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Neuroactive Steroids in Depression and Anxiety Disorders: Clinical Studies

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Neurosteroids · γ-Aminobutyric acid type A receptor · Ligand-gated ion channel · Antidepressants · Partial sleep deprivation · Transcranial magnetic stimulation · Electroconvulsive therapy · Cholecystokinine-tetrapeptide · Panic disorder

Abstract
Certain neuroactive steroids modulate ligand-gated ion channels via non-genomic mechanisms. Especially 3α-reduced pregnane steroids are potent positive allosteric modulators of the γ-aminobutyric acid type A ($GABA_A$) receptor. During major depression, there is a disequilibrium of 3α-reduced neuroactive steroids, which is corrected by clinically effective pharmacological treatment. To investigate whether these alterations are a general principle of successful antidepressant treatment, we studied the impact of nonpharmacological treatment options on neuroactive steroid concentrations during major depression. Neither partial sleep deprivation, transcranial magnetic stimulation, nor electroconvulsive therapy affected neuroactive steroid levels irrespectively of the response to these treatments. These studies suggest that the changes in neuroactive steroid concentrations observed after antidepressant pharmacotherapy more likely reflect distinct pharmacological properties of antidepressants rather than the clinical response. In patients with panic disorder, changes in neuroactive steroid composition have been observed opposite to those seen in depression. However, during experimentally induced panic induction either with cholecystokinine-tetrapeptide or sodium lactate, there was a pronounced decline in the concentrations of 3α-reduced neuroactive steroids in patients with panic disorder, which might result in a decreased GABAergic tone. In contrast, no changes in neuroactive steroid concentrations could be observed in healthy controls with the exception of 3α,5α-tetrahydrodeoxycorticosterone. The modulation of $GABA_A$ receptors by neuroactive steroids might contribute to the pathophysiology of depression and anxiety disorders and might offer new targets for the development of novel anxiolytic compounds.

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Introduction

In the past decades, considerable evidence has emerged that certain steroids not only act as transcription factors in the regulation of gene expression [1] but may also alter neuronal excitability through interaction with specific neurotransmitter receptors [2–5]. The term 'neuroactive steroids' has been adapted for steroids with these particular properties. Furthermore, a variety of neuroactive steroids may be synthesized de novo from cholesterol in the

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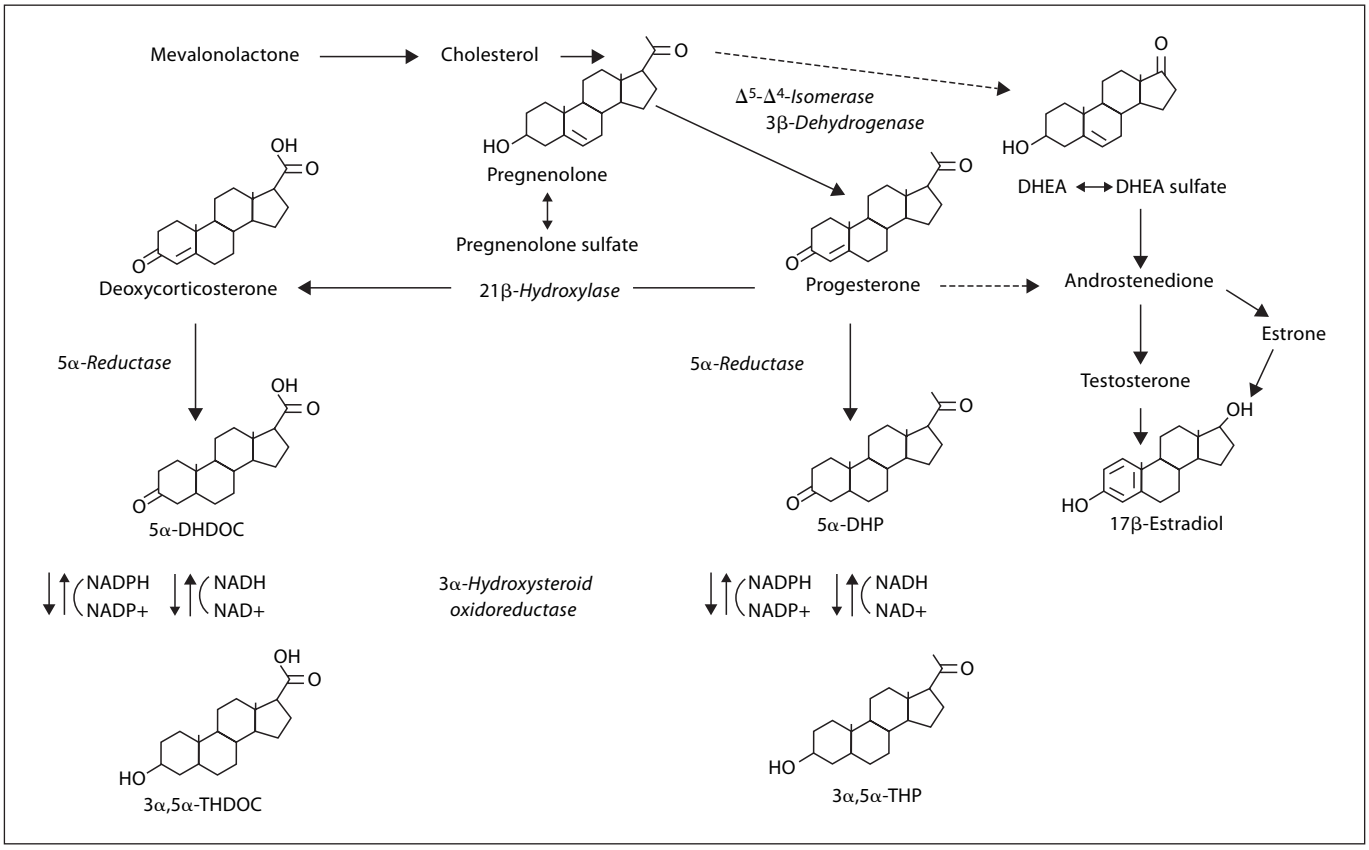

Fig. 1. Biosynthesis of 3α-reduced neuroactive steroids. Reproduced with permission from Rupprecht and Holsboer [5].

brain without the aid of peripheral sources [6]. These neuroactive steroids have been defined as 'neurosteroids' [7].

The main precursor molecule for the synthesis of neuroactive steroids is pregnenolone which is a precursor for dehydroepiandrosterone (DHEA). Pregnenolone may also be converted into progesterone which may be further reduced into the 3α-pregnane metabolites 5α-dihydroprogesterone (5α-DHP) and 5α-dihydrodeoxycorticosterone (5α-DHDOC). These molecules serve as precursors for the so-called 3α-reduced neuroactive steroids 3α,5α-tetrahydroprogesterone (3α,5α-THP; allopregnanolone), 3α,5β-tetrahydroprogesterone (3α,5β-THP; 5β-pregnan-3α-ol-20-one) and 3α,5α-tetrahydrodeoxycorticosterone (3α,5α-THDOC; 3α,21-dihydroxy-5α-pregnan-20-one; allotetrahydrodeoxycorticosterone). In particular, these 3α-reduced neuroactive steroids are potent positive allosteric modulators of the γ-aminobutyric acid type A ($GABA_A$) receptor because they increase the frequency and/or duration of openings of the GABA-gated chloride channel [2, 4]. Thereby, 3α,5α-THDOC derives mainly from the adrenal gland and the synthesis of its precursor deoxycorticosterone (DOC) is under the control of corticotropin (ACTH) (fig. 1). A detailed review on steroid biosynthesis in the central nervous system is given elsewhere [8]. In view of their GABA-enhancing properties, such 3α-reduced neuroactive steroids are of major interest for depression and anxiety disorders. In contrast, the sulfate esters of pregnenolone or DHEA display GABA-antagonistic properties [9, 10]. Although the majority of studies have focused on the modulatory potential of neuroactive steroids at the $GABA_A$ receptor, also other receptors, for example the N-methyl-D-aspartate-gated ion channel [11] or the σ_1 receptor [12], may be a target for neuroactive steroids. However, in view of their GABA-enhancing properties, 3α-reduced neuroactive steroids are of particular interest for neuropsychopharmacological research. Preclinical studies suggested that neuroactive steroids may modulate anxiety and depression-related behavior. Moreover, it has

been suggested that neuroactive steroids may be involved in the therapeutical effects of antidepressant drugs, and several clinical studies suggested that changes in neuroactive steroid concentrations might be involved in the pathophysiology and course of certain psychiatric disorders. This review will in particular focus on the role of neuroactive steroids in depression and anxiety disorders.

Neuroactive Steroids as Endogenous Modulators of Depression and Anxiety Disorders

Pregnenolone, the main precursor molecule for steroid hormone and neuroactive steroid synthesis, and its sulfated derivate pregnenolone sulfate (PS) may directly modulate neurotransmitter receptors [13]. Preclinical studies suggested that pregnenolone/PS modulate depression and anxiety-related behavior. PS has been shown to exert an antidepressant-like profile in the forced swimming procedure, probably throughout interaction with σ_1 receptors [14]. In addition, in animal models of anxiety-related behavior, a biphasic response curve has been shown for PS [15], being anxiogenic at higher and anxiolytic at lower doses [15]. This effect is compatible with a demonstrated mixed agonistic/antagonistic profile at $GABA_A$ receptors [16–18]. In line with these preclinical results, a pathophysiological role of pregnenolone and its sulfate conjugate has been suggested in affective disorders. Decreased PS levels have been found in patients suffering from depression [19], generalized anxiety disorder [20] and generalized social phobia [21]. In contrast, in women suffering from mixed anxiety-depressive disorder [22] or from premenstrual syndrome (PMS) [23], elevated PS plasma concentrations have been observed, suggesting that the pattern of dysregulated pregnenolone/PS levels may vary with different psychiatric disorders.

Because of certain similarities concerning the molecular mechanisms of PS and DHEA/DHEA sulfate (DHEAS), similar effects on depression and anxiety-related behavior might be expected. Like PS, also DHEAS has been shown to exert antidepressant-like effects in the forced swimming procedure, which are mediated throughout interaction with σ_1 receptors [14, 24]. In addition, compatible with a positive allosteric modulation of $GABA_A$ receptors at lower concentrations, DHEA/DHEAS showed anxiolytic activity in the plus maze test in mice [25].

In humans, a variety of studies focused on DHEA/DHEAS plasma levels as an additional neuroendocrinological marker of depression. However, these studies revealed inconsistent results. In patients suffering from depression, decreased DHEAS plasma levels [26, 27] and DHEA salivary concentrations [28] have been observed. In contrast, other studies reported significant elevations of DHEAS 24-hour urinary levels [29] and diurnal minimal and mean DHEA plasma concentrations [30].

In addition, amelioration of depressive symptomatology has been associated with a decrease in DHEA/DHEAS levels. In patients suffering from depression, elevated DHEAS plasma levels decreased after antidepressant pharmacotherapy [31]. Furthermore, recently, remission of late-life depression has been associated with a decline in DHEA/DHEAS levels, an effect that was not observed in nonremitted patients [28]. In line with these observations, elevated baseline concentrations of DHEAS have been shown to predict nonresponse to electroconvulsive therapy (ECT) in depressed psychotic patients [32].

In line with a GABA-enhancing potential, anxiolytic effects of progesterone, the main precursor molecule for 3α-reduced neuroactive steroids, have been shown in several preclinical trials. It has been suggested that the in vivo conversion of progesterone into 3α-pregnane steroids accounts for its anxiolytic effects and not the direct interaction with intracellular progesterone receptors. Progesterone elicited anxiolytic effects in ovarectomized rats [33] and in mice lacking intracellular progesterone receptors [34]. These anxiolytic effects of progesterone were accompanied by an increase in 3α,5α-THP concentrations [33, 34], suggesting that the anxiolytic properties of progesterone are mediated by its in vivo conversion to the 3α-reduced metabolite [33].

In humans, a pathophysiological role of progesterone has been suggested in anxiety disorders. In women suffering from panic disorder, an increase in progesterone levels has been reported during the midluteal phase of the menstrual cycle [35], where phobic symptomatology improved significantly [35]. Thus, the menstrual cycle-related surge of progesterone and its GABAergic metabolites might contribute to the clinical amelioration of panic disorder [35]. Furthermore, compared with healthy controls, progesterone plasma concentrations have been found to be elevated in drug-free male panic disorder patients and have been suggested to reflect a counterregulatory defense mechanism against the occurrence of panic attacks [36]. In addition, progesterone plasma levels have been shown to correlate significantly with state anxiety scores in healthy males [37] and in men suffering from panic disorder [36]. However, no association has been found in women suffering from panic disorder [35],

thereby suggesting that the anxiety modulatory action of neuroactive steroids might depend on gender [36].

In view of their GABA-enhancing properties, the majority of preclinical studies focused on possible anxiolytic properties of 3α-reduced neuroactive steroids. In different animal models of anxiety-related behavior, a clear anxiolytic profile has been shown for 3α,5α-THP and 3α,5β-THP [38–43]. A similar anxiolytic potential has been demonstrated for the peripheral 3α-pregnane steroid 3α,5α-THDOC [41, 42, 44]. Although first studies investigating 3α-reduced neuroactive steroid levels in anxiety disorders found no differences in 3α,5α-THP levels between patients suffering from mixed anxiety-depressive disorder [22], generalized anxiety disorder [20] or generalized social phobia [45] and healthy controls, first studies of our research group in patients with panic disorder suggested that 3α-reduced neuroactive steroids may play a pivotal role in human anxiety.

Compared with healthy controls, plasma concentrations of 3α-reduced neuroactive steroids were elevated, while the concentrations of 3β,5α-THP, an antagonistic stereoisomer of 3α,5α-THP, were decreased [46]. In line with this finding, in women suffering from panic disorder and agoraphobia, increased plasma concentrations of 3α,5α-THP have been observed during the early follicular and premenstrual phase [35]. The observed elevations of 3α-reduced neuroactive steroids and the concomitant decrease in the functional GABA-antagonistic isomer in panic disorder patients in the absence of panic attacks might be interpreted as endogenous counterregulatory mechanisms against the occurrence of spontaneous panic attacks [47]. This hypothesis was further supported by our studies investigating neuroactive steroid concentrations during experimental panic induction, which is a well-established model for the pathophysiology of panic disorder.

Experimental panic induction was followed by pronounced changes in neuroactive steroid concentrations, which were indeed the opposite to those seen in panic disorder patients in the absence of panic attacks. Challenge with sodium lactate or cholecystokinin-tetrapeptide (CCK-4) was accompanied by a significant decrease in 3α,5α-THP and 3α,5β-THP concentrations and a concomitant increase in 3β,5α-THP levels in patients with panic disorder [48], compatible with a decreased GABAergic tone during panic attacks. In contrast, no such changes in neuroactive steroid compositions following challenge with sodium lactate or CCK-4 could be detected in healthy controls [48], even if subjects exhibited a comparable level of CCK-4-induced panic anxiety [49]. Therefore, the observed alterations in neuroactive steroid levels in patients with panic disorder during experimental panic induction do not merely reflect the level of anxiety but appear to be related to the pathophysiology of panic attacks in panic disorder [48, 49].

However, panic induction with CCK-4, which is known to elicit a marked stimulation of cortisol and ACTH release [50], was accompanied by a significant rise in 3α,5α-THDOC levels in healthy controls [51] (fig. 2). As preclinical data suggested a role for 3α,5α-THDOC in the regulation and termination of the endogenous stress response [52], the observed rise in 3α,5α-THDOC levels might be a consequence of the CCK-4-induced ACTH release and might contribute to the termination of the panic/stress response following challenge with CCK-4 in humans.

In addition to the observed alterations in 3α-reduced neuroactive steroids in panic disorder, increasing evidence comes from preclinical and clinical studies that 3α-reduced neuroactive steroids play an important role as endogenous modulators of major depression. In different animal models of depression-related behavior, a dysregulation of 3α-reduced neuroactive steroids has been observed, which has been suggested to constitute a pathophysiological factor in the development of depression-related behavior. Protracted social isolation in mice is followed by a behavioral adaptation syndrome and a decreased response to GABAergic drugs, which shares some features of depression. In the frontal cortex of such animals, the concentrations of 3α,5α-THP and 5α-DHP were decreased [53, 54] due to a diminished expression of 5α-reductase type I protein and mRNA [53], suggesting that a dysregulated biosynthesis of 3α-reduced neuroactive steroids might contribute to the behavioral and neurochemical alterations found in this mouse model of depression [54, 55].

Olfactory bulbectomy represents a further rodent paradigm for depression. After olfactory bulbectomy, a significant decline in 3α,5α-THP levels has been observed in distinct cerebrocortical areas [56] concurrently with the development of behavioral, neurochemical and neuroendocrine changes, which might contribute to the development of the depression-related bulbectomy syndrome [56]. Thus, the decline in 3α,5α-THP levels might reflect a distinct pathophysiological mechanism underlying the depression-related behavioral alterations in the bulbectomy syndrome [56].

In line with these preclinical investigations, alterations in 3α-pregnane neuroactive steroids have been observed in humans suffering from major depression. In two independent samples of depressive patients, decreased levels of 3α-reduced neuroactive steroids have been found both in

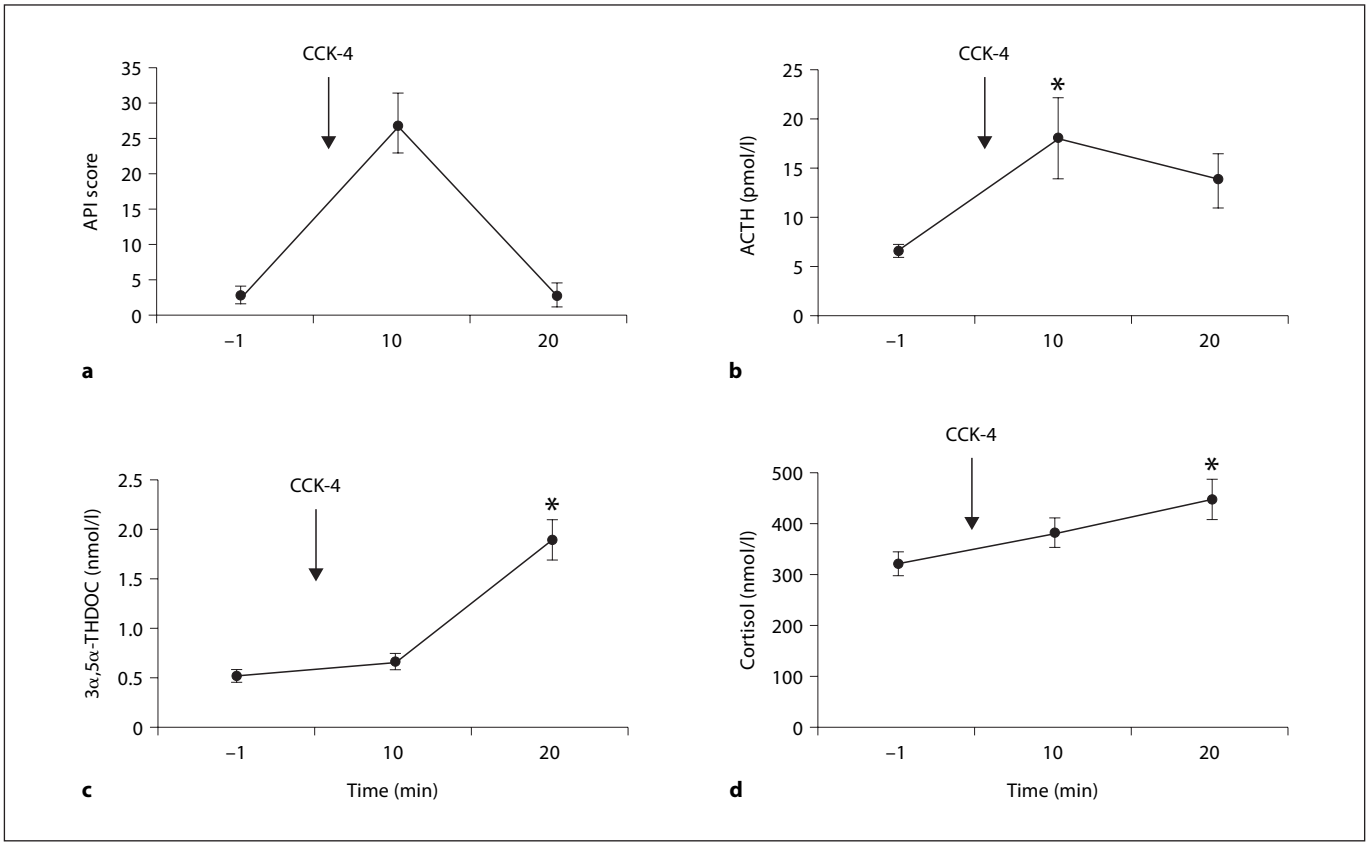

Fig. 2. Panic response (acute panic inventory score; API) (**a**) and plasma concentrations of ACTH (**b**), 3α,5α-THDOC (**c**) and cortisol (**d**) in healthy controls before (–1 min) and after experimental panic induction with 50 μg CCK-4 (10–20 min after challenge). Data are presented as mean ± SEM. * Statistical significance at the $p < 0.05$ level in post hoc tests following MANOVA. Reproduced with permission from Eser et al. [51].

plasma [57] and in cerebrospinal fluid (CSF) [58]. The concentrations of 3α,5α-THP and 3α,5β-THP were reduced in plasma and CSF, while there was an increase in 3β,5α-THP, which may act as a functional antagonist for those GABA-agonistic steroids [57]. Furthermore, 3α,5α-THDOC plasma levels were found to be elevated during depression, probably as a consequence of hypothalamic-pituitary-adrenal axis overdrive [59].

Therapeutic Potential of Neuroactive Steroids in the Treatment of Major Depression and Anxiety Disorders

Therapeutic Properties of Synthetic Derivates of Neuroactive Steroids

Corresponding to preclinical data suggesting antidepressive and anxiolytic effects of exogenously administered pregnenolone and PS, first clinical investigations evaluated the putative therapeutical effects of pregnenolone in humans. Although the first study in healthy volunteers revealed no improvement in mood, memory, self-rated sleep quality or subjective well-being after 4 weeks of treatment with pregnenolone [60], a tendency for pregnenolone to reduce subjective depression ratings was observed [60]. Furthermore, in an additional subgroup analysis, pregnenolone significantly reduced the sedative effects of a single dose of diazepam [60]. In this context, it was hypothesized that pregnenolone, due to its $GABA_A$ receptor antagonistic profile, might antagonize acute benzodiazepine effects, and therefore, might be of putative benefit for the treatment of certain psychiatric conditions [60].

In line with observed alterations in DHEA/DHEAS levels in depressed patients, first studies investigating the therapeutical effects of DHEA revealed promising results in the treatment of major depression. Already the first

open-label study demonstrated a significant improvement in depressive symptoms after 6 months of DHEA therapy [61]. Further double-blind placebo-controlled trials confirmed these results. In midlife-onset dysthymia, 60% of the patients responded to treatment with DHEA after 6 weeks [62]. Furthermore, administration of DHEA either as a monotherapy or as an augmentation to stable antidepressant regimens significantly decreased depressive symptoms in unipolar and bipolar depression [63]. Recently, it has been demonstrated that even monotherapy with DHEA significantly improved symptoms of minor and major midlife-onset depression [64].

So far, putative therapeutic properties of DHEAS have not been investigated in anxiety disorders. However, in schizophrenic patients additionally treated with DHEA, anxiety symptoms improved [65], thereby suggesting that this neurosteroid may also possess beneficial effects in the treatment of anxiety-related symptoms.

Clinical studies concerning putative therapeutical effects of progesterone in major depression or anxiety disorders are lacking so far. Nevertheless, administration of progesterone might constitute a supplementary treatment strategy for several clinical symptoms found in depression, as progesterone exerts pronounced GABAergic effects on sleep [66]. In addition, several studies focused on the putative beneficial effects of progesterone administration in patients suffering from PMS, which in part overlaps with depressive symptomatology. While some investigations reported an improvement in mood [67–69] in women suffering from PMS, others found no superiority to placebo treatment [70–72]. Furthermore, the previously recommended prophylactic postpartum use of progesterone in women who had experienced postpartum depression in the past [73] was challenged by an observed enhanced risk of postpartum depression after progesterone therapy [74]. Thus, no definite conclusion can be drawn at the moment as to whether or not synthetic progestins might constitute a useful strategy for the treatment of anxiety or depression [75].

Modulation of Endogenous Neuroactive Steroid Levels as a Putative Pharmacological Mechanism of Antidepressant Drugs

Preclinical studies suggested that neuroactive steroids may not only directly modulate anxiety and depression-related behavior but that neuroactive steroids may also be involved in the therapeutical effects of antidepressant drugs. Most evidence for this suggestion came from studies investigating the impact of antidepressant treatment on endogenous 3α-reduced neuroactive steroid levels.

In the depression-related olfactory bulbectomy model, chronic treatment with three different classes of antidepressants reversed the decline in 3α,5α-THP levels in rats after 3 weeks [76]. This time interval is typically necessary to counteract the depression-related behavioral deficits of the bulbectomy syndrome by pharmacological treatment [76]. Therefore, it has been suggested that normalization of 3α,5α-THP levels might contribute to the therapeutic effects of various antidepressants in this animal model of depression [76]. However, the molecular mechanisms underlying the effects of antidepressant drugs on neuroactive steroid concentrations are still under investigation.

Acute administration of the selective serotonin reuptake inhibitor (SSRI) fluoxetine in rats was followed by a significant increase in 3α,5α-THP in different brain regions [77, 78] and a concomitant decrease in the precursor molecule 5α-DHP [77]. In contrast, the tricyclic antidepressant imipramine had no effect on neuroactive steroid concentrations [77], suggesting a specific action of fluoxetine on 3α-hydroxysteroid dehydrogenase (3α-HSD), the enzyme that catalyses the conversion of 5α-DHP to 3α,5α-THP [77]. This hypothesis was supported by the finding that SSRIs but not tricyclic antidepressants shift the activity of the 3α-HSD towards the reductive direction [79], thereby enhancing the efficiency of the conversion of 5α-DHP to 3α,5α-THP [79], although these findings were not confirmed in another study [80]. Furthermore, preclinical studies investigating the effects of mirtazapine on neuroactive steroid composition revealed conflicting results. Mirtazapine is an antidepressant which acts as an antagonist of α_2,5-HT_2,5-HT_3 and histamine H_1 receptors, a mechanism different from SSRIs and tricyclic antidepressants. Single injections of mirtazapine increased 3α,5α-THP brain and plasma levels, while mirtazapine long-term administration did not affect neuroactive steroid levels [81]. However, recently, we were able to demonstrate a dose-dependent inhibitory effect of mirtazapine on the activity of a microsomal 3α-HSD [82]. Although 3α-HSD can act bidirectionally in vitro, in the living brain, due to the intracellular availability of respective cofactors, cytosolic 3α-HSD is expected to almost exclusively catalyze the conversion of 5α-DHP into 3α,5α-THP (reductive pathway), whereas microsomal 3α-HSD is expected to catalyze the conversion of 3α,5α-THP into 5α-DHP (oxidative pathway) [82]. Mirtazapine did not affect the reductive direction but inhibited a microsomal isoform of 3α-HSD, thereby

inhibiting the oxidation of 3α,5α-THP into 3α-DHP (fig. 3). This effect is compatible with an enhanced formation of 3α-reduced neuroactive steroids similar to the effect of SSRIs [82].

In depressed patients, a variety of studies suggested that antidepressant drugs might correct the observed disequilibrium in 3α-reduced neuroactive steroid composition and that this correction might contribute to the therapeutical effects of antidepressant drugs. Administration of fluoxetine has been shown to increase 3α,5α-THP and 3α,5β-THP plasma [57] and CSF levels [58] and to concomitantly decrease 3β,5α-THP concentrations in patients suffering from depression [57]. However, in contrast to preclinical data, treatment with tricyclic antidepressants influenced 3α,5α-THP, 3α,5β-THP and 3β,5α-THP levels in a similar way to SSRIs [57].

To answer the question whether changes in neuroactive steroid concentrations contribute to the clinical effects of antidepressant treatment or whether they are related to specific pharmacological properties of antidepressant drugs, our group investigated the impact of different nonpharmacological treatment strategies on neuroactive steroid concentrations in major depression.

Partial sleep deprivation (PSD), which is known to rapidly but only transiently ameliorate depressive symptoms, was applied in depressed inpatients as a monotherapy. Neuroactive steroid levels were determined the day before and after PSD and after one night of recovery sleep [83]. PSD ameliorated depressive symptoms in the majority of patients, although this therapeutical effect was only transient and followed by a relapse of symptoms the day after recovery sleep. Nonresponders compared with responders showed significantly higher plasma concentrations of 3α,5α-THP and 3α,5β-THP before and after PSD; however, no alterations in neuroactive steroid levels could be detected after PSD in either group [83].

In addition, we investigated the impact of repetitive transcranial magnetic stimulation (rTMS) as a medium-term nonpharmacological treatment strategy [84]. However, even though about half of the patients significantly improved after 2 weeks of rTMS monotherapy, no alterations in 3α,5α-THP, 3α,5β-THP and 3β,5α-THP levels could be found either in responders or nonresponders [84], suggesting that the antidepressive effects of this medium-term biological treatment strategy are not linked to alterations in 3α-reduced neuroactive steroid levels. Finally, to rule out the possibility that the antidepressive effects of PSD or rTMS may have been too weak to interfere with neuroactive steroid concentrations, the impact of ECT was studied on neuroactive steroids. ECT is still considered as the most effective biological treatment strategy in severe treatment-resistant major depression. Neuroactive steroids were quantified in 31 pharmacotherapy-resistant depressed patients before and after 4 weeks of ECT [85]. Sixteen out of 31 patients responded to ECT and about half of those patients achieved a full remission from major depression. However, remitters, responders and nonresponders did not differ in neuroactive steroid levels nor did ECT influence 3α,5α-THP, 3α,5β-THP and 3β,5α-THP concentrations [85].

Therefore, in contrast to the previously reported changes in 3α-reduced neuroactive steroid concentrations following antidepressant pharmacotherapy, none of the investigated nonpharmacological treatment strategies had any impact on neuroactive steroid levels despite

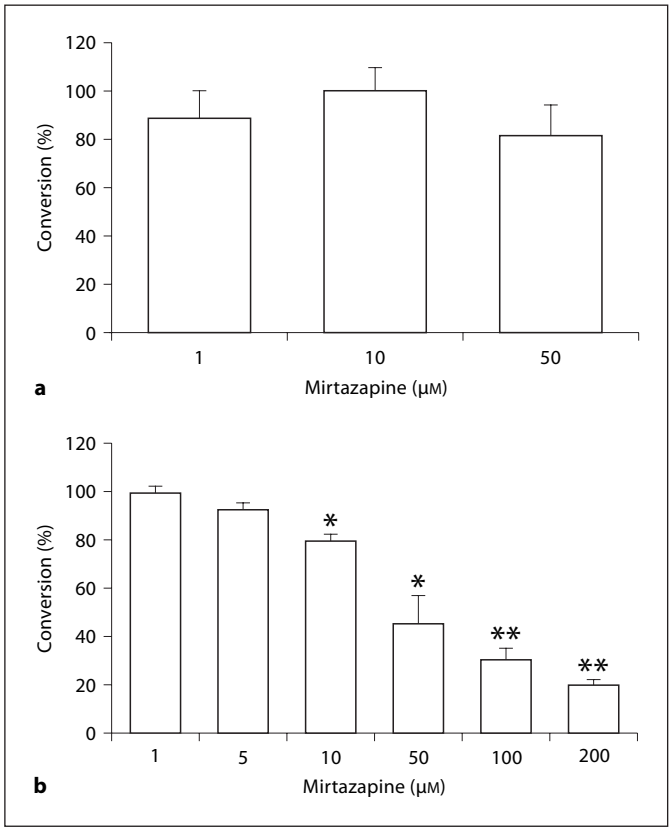

Fig. 3. Impact of mirtazapine at different concentrations on the activities of both human cytosolic 3α-HSD type 3 (reductive pathway) (**a**) and human microsomal 3α-HSD (oxidative pathway) (**b**). Data are presented as means ± SEM of at least 3 independent experiments and are indicated as percentage of vehicle (conversion rates obtained in the vehicle are set at 100%). * Statistical significance at $p < 0.05$; ** statistical significance at $p < 0.001$. Reproduced with permission from Schule et al. [82].

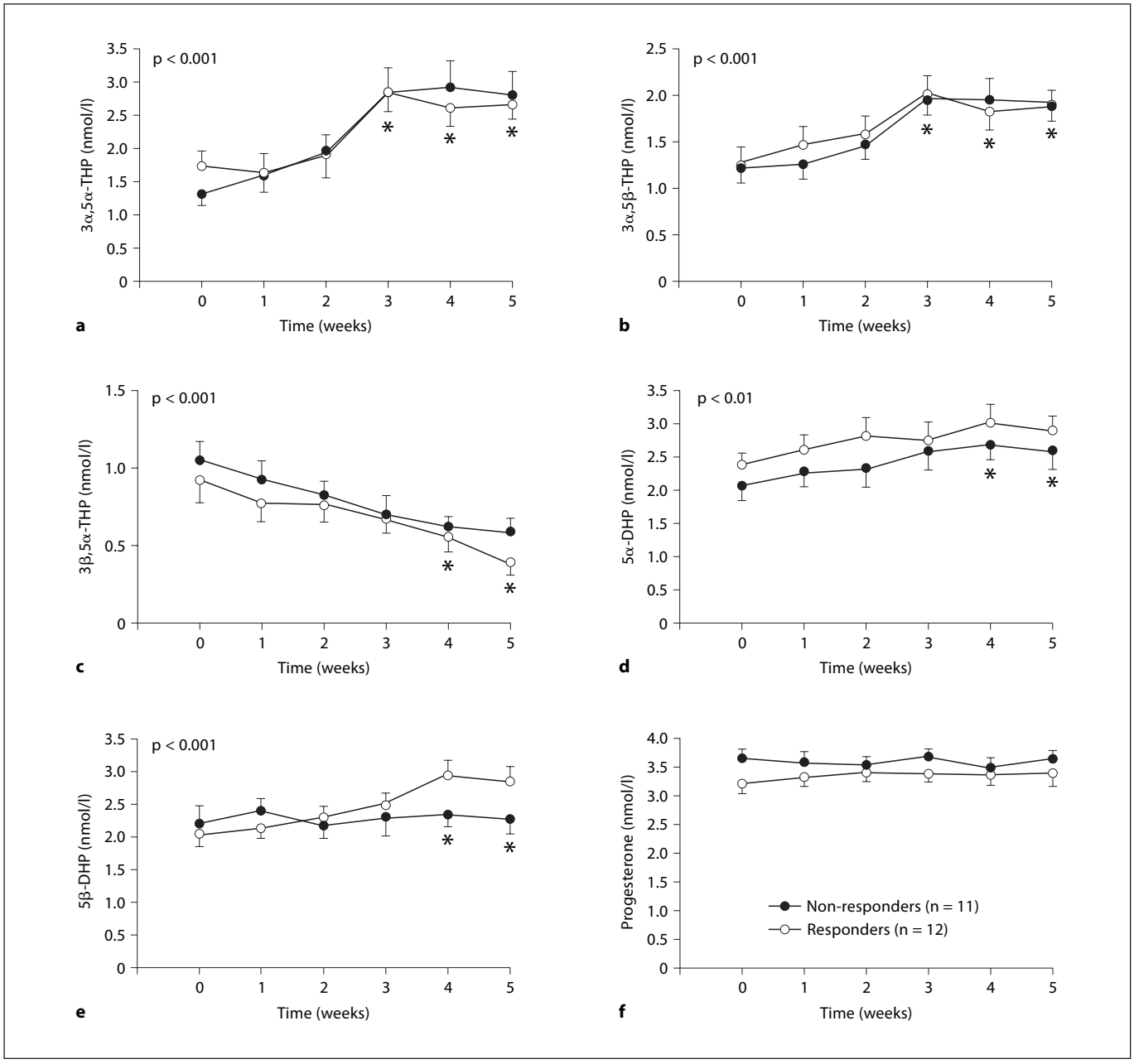

Fig. 4. Plasma concentrations of 3α,5α-THP (**a**), 3α,5β-THP (**b**), 3β,5α-THP (**c**), 3α-DHP (**d**), 5β-DHP (**e**) and progesterone (**f**) in nonresponders and responders to mirtazapine treatment on week 0 up to week 5. Data represent means ± SEM. * Significant difference compared with week 0 in test with contrasts. Reproduced with permission from Schule et al. [82].

a pronounced antidepressive effect. These findings confirmed the hypothesis that the observed alterations in neuroactive steroid concentrations following antidepressant pharmacotherapy are indeed related to specific pharmacological properties of antidepressant drugs.

Furthermore, our research group recently investigated the impact of mirtazapine monotherapy on neuroactive steroid composition in patients suffering from major depression. We found increased 3α,5α-THP, 3α,5β-THP, 5α-DHP and 5β-DHP concentrations, whereas 3β,5α-

THP levels decreased after 5 weeks of mirtazapine monotherapy [82]. However, these changes in neuroactive steroid concentrations were comparable in responders and nonresponders and were not correlated to the clinical response (fig. 4). Therefore, so far, our data do not support the hypothesis that the normalization of endogenous neuroactive steroid levels is essential for the clinical response in the treatment of depression, and a lack of effect on neuroactive steroid concentrations, as noted after nonpharmacological treatment, does not preclude antidepressive efficacy.

Nevertheless, the interference with neuroactive steroid composition still constitutes a promising new pharmacological treatment strategy in depression and anxiety disorders as preclinical data suggested beneficial effects of new mitochondrial benzodiazepine receptor (MBR) ligands. The biosynthesis of GABAergic neuroactive steroids, which is under the control of the MBR [86], might be enhanced throughout treatment with specific MBR agonists [86], and these MBR agonists have been shown to exert pronounced anxiolytic effects in animal models without sedation and abuse liability [86, 87].

Conclusion

There is considerable preclinical and clinical evidence that neuroactive steroids are important endogenous modulators of depression and anxiety-related behavior and might have therapeutic potential for the treatment of depression and anxiety disorders. A definitive proof whether neuroactive steroids have indeed a therapeutical potential for the treatment of affective disorders and are superior to already existing psychopharmacological drugs will come from systematic clinical studies in this new area of research. Such novel therapeutic strategies might either be based on synthetic derivates of endogenous neuroactive steroids or on the modulation of neurosteroid synthesis either by classical antidepressants or other compounds interfering with neurosteroidogenic enzymes. Additionally, the peripheral benzodiazepine receptor may constitute a further target to influence the equilibrium of endogenous neuroactive steroids.

Furthermore, it remains to be elucidated whether neuroactive steroids may serve as biomarkers in the differential diagnosis of affective disorders. However, in this context, it has to be determined to what extent neuroactive steroid plasma levels essentially reflect brain concentrations. Although it has been suggested that plasma levels are likely to reflect brain levels, because neuroactive steroids can easily cross the blood brain barrier, this does not exclude the possibility of local alterations in brain concentrations of neuroactive steroids that are not detected by plasma or CSF measurements. Therefore, further research is needed to develop highly sensitive and specific technologies of neurosteroid determination, which are both economical and of reasonable labor intensity.

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