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The role of neurosteroids in the anxiolytic, antidepressive- and anticonvulsive effects of selective serotonin reuptake inhibitors

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Summary

The introduction of SSRIs to the clinic was a turning point in the treatment of depression and related mental disorders. Nowadays, it is becoming more and more evident that SSRIs are equally effective in anxiety states and some types of epilepsy. However, the mechanism of their central action is not fully understood. They not only block the serotonin transporter, but also bind to different types of monoaminergic receptors (serotonergic, dopaminergic) and interact with the synthesis of neurosteroids, in this way modifying the excitability of the central nervous system. The aim of this review is to update information on the preclinical and clinical effects of SSRI, with special emphasis put on the probable role of neurosteroids and the GABAA receptor complex in the mechanism of their action.

key words: **SSRI • neurosteroids • antidepressants • antileptic**

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BACKGROUND

In the late 1980s, the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, was introduced to clinical use. This marked a turning point in the pharmacotherapy of depression, since SSRIs proved to be as efficacious as TADs (tricyclic antidepressants), and much safer in use. They are not toxic in overdose and cause many fewer undesirable side effects [1,2]. Over the last 10 years the spectrum of clinical applications of SSRIs has increased considerably. Clinical observations confirmed the efficacy of SSRI in the treatment of panic disorder, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder (PTSD), generalized anxiety disorder, pre-menstrual syndrome (PMS), and epilepsy. These findings suggest the importance of the serotonergic system in the etiology of the aforementioned neurological and psychiatric disorders [3–11].

Neurosteroids, powerful modulators of the $GABA_A$ receptor system, take part in maintaining the proper brain activation level, learning and memory processes, and in modulating aggressive behavior [12–15]. They are important for the regulation of many central nervous system processes related to stress and fear reactions [16], and also influence the convulsion threshold [17]. Mood changes in menstrual cycle, post-partum depression, endogenous depression, and epilepsy are also associated with neurosteroids [18–21]. Moreover, research on neurosteroids is opening up prospects for the development of new pharmacological agents (e.g. ganaxolone, a new antiepileptic agent) [22].

Considering the fact that SSRIs have been used in the clinic already for years, it seems surprising that their action in the central nervous system (CNS) is not well understood. The observation that fluoxetine and some other SSRIs may increase the concentration of neurosteroids in the CNS is a relatively recent finding [23,24]. Accordingly, the initially lowered CSF levels of allopregnanolone in patients with unipolar depression are normalized by fluoxetine and fluvoxamine treatment [25]. Taking into consideration the influence of SSRIs on the serotonergic (5-HT) [10] and GABAergic systems [26], as well as the neurosteroid level in the CNS [23,27], it can be hypothesized that they may be useful in the treatment of epilepsy, especially in cases of epilepsy with co-morbid depression. Epilepsy is a chronic disease with spontaneous and repeated myoclonic, tonic or clonic seizures [28]. It affects different aspects of life, especially mood, with gradually evolving depression [29]. There are many different types of epilepsy, some of which are treatment-resistant [30,31], resulting in poor social functioning of the patients. Moreover, anti-epileptic therapy may cause many undesirable side effects, such as emotional and behavioral disturbances [28,32].

The aim of the present paper is to review currently available information on the probable role of neurosteroids and the $GABA_A$ receptor complex in the mechanisms of action of SSRIs.

SSRI MECHANISMS AND ACTION PROFILE

Serotonergic neurons are localized in the raphe nuclei in mesencephalon and medulla oblongata. The 5-HT axons form two main serotonergic pathways: ascending (from medial and dorsal nuclei to frontal cortex, striatum, thalamus, amygdala, hypothalamus and hippocampus), and descending (from caudal raphe nuclei to the spinal cord). Abnormal serotonergic neurotransmission in various brain areas is thought to be a factor in several distinct psychiatric disorders, including depression and anxiety [10]. It has been hypothesized that serotonergic pathways, both excitatory (from raphe nuclei to amygdala) and inhibitory (to periaqueductal gray matter, PAG, and locus coeruleus), are possible targets for the action of SSRIs [5]. Serotonergic input also modulates glutamatergic pathways from prefrontal cortex to thalamus and amygdala, as well as the projections from amygdala to PAG, hypothalamus and brain stem. Accordingly, it has been found that a spontaneous discharge of PAG neurons may result in panic attacks, which can be attenuated by SSRIs [5,33]. Therefore, SSRIs may affect emotional processes by influencing projections from cortex and thalamus to amygdala, and downstream to mesencephalon and brain stem [6].

Selective serotonin reuptake inhibitors (SSRI) are commonly used for the treatment of depression. During the last decade the number of therapeutic indications for these drugs have increased considerably, including obsessive-compulsive disorder, panic attacks, premenstrual dysphoria and other psychiatric diseases. SSRIs inhibit the reuptake of serotonin (5-HT) into the presynaptic nerve terminal, thus increasing the serotonin concentration in the synaptic cleft. After about three weeks of repeated SSRI administration, desensitization of $5HT_{1A}$ autoreceptors occurs, resulting in an enhancement of serotonin neurotransmission, with the synaptic concentration of serotonin reaching therapeutic levels, especially in limbic structures and brain cortex [34,35]. Some studies indicate that prolonged treatment with SSRIs increases the inhibitory processes in brain limbic structures involved in the regulation of emotional processes due to hyperpolarization of neuronal membranes [36]. It is suggested that the psychotropic effects of SSRIs are also associated with other mechanisms, not directly related to their inhibitory influence on serotonin transportation [10]. For example, the efficacy of SSRIs in the treatment of depressive and obsessive-compulsive disorders may depend on their direct interactions with postsynaptic $5HT_{1A}$ and $5HT_{2C}$ receptors [1,37]. Some data suggest that SSRIs may modulate the activity of the monoaminergic and cholinergic systems, eg. sertraline is known to bind to dopaminergic receptors, and paroxetine to muscarinic [38,39]. Moreover, Shores et al. found that short-term sertraline treatment attenuates the activity of the sympathetic nervous system in healthy subjects, as indicated by decreased noradrenaline turnover [40].

It is common knowledge that a certain number of anxiolytic agents show an anticonvulsant action as well (e.g. benzodiazepines and barbiturates), and this fact indi-

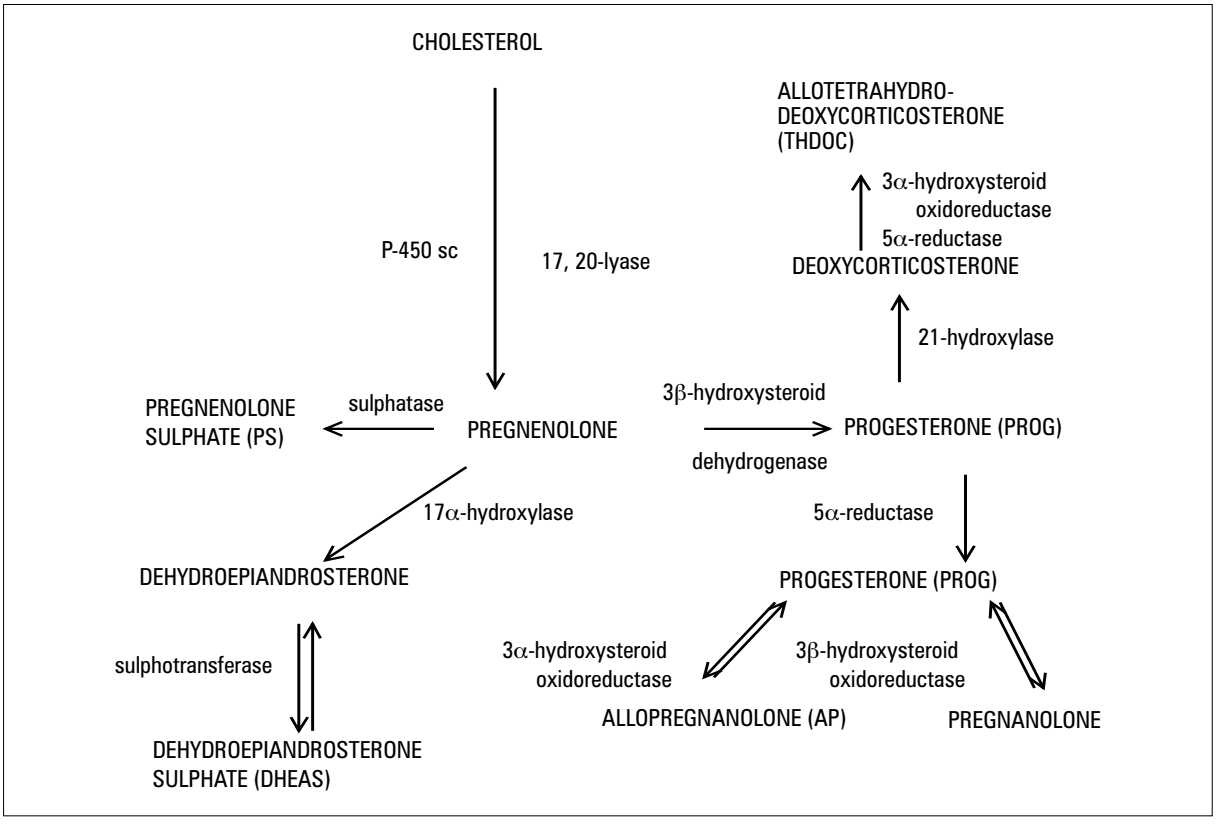

Figure 1. Biosynthesis and metabolism of some neurosteroids in the CNS.

Table 1. Putative pharmacological profile of selected neurosteroids most intensively studied in preclinical and clinical experiments.

Neurosteroids	Putative pharmacological profile
Progesterone	Positive $GABA_A$ receptor modulator
	Negative glycine receptor modulator
	Negative nicotine receptor modulator
Allopregnalone	Positive $GABA_A$ receptor modulator
Allotetrahydrodeoxycorticosterone	Positive $GABA_A$ receptor modulator
Pregnenolone sulfate	Negative $GABA_A$ receptor modulator
	Positive NMDA receptor modulator
	Negative glycine receptor modulator
Dehydroepiandrosterone sulfate/	Negative $GABA_A$ receptor modulator
Dehydroepiandrosterone	Positive NMDA receptor modulator

rectly indicates similar localization of anxiety and seizure-related processes [41]. It is likely that the inhibition of limbic structures in the temporal lobe may be responsible for the anticonvulsant effects of SSRIs [42]. Moreover, direct modulation of $GABA_A$ receptors through a novel modulatory site has recently been found for fluoxetine [43]. In animal studies, fluoxetine enhances the effects of several antiepileptics, and has been shown to suppress seizure activity in both normal and epilepsy-prone rats [43]. The mechanism underlying this anticonvulsant activity may involve changes in endogenous neurosteroids, or an action through a modulatory site on the $GABA_A$ receptor [43].

NEUROSTEROIDS: BIOSYNTHESIS, FUNCTION AND POTENTIAL THERAPEUTIC USES

Studies performed in the last few years have clearly indicated that neurosteroids may modulate numerous brain functions. They are already pharmacologically active in nanomolar concentrations [44]. The effects of steroids on CNS neurotransmitter functions are complex and involve also non-genomic action. Considerable data have been accumulated demonstrating that neurosteroids rapidly alter the excitability of neurons by binding to membrane-bound receptors for inhibitory and/or excitatory neurotransmitters [45]. Neurosteroids have been found to exert clear pharmacological effects on the $GABA_A$ receptors, glycine receptors, ionotropic glutamate receptors, voltage-activated calcium channels, and (in higher concentrations) cholinergic receptors (Table 1) [45,46]. Neurosteroids directly regulate the activity of the $GABA_A$ receptor/chloride ionophore complex via the allosteric binding site. For example, pregnane derivatives (Figure 1) have been found to enhance [^{3}H]-muscimol binding to $GABA_A$ receptors [12]. Moreover, some data have demonstrated that neurosteroids have a pharmacological profile very similar to that of benzodiazepine derivatives. The neurosteroids produce anxiolytic, anticonvulsant and anesthetic effects similar to those of diazepam and midazolam [12–14]. Clinical studies have demonstrated that progesteron administered to women with menopause potentiates the hypnotic effect of triazolam, a $GABA_A$-benzodiazepin receptor agonist [47].

Preclinical evaluation has predicted the efficacy of neuroactive steroids in the treatment of several central pathological states, such as anxiety, depression, seizure disorders, pre-menstrual syndrome (PMS), post-partum depression, mood disorder in pregnancy, catamenial epilepsy, and Alzheimer's disease [24,45,48].

In the literature there are many well-documented reports on the effects of dehydroepiandrosterone (DHEA) on CNS functions [44]. DHEA belongs to drugs noncompetitively decreasing $GABA_A$ and enhancing NMDA-induced currents in neuronal membranes, thus it moderately stimulates the excitatory central processes, including learning and memory [49]. DHEA concentration decreases with age, in serious illnesses and in a stressful situation [49]. Some studies have reported preliminary evidence for beneficial DHEA effects in the treatment of different CNS pathologies, including multiple sclerosis and traumatic brain injury [50,51]. Moreover, DHEA replacement in healthy volunteers in age-advanced subjects increases their feeling of well-being [52]. Experimental data also support the notion that the excitatory neurosteroids pregnenolone sulfate (PS) and DHEAS improve memory in aging mice and prevent pharmacologically induced amnesia [53].

Another set of data strongly indicates that neuroactive steroids may play a direct role in the pathophysiology of depression and anxiety disorders. The brain concentration of the $GABA_A$-receptor agonistic neurosteroids has been reported to decrease [25], and $GABA_A$-receptor antagonistic neurosteroids to increase during stress [54]. Accordingly, the concentration of allopregnanolone in cerebrospinal fluid (CSF) has been found to be reduced during clinically diagnosed depression [25]. Given the psychopharmacological profile of neurosteroids, the lowered CSF allopregnanolone concentration could account for some of the sleep and cognitive disturbances accompanying depression [49].

Clinical results show that women with PMS have lower concentrations of allopregnanolone in blood plasma, and high levels of allopregnanolone correlate with a feeling of well-being in women with PMS [18,55]. It is becoming more and more clear that physiologically decreased concentration of allopregnanolone may be responsible for some behavioral symptoms in PMS, such as anxiety, mood and sleep disorders, and impaired attention [55]. It is important to stress that lower sensitivity to psychotropic drugs (benzodiazepine derivatives) has been found in patients with PMS, in comparison to controls [56]. There have been a large number of studies performed showing SSRI superiority over non-serotonergic antidepressants in the treatment of PMS [57]. SSRIs improve premenstrual irritability and dysphoria, with rapid onset of action, suggesting a different mechanism of action than in the treatment of depression. It is generally acknowledged that neurosteroids, such as progesterone metabolites, are involved in the rapid action of SSRIs in PMS [57].

Anxiety and depression in the post-partum period are also associated with a drastic decrease in serum levels of the GABA-agonistic neurosteroids [19,58]. In these patients, DHEA treatment reduces some depressive symptoms, and improves memory and the feeling of well-being; these effects were associated with a rise in blood concentration of neurosteroids and cortisol [59]. In a preclinical model of depression using olfactory bulbectomized rat (OB), allopregnanolone levels were significantly decreased following olfactory bulb removal in the amygdala and frontal cortex [48], indicating a strong region-specific dysregulation of allopregnanolone homeostasis in the brains of OB rats. Interestingly, Uzunova [25] showed that fluoxetine and paroxetine given at equimolar doses, which attenuated the pathological symptoms in the rats, produced an almost complete inhibition of serotonin uptake, and a two- and fourfold increase in brain allopregnanolone concentration. This finding shows a close correlation between SSRI action and neurosteroid activity in the brain [23,25].

SSRIs AND NEUROSTEROIDS

In the last decade, firm evidence has emerged from preclinical and clinical research indicating that some psychotropic drugs may alter the levels of neurosteroids in the brain [23]. For example, clozapine and olanzapine were found to increase the brain concentration of allopregnanolone and allotetrahydrodeoxycorticosterone (THDOC) in rats [60–62]. Moreover, some atypical antipsychotic drugs, unlike haloperidol (a typical antipsychotic drug), have demonstrated an anxiolytic effect in animal models of anxiety [23]. It has been concluded that their anxiolytic action is not due to $GABA_A$ receptor agonism directly, but depends on stimulation of the activity of 3α-hydroxysteroid dehydrogenase, the enzyme converting dihydroprogesterone to allopregnanolone [63].

SSRIs can also potently affect neurosteroid-$GABA_A$ receptor-related central functions, as well as brain levels of allopregnanolone. Preclinical reports indicate an increase in allopregnanolone concentration in different brain regions, such as the olfactory bulb, striatum, hippocampus and prefrontal cortex, after acute and chronic SSRI treatment [27]. However, the enhancement of neurosteroid concentration after fluoxetine and paroxetine is not in equal proportion to the potency of serotonin reuptake blockade [27]. Similarly, Khisti and Chopde demonstrated increased levels of allopregnanolone after fluoxetine administration in the modified Porsolt's test (a preclinical model of depression) [24].

As mentioned above, fluoxetine treatment improves the most common physical, emotional and mental symptoms associated with pre-menstrual dysphoric disorder [57]. Moreover, a lower frequency of seizure was observed in epileptic patients after adjunctive SSRI medication [11]. Used clinically, this drug enhanced seizure control caused by the traditional anticonvulsants phenytoine and carbamazepine [64]. Fluoxetine has been preliminary reported to exert a protective action against seizures in many animal models of epilepsy, and $GABA_A$ receptor antagonists have been found to reverse its anticonvulsant action (e.g. bicuculline) [42]. This antidepressive drug has revealed anticonvulsant potential in such models as maximal electroshock (MES) and audiogenic seizures [42].

Many lines of evidence indicate that the mechanism of anticonvulsant action of SSRIs may depend on the modulation of 5-HT transmission, indirectly affecting neurosteroid metabolism. In animal models of epilepsy, the serotonin precursor, 5-hydroxytryptophan (5-HTP), inhibited the frequency of seizures [65,66]. On the other hand the depletion of endogenous 5-HT by pretreatment with parachlorophenylalanine (PCPA, a serotonin synthesis blocker) has been reported to lower the seizure threshold [67]. Moreover, activation of 5-HT_1 and 5-HT_2 receptor has been found to modify seizure activity [67]. Some authors suggest that 5-HT_{2C} receptors play a particular role in this respect [68].

It is very likely that the effects of SSRIs not only depend on modulating the function of neurotransmitter systems, but are also related to changes in the activity of the enzymes engaged in allopregnanolone synthesis and metabolism [69]. The mechanism by which SSRIs enhance CSF allopregnanolone levels is thought to involve direct stimulation of 3α-hydroxysteroid oxydoreductase, an enzyme that catalyses the reduction of 5α-dihydroxyprogesterone into allopregnanolone [70]. The administration of indometacin, a selective non-competitive 3α-hydroxysteroid oxydoreductase enzyme inhibitor, significantly blocks the antidepressant-like effects of neurosteroids (such as allopregnanolone), and modifies the antidepressant effects of SSRIs (such as fluoxetine) [24]. Indometacin *per se* inhibits the oxydation of allopregnanolone, and increases its concentration in the brain [71]. However, in one study indometacin given with progesterone reduced the level of allopregnanolone in the CNS, without altering the concentrations of progesterone and pregnanedione [71]. Moreover, it has recently been shown that, at a concentration up to 50 μM, 3α-hydroxysteroid oxydoreductase is not activated by fluoxetine, paroxetine, sertraline, carbamazepine, or clozapine [72]. Thus the mechanism by which SSRIs induce an increase in CSF allopregnanolone levels remains to be elucidated.

Two points deserve special attention when discussing the data pertaining to the effects of SSRIs on allopregnanolone concentration. The results obtained with indomethacin may be misleading, since this drug is also a very potent inhibitor of cyclooxygenase, an enzyme also found in the brain and reported to modulate brain functions [73]. Furthermore, Robinson [43] has recently shown, using electrophysiological methods, that fluoxetine may directly increase $GABA_A$ receptor activity through a novel modulatory site at the receptor complex. These data could explain the direct anti-seizure and benzodiazepine-like properties of fluoxetine, without referring to its interaction with neurosteroid metabolism.

CONCLUSIONS

In conclusion, there is growing evidence that SSRIs may play a role in the regulation of CNS excitability and mood-related processes. They have already been found to be effective in the treatment of several mental and emotional disorders, and some preclinical studies have demonstrated their potential usefulness for the treatment of epilepsy. Given, however, the equivocal results of experimental and clinical data, further studies are needed to establish the mechanism underlying their multidimensional action in the CNS.

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