panic disorder. However, DHEA did not differ in patients in relation to controls. Like Strohle et al. (2003), Brambilla et al. also interpret the results in teleological terms, i.e., as a sign that NAS with anxiolytic activity such as THP and THDOC increase in panic disorders as a homeostatic mechanism to counteract the hyperactivity of the hypothalamo-pituitary adrenal axis and to improve a reduced $GABA_A$ receptor sensitivity in the syndromes.

Heydari and Le Melledo (2002) found that patients with generalized anxiety disorder or generalized social phobia, but not with panic disorder, had lower plasma levels of PS than healthy volunteers. They interpret the lower levels of PS in pathological anxiety as a homeostatic attempt of the organism to reduce anxiety through a less negative modulation of the $GABA_A$ receptor and a less positive modulation of the NMDA receptor. As all teleologically based hypotheses, this is difficult to prove.

In another panic related condition, combat-related posttraumatic stress disorder (PTSD), Spivak et al., 2000, report that plasma levels of DHEA and DHEAS were higher than baseline values.

Discrepancies in the results reported by different groups relate to what nobelist A. Houssay said already in 1957, " in the whole organism one hormone never works alone. In every case, the action of one hormone is related to the balance of hormones present. If we study any function we find that it does not depend on one hormone, but on a balance between hormones acting together or in a consecutive way."

To increase GABAergic tone and potentially improve treatment of panic disorders, Zwangzer and Rupprecht (2005) raised GABA transaminasa inhibitors and/or inhibitors of GABA transporters to enhance GABA endogenous activity. In both healthy volunteers panic induced with CCK4, and in patients with panic disorders, these drugs produced a reduction of symptom intensity, suggesting another line of treatment for these disorders. This is a new approach to the modulation of endogenous GABA tone.

Seizures have been reported in patients with adrenal adenomas presenting with elevated plasma DHEA. Heuser (1987) reported that IV or IP injections of DHEA in the l00 mg/kg range induced seizures in cebus monkeys.

3.2. Effects of inhibition of 5α-reductase on behavior

Experiments with 4 azasteroid, (17β CNT butyl finasteride carbomoyl-4-aza 5 and androst 1-en 3 one), a 5α-reductase inhibitor, provide further evidence of the role of Finasteride in psycho- -as well as in general pathology (Ellis et al., 2005). Finasteride inhibits 5α-reductase, the rate limiting enzyme for the metabolism of P, DOC and testosterone (T), decreasing the formation of ring A reduced metabolites. In rats, injection in the hippocampus or systemic administration of the drug increased anxiety and depression-like behaviors (Frye and Walf, 2004). Similar effects were observed with Finasteride injected in the amygdala (Wualf et al., 2005).

In the clinic, Finasteride is used for the treatment of androgenic alopecia and benign prostate hyperplasia (BPH). The drug decreases the formation of dihydro T (DHT), believed to be the acting steroid in the pathogenesis of the disorder. Could the decrease formation of reduced metabolites like THP and THDOC lead to the appearance of mood disturbances in patients treated with the drug?

Out of 23 patients with alopecia treated with Finasteride, 19 reported depression symptoms, i.e., low mood, anxiety. Suspension of treatment resulted, after 10 to 12 days, in a return to regular, stable mood (Altomare and Capella, 2002). A recent review (Townsend and Marlowe, 2004) concluded that, at least for the treatment of hirsutism, Finasteride is psychologically well tolerated by women. Besides gender difference in response to the drug, other factors play a role in the potential depressogenic effects of Finasteride. One of them is the disorder for which the drug is used. BPH makes men more vulnerable to developing depression-like disorders when treated with Finasteride (Clifford and Farmer, 2002).

Finasteride has been used to study potential effects of P metabolites in sexual behavior (Cilotti et al., 2001; Rittmaster, 1997; Zlotta et al., 2005). THP enhances proceptive behavior in rats, as shown by reduction of these behaviors after simultaneous treatment with P and Finasteride. Thus both progesterone and its reduced metabolites are necessary for full expression of proceptive behavior and lordosis (Frye et al., 1998; Zimmerberg et al., 2005).

3.3. Neurosteroids, neuroactive steroids, and salient symptoms of depression

A great amount of work has been done on NAS changes in and after treatment of depression syndromes either with antidepressants (reviews in Broekhoven van and Verkes, 2003; Dubrovsky, 2005a,b; Pisu and Serra, 2004; Romeo et al., 1998; Uzunova et al., 2004), or with non-pharmacological treatments, viz., repetitive transcraneal magnetic stimulation (rTMS) (Padberg et al., 2002), sleep deprivation (Schüle et al., 2003), electroconvulsive therapy (ECT) (Baghai et al., 2005).

The fact that depressions can improve with non-pharmacological treatments and no changes in NAS plasma levels indicates that NAS changes are not essential in recovery. However there is a caveat with this proposition. As adrenocorticotropic hormone (ACTH) can modulate NS biosynthesis as well as affect NAS levels (Torres et al., 2001; Torres and Ortega, 2003), it is conceivable that after reaching specific CNS targets, e.g., hippocampus, amygdala, by volume transmission (Agnati et al., 2000), an excess of ACTH could disrupt the balance between excitatory and depressant NS biosynthesis, and affect core symptoms of depression such as anxiety, memory dysfunction, sleep, and sexual disturbances. Some of these symptoms may then have a paracrine component (Dubrovsky, 2006). Peripheral levels of steroid hormones do not always correlate with manifested behavior (Starkman et al., 1981, 1986).

Since the classical work of Papez, the hippocampal formation (HF) has been recognized as an essential component of emotional behavior, a notion later reemphasized and extended by MacLean (1993) in his triune brain theory. But as important as its involvement in emotional behavior, the HF is also essential for cognitive activities (Squire and Kandel, 1999).

Hippocampal lesions severely interfere with memory processes, encoding, laying down and retrieval as well as learning (Kandel, 2006).

The hippocampus also participates in attentional processes. In turn, there is a great deal of interaction between memory and attention (Schacter, 2001). 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 (Dubrovsky, 1993).

Memory disturbances are almost a constant feature of depression syndromes (Lishman, 1972, 1974; Lloyd and Lishman, 1975), so much so that Lishman considers that they play a primary role in the pathogenesis and maintenance of the disorders (Lishman, 1972, 1974). Weingartner and Silberman (1982) 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 (1972, 1974) and Lloyd and Lishman (1975) 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 negatively connotated words. Also in depressed patients, response biases were observed, unpleasant material was handled in a preferential way to neutral or pleasant material in a signal detection analysis study (Dunbar and Lishman, 1984). The fact that congruence between affective state and tone of material recalled interact during retrieval is well documented (Bower, 1983; Schacter, 2001; Teasdale et al., 1999).

Current data indicate that memories with different contents, i.e., positive or negative, correspond with different biochemical mediators and/or different neuronal circuits (Kandel, 2006), that may change their mode of activity by different internal milieus (Dubrovsky, 2000). These proposals, already made by von Monakow (1825), have recently received some experimental support (Schacter, 2001). Depressed individuals and controls show different patterns of electrical brain activity during encoding of positive and negative information (Deldin et al., 2001).

It would be expected that the effects of a $GABA_A$ positive allosteric modulator like THP is detrimental to memory functions on account of its benzodiazepine-like actions (Lancel et al., 1997). Mayo et al. (1993) reported that injection of 2 ng of THP in the nucleus basalis magnocellularis of rats, disrupted performance in a two-trial recognition task when injected before an acquisition trial. No effects were observed if injections were effected after acquisition trials, suggesting that THP interferes with learning processes during the acquisition phase. In contrast, pregnenolone sulfate (PS) infused into the ventricles enhanced memory performance in mice (Ladurelle et al., 2000), it is thought to act, in part, by increasing hippocampal acetylcholine release (Griffin and Mellon, 1999), and as positive modulators at NMDA receptor sites (Rupprecht, 2003).

Johansson et al. (2002) showed that THP inhibited learning in the Morris water maze test. In contrast, data of Frye and Sturgis (1995) showed that both THP 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 NAS were surprising given the opposite effects that THP and DHEAS have on $GABA_A$ receptor complex: while THP has positive allosteric agonistic modulatory actions, DHEAS at high doses acts as a negative allosteric modulator at these synapses.

Treatment with high doses of THP enhances dopamine release and dopaminergic response to morphine in the rat nucleus accumbens (Rouge-Pont et al., 2002). Behaviorally, THP by its action at the $GABA_A$ receptors, increases GABAergic tone, leading to a behavioral profile similar to that of dopamine receptor antagonists, e.g., haloperidol (Khisti et al., 2002).

Memory enhancing effects of DHEAS in aging mice were described by Flood and Roberts (1988). These effects were explained by the agonist effects of DHEAS on the sigma l receptor (Urani et al., 1998), a hypothesis supported by other experimental data. Memory tasks are impaired by dizocilpine, a noncompetitive NMDA receptor antagonist, and scopolamine (Zou et al., 2000). Treatment with DHEAS improves performance in animals treated with these drugs. However, treatment with NE-100, a sigma l receptor antagonist, inhibits the improvement. The results indicate that, in this instance, DHEAS acts via sigma receptors (Zou et al., 2000). The cognitive enhancing effects of DHEAS observed in ancestral species have been difficult to replicate in humans (Bloch et al., 1999; Huppert and Van Niekerk, 2001). At sigma receptor sites, DHEAS acts as an agonist, different from pregnenolone, which behaves as a sigma inverse agonist, thus acting as an antagonist (Monnet et al., 1995).

The NAS and steroid hormone DHEAS has also been studied in depression syndromes. DHEAS counteracts glucocorticoid actions, one plausible mechanism for its AD effects (Hechter et al., 1997). DHEAS also inhibits dexamethasone-induced suppression of lymphocytes and thymic involution (Hechter et al., 1997), and counteracts the decremental effects of corticosterone on long-term potentiation (LTP) (Kaminska et al., 2000), as well as the impairment of contextual fear conditioning (Fleshner et al., 1997). DHEAS also provides protection from the neurotoxic effects of glucocorticoids (GC) (Kerr et al., 1992) at the neuronal level (Kimonides et al., 1999). DHEAS decreases plasma cortisol levels (Wolkowitz et al., 1999), and like THP and some AD, DHEAS improves performance in the Porsolt forced swimming test (Reddy et al., 1998).

Early results lead to the hypothesis that DHEAS may be useful in the treatment of depressive syndromes, in particular those presenting with hypercortisolemia (Dubrovsky, 1995b, 1997), a hypothesis later validated in the clinic. In open label as well as in double blind, randomized, placebo-controlled studies (Wolkowitz et al., 1999; Schmidt et al., 2005), oral administration of DHEAS decreased symptoms in patients with major forms of the syndrome, as well as with dysthymia (Bloch et al., 1999). It is important to note that the symptoms that improved most significantly with DHEA treatment were anhedonia, loss of energy, sadness, worry, emotional numbness, and lack of motivation. No specific effects on cognitive function or sleep disturbances were noted. Thus, although of benefit for some symptoms of depression, DHEA does not affect the entire spectrum.

Other mechanisms are involved in the antidepressant actions of DHEA. One of them is the agonistic action of DHEA on Sigma 1 receptors (Urani et al., 2001). Enhancement of noradrenaline and serotonin neurotransmission has antidepressant effects, in vitro data indicate that at sigma ligands, DHEAS inhibit noradrenaline presynaptic uptake in brain synaptosomes (Kinouchi et al., 1989; Monnet et al., 1995). Noradrenaline release is stimulated by activation of $GABA_A$ receptors on noradrenergic nerve terminals. Furthermore, treatment with DHEAS increases the number of NMDA receptors (Wen et al., 2001) and potentiates NMDA-evoked noradrenaline release via sigma receptors (Monnet et al., 1995).

The NAS THP, THDOC, DHEA, PS, androstenedione, and 17β estradiol, affect the development and duration of LTP. Work in the field has recently been reviewed (Dubrovsky, 2005b). LTP is recognized as a putative model for associative learning. Experiments on the effects of NAS on the LTP of the hippocampus, a fundamental brain region for memory function,

serve as a preclinical model for the investigation of NAS and memory. In addition, the preparation allows the study of actions and counteractions of NAS, a good paradigm for therapeutic essays (Dubrovsky et al., 1996; Kaminska et al., 2000).

Sleep disturbances present with high incidence in depressive disorders. In a study of 35 patients with depression syndromes, 70% of them complained of sleep disturbances (Starkman et al., 1986). A marked reduction, even absence, of stages 3 and 4, delta sleep has been reported (Kupfer et al., 1973). Similar changes were reported to occur in patients suffering from Cushing's syndromes (Krieger, 1978). Early onset of REM sleep (Kupfer et al., 1973) is also characteristic of depression syndromes, although not exclusive to them.

NAS play a role in sleep modulation (Damianisch et al., 2001; Muller-Preuss et al., 2002), and as sleep disturbances are one of the salient symptoms of depression, it is likely that NAS are associated with them.

3.4. Acute and chronic stress

Various acute stress paradigms decrease [^{3}H]GABA binding and GABA-induced Cl^- fluxes through the receptor-associated ion channel (Barbaccia et al., 1994; Dubrovsky, 2004b). Stressful conditions also induce a rapid and marked increase in the rat brain concentration of NS like THP and THDOC (Barbaccia et al., 1996; Purdy et al., 1991). These increases were interpreted as an adaptive mechanism to counteract the decrease in $GABA_A$ receptor function induced by acute stress (Barbaccia et al., 1996).

Chronic stress is an important factor in the development of depression syndromes, chronic illness being a major contributor to the process (Dubrovsky, 1995b, 1998, 2004b). But, contrary to Selye's ideas (1936), each stress stimulus will induces a particular hormonal profile likely to be associated with specific disorders (Dubrovsky, 1998, 2000; Mason, 1971; Reincke et al., 1995). Selye's monolithic concept of stress as consisting only of unspecific nonselective responses of the hypothalamic hypophyso adrenal axis (HHAA) (Selye, 1936) was criticized from the outset (Cannon, 1935). How could the same pattern of hormone responses have adaptive utility in response to diverse stimuli which pose diametrically opposite metabolic needs on the body as do, e.g., heat, cold, physical exhaustion, sickness, etc.

Mason (1974) raised further criticisms. "I had long been troubled by the apparent incompatibility of the general adaptation syndrome with the concept of homeostasis". Mason challenged the concept of nonspecificity of the stress response and disclosed the opposite to be the case, i.e., that the responses of organisms to distinct stressors were selective and specific (Mason, 1971). Further, he revealed that neuroendocrine responses to nocuous stimuli were not restricted to the HHAA, but extend to the entire neuroendocrine system. NAS also play a role in stress responses (Morrow et al., 1995).

Mason (1974) reemphasized the importance of psychological factors in the response to stress originally noted by Cannon (1928). In contrast to Selye's monolithic view, responses are mosaic-like (Dubrovsky, 2000; Pakak and Palkovits, 2001).

The hormonal profile response elicited by different stress stimuli depends greatly on how individual subjects evaluate or appraise the stimuli. The "coping filter" is "the best understood, and best developed concept in the stress literature, and "the psychological filtering mechanism of defense is only identified in humans" (Ursin, 1998).

Cell death, dendritic shrinkage, decreased levels of neurotrophins, brain development growth factor (BDGF), and reduction of neurogenesis in hippocampal granule cells (Castren, 2004; Czeh et al., 2001; Mahlberg, 2004; Nestler et al., 2002; Santarelli et al., 2003), are associated with chronic stress.

4. Neuroprotection and neurogenesis. Amines and NAS effects

Some NAS have neuroprotective properties and exert selective effects on neurogenesis. Data on this topic have recently been reviewed (Magnaghi et al., 2001; Schumacher et al., 2000, 2001; Young, 2002).

Recent developments suggest that some AD initiate a cascade of processes leading to the differentiation of glial cells, necessary for the recovery from depression. Isoproterenol and serotonin induce the elevation of glial fibrillary acidic protein (GFAP) mRNA levels. The processes are dependent on the activation of $GABA_A$ receptors via ring A-reduced metabolites of pregnene steroids (Morita et al., 2006).

Glia activities are influenced by neurons, the existence of neurotransmitter-mediated signaling pathways in glial cells is well established (Chui and Kriegler, 1994; Hansson, 1989; Morita et al., 2005). The expression of GFAP gene is considered an index of glial cell differentiation. Progesterone (P), and its 5α-reduced metabolite dehydro P (DHP), increase GFAP gene mRNA levels in type 1 rat astrocytes. Since the effects are faster and more pronounced with DHP, it is thought to be the acting steroid. In intact, but not in spinal transected rats, P also stimulates immunocytochemical staining for myelin-basic protein (MBP) and the number of oligodendrocyte cells expressing the chondroitin sulfate proteoglycan NG2 lesions rats (De Nicola et al., 2003).

Adrenergic (isoproterenol) as well as indolamines (serotonin) elevate GFAP mRNA and protein levels in glial cells through the elevation of intracellular cyclic AMP levels (Le Prince et al., 1991; Koschel and Tas, 1993; Melcangi et al., 1992; Papodopoulos and Guarneri, 1994; Segovia et al., 1994; Shain et al., 1992). In turn, the cyclic AMP-mediated intracellular signaling system, activated by β-adrenergic stimulation, is implicated in the regulation of glial cell metabolism and gene expression (Chui and Kriegler, 1994).

Adrenergic and serotonergic stimulation of glioma cells also enhance the expression of 5α-reductase genes in these cells (Morita et al., 2004). Adrenergic activation increases 5α-reductase expression through the activation of cyclic AMP/protein kinase A-mediated signaling pathway. Serotonin, in turn, induces 5α-reductase gene activation by enhancing the expression of transcription factor Egr-1 expression (Morita et al., 2006).

The increase of GFAB mRNA levels induced by isoproterenol and serotonin are suppressed by pretreatment of the cells with Finasteride, which also abolishes the stimulatory effects of P and DHP on GFAP gene expression. Adrenergic and serotonergic

increase of 5α-reductase gene expression in glial cells occurs prior to the activation of GFAP gene expression.

Isoproterenol- and serotonin-induced elevation of GFAP mRNA levels is also inhibited by pretreatment of the cells with bicuculline, a selective $GABA_A$ receptor antagonist. Thus the increase of GFAP mRNA levels produced by indol and catecholamines depends on DHP, a NAS that positively modulates GABA receptors directly (Koksma et al., 2003), or most likely after its conversion to 3α THP (Dubrovsky, 2005a,b).

In part, regulation of astrocyte morphology and differentiation is mediated by GABA (Mong et al., 2002). Thus, adrenergic and serotonergic activation of GFAP gene expression depends on the effects of 5α-reduced steroid metabolites on the $GABA_A$ receptors of glioma cells (Morita et al., 2006), data that suggest that jointly, amines and NAS enhance glial growth differentiation, an important process for recovery from depression.

In the clinic, lower levels of GABA in CSF have been found in depressed patients (Gerner and Hare, 1981; Gold et al., 1980). Intravenous injections of the SSRI citalopram in control subjects (Bhagwagar et al., 2004) as well as following electroconvulsive seizures (ECS) treatment in depressed patients (Sanacora et al., 2003), increase GABA concentrations in the visual cortex, up to 50%, measured by magnetic resonance spectroscopy (MRS).

Long-term (more than 3 weeks), but not short-term, treatment with different classes of drugs used as antidepressants, e.g., selective serotonin reuptake inhibitors (SSRI), selective serotonin noradrenaline reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), bupropion which inhibit dopamine (DA) reuptake, and tianeptine, which enhances serotonin reuptake, increases cell proliferation and neurogenesis in the hippocampus (Castren, 2004; Czeh et al., 2001; Mahlberg, 2004; Santarelli et al., 2003).

Electroconvulsive seizures (ECS) also increase hippocampal neurogenesis in the adult rat (Hellsten et al., 2002). Simultaneously, there is an increase of endothelial cell proliferation which may act to support the increased neural proliferation and neuronal activity or vice versa, possibly leading to structural changes within the hippocampus, of importance for the antidepressant effects of electroconvulsive seizures (Hellsten et al., 2004).

Neuroactive steroids can also protect neural cells from apoptosis. Charalampopoulos et al. (2004) reported that DHEA and THP protect sympatho-adrenal medulla cells against apoptosis via anti-apoptopic Bcl-2 proteins. Decline of DHEAS during aging or stress makes the adrenal medulla more susceptible to proapoptotic challenges. Bcl-2 is physiologically involved in preventing cell death by decreasing the generation of reactive oxygen species (ROS) within mitochondria (Jayanthi et al., 2004).

Li et al. (in press) reported that administration of DHEAS for 3 days after transient incomplete forebrain ischemia prevented severe impairment of LTP, a detrimental effect of the ischemia. Phosphorylation of NMDA receptor subunit 2B (NR2B) significantly decreased after ischemia. Administration of DHEAS lessened the reduction of tyrosine phosphorylation of NR2B. Brussard and Koksma (2003) associated the NAS THP to the translocation of particular PKC isomers towards the membrane.

4.1. Commentary: why NAS are not biological markers

Notwithstanding the extensive amount of work done on the possibility of using NAS levels as specific markers for or indices of psychiatric disorders, these efforts have so far been unrewarding (Dubrovsky, 2005a,b; van Praag et al., 1987). This failure is not restricted to NAS; it is rare that the interaction between laboratory and clinical data, which proved so important for the advancement of general medicine, is part of psychiatric practice.

To explain this state of affairs it is necessary to consider recent developments in neurobiology, which underlie the incompatibility between current psychiatric classifications and fundamental neuroscience.

4.2. Current classifications

The two most widely used classifications, International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (1994) (DSM IV), are based on Plato's essentialist philosophy, initially endorsed by Kraepelin (1968).

For essentialists, all seemingly variable phenomena of nature could be sorted out into classes, each endowed with a unique essence that allows its typological classification. In these classifications, psychiatric disorders are considered to be discrete, categorical units, with rarity points between them, i.e., showing clear boundaries that distinguish one from the other (Kendell, 1975).

However by the 1860s essentialism was replaced by Darwin's most revolutionary idea, population thinking or, the variational model of evolution (Mayr, 1982). This idea acknowledges the variable group as primary and treats variation as intrinsic and fundamental, "…variation itself is the proper object of biological study for it is the ground of biological being…" (Lewontin, 2000).

4.3. Recent studies and interpretations of brain organization

The fact that extensive neural nets connect brain regions involved in affective and cognitive behaviors, and that interactions between them are essential for appropriate behavior (Damasio, 1999), challenges the notion that affection and cognition are absolute, distinct behavioral categories (Dubrovsky, 1995a, 2002, 2004a,b).

The classical notion that the cerebral cortex is organized into sensory, association and motor regions, begun to be questioned in the 1960s (Diamond and Hall, 1969; Diamond, 1983; Mountcastle, 1998). Zones that did not respond to peripheral stimuli, or in which it was not possible to demonstrate degenerated axons, were named association cortices.

The ideas of associationist psychologists and empiricist philosophers like Locke and Hume played a fundamental role in adjudicating functions to association cortices. As these regions were thought to receive afferent fibers mainly from primary cortices, it was believed that in association cortices association of sensation gives rise to perception.

However the introduction of new experimental methods disclosed that association cortices do respond to stimuli from

the periphery and show degenerated axons after thalamic lesions (Sherman and Guillery, 2002). Fibers reaching association cortices directly, signal specific attributes from the exterior and interior worlds of an individual (Diamond and Hall, 1969; Diamond, 1982, 1983; Butler and Hodos, 2004).

It is more appropriate to deduce behavior in which different regions are involved from what is known about physiological processes in these regions, rather than to attribute to them behaviors whose implementation we know nothing about.

4.4. Parallel processing. Binding

The recognition that processing of sensory signals is carried out in primary and in so-called association cortices (Diamond, 1982; Dubrovsky and Garcia-Rill, 1971; Dubrovsky et al., 1971; Zeki, 1993), marked the end of sequential methods to study sensory processing, and the collapse of the concept of hierarchical organization for the analysis and synthesis of sensory signals.

But how are different sensory components gathered into one global image to produce perceptual unity? This is the binding problem, a central issue in neuroscience (Crick, 1994).

Proposed solutions revolve around the hypothesis that binding is the result of synchronization of brain activity. Llinas (2001) describes the hypothesis this way: "Spatial mapping creates a finite universe of possible representations. The addition of a second component capable of generating new combinations of such spatial mappings by means of temporal conjunction generates an immensely larger set of representations and categorization is achieved by the superposition of spatial and temporal mappings via thalamo-cortical resonant iteration". As ANS modulate neuronal excitability, it is likely that they play a role in synchronization mechanisms in the brain. Thus, doses of DHEA larger than 150 mg can trigger seizures in primates (Heuser, 1957), while NAS like THP and THDOC suppress seizure activity (Dubrovsky, 2005,a,b).

4.5. Development, evolution, and functional aspects of brain activity

Investigations in evolutionary developmental biology (evo-devo) uncovered information about brains that conflicts with established notions. Among other findings, evo-devo revealed that animals, from flies to humans, share a large cohort of developmental genes (Carroll, 2005; Kirschner and Gerhart, 2005), and that besides the acquisition of new neural groups, brains evolve by expansion of the domain of some Hox genes, independent of traditional adaptive interpretations (Allman, 1999; Butler and Hodos, 2004). New results on the physiology of neural networks show that the tasks they perform depend upon what influences its components are being subjected to at the time. Thus, they can perform in any one of several modes (Dubrovsky, 2001; Getting, 1989). Hence, dysfunction(s) of one brain circuit can be associated, in time, with different symptoms.

The data reviewed above indicate that when the human brain succumbs to psychiatric pathology, attempts to classify the resulting disorders within the context of typological essentialist taxonomies are unlikely to succeed. Psychiatric disorders lack both essential clinical characteristics and specific biological markers. This helps to explain why nosological focus has brought biological psychiatry little in return, as well as the lack of diagnostic and therapeutic gains after a large number of studies on NAS and psychopathology (Dubrovsky, 2005b; Rupprecht et al., 2004; van Praag et al., 1987).

However, nosological nonspecificity of a given biological variable like NAS does not mean it is not specific at all. It may be that the variable relates not to a disorder as such, i.e. depression, but to a component of that disorder, to a particular psychological dysfunction(s) (Dubrovsky et al., 2004c; van Praag, 1987). Psychological dysfunctions are rarely nosologically specific, but tend to occur in a variety of psychiatric disorders. This is why many biological variables in psychiatric disorders defy nosological borders (Kendell, 1975, 1989; van Praag et al., 1987).

Some of the NAS reviewed, THP, THDOC, DHEAS, PS, 17β estradiol, modulate memory, sleep, anxiety, mood and sexual function. Thus although nosologically not exclusively associated with depression, NAS play important roles in the control of salient symptoms of the syndrome. But these symptoms are present in other psychiatric disorders, and in principle NAS should play a role in them. Strous et al. (2003) presented data in keeping with this notion, they reported that treatment augmentation with DHEA markedly improved negative, depressive and anxiety symptoms in schizophrenia patients, the same effects DHEA has in depressed patients (Bloch et al., 1999; Schmidt et al., 2005).

In view of the results discussed above, we propose that it would be better to relate dysregulation of NAS to psychological dysfunctions rather than to nosologically defined disorders.

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