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The role of allopregnanolone in depression and anxiety

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ABSTRACT

Neuroactive steroids such as allopregnanolone do not only act as transcriptional factors in the regulation of gene expression after intracellular back-oxidation into the 5-α pregnane steroids but may also alter neuronal excitability through interactions with specific neurotransmitter receptors. In particular, certain 3α-reduced metabolites of progesterone such as 3α,5α-tetrahydroprogesterone (allopregnanolone) and 3α,5β-tetrahydroprogesterone (pregnanolone) are potent positive allosteric modulators of the $GABA_A$ receptor complex. During the last years, the downregulation of neurosteroid biosynthesis has been intensively discussed to be a possible contributor to the development of anxiety and depressive disorder. Reduced levels of allopregnanolone in the peripheral blood or cerebrospinal fluid were found to be associated with major depression, anxiety disorders, premenstrual dysphoric disorder, negative symptoms in schizophrenia, or impulsive aggression. The importance of allopregnanolone for the regulation of emotion and its therapeutical use in depression and anxiety may not only involve GABAergic mechanisms, but probably also includes enhancement of neurogenesis, myelination, neuroprotection, and regulatory effects on HPA axis function. Certain pharmacokinetic obstacles limit the therapeutic use of natural neurosteroids (low bioavailability, oxidation to the ketone). Until now synthetic neuroactive steroids could not be established in the treatment of anxiety disorders or depression. However, the translocator protein (18 kDa) (TSPO) which is important for neurosteroidogenesis has been identified as a potential novel target. TSPO ligands such as XBD 173 increase neurosteroidogenesis and have anxiolytic effects with a favorable side effect profile.

Contents

1. Background

Neuroactive steroids act as transcriptional factors in the regulation of gene expression. The induction of DNA binding and transcriptional activation of the progesterone receptor requires intracellular oxidation of the neuroactive steroids into progesterone receptor active 5 alpha-pregnane steroids (Rupprecht et al., 1993). However, neuroactive steroids may also alter neuronal excitability through interactions with specific neurotransmitter receptors (Rupprecht and Holsboer, 1999; Rupprecht, 2003). These steroids are synthesized from cholesterol or steroidal precursors (Fig. 1). The formation of pregnenolone from cholesterol is regulated by the translocator protein TSPO (18 kD), formerly called peripheral or mitochondrial benzodiazepine receptor, which is mainly located in the outer mitochondrial membrane and favors the transport of cholesterol to the inner

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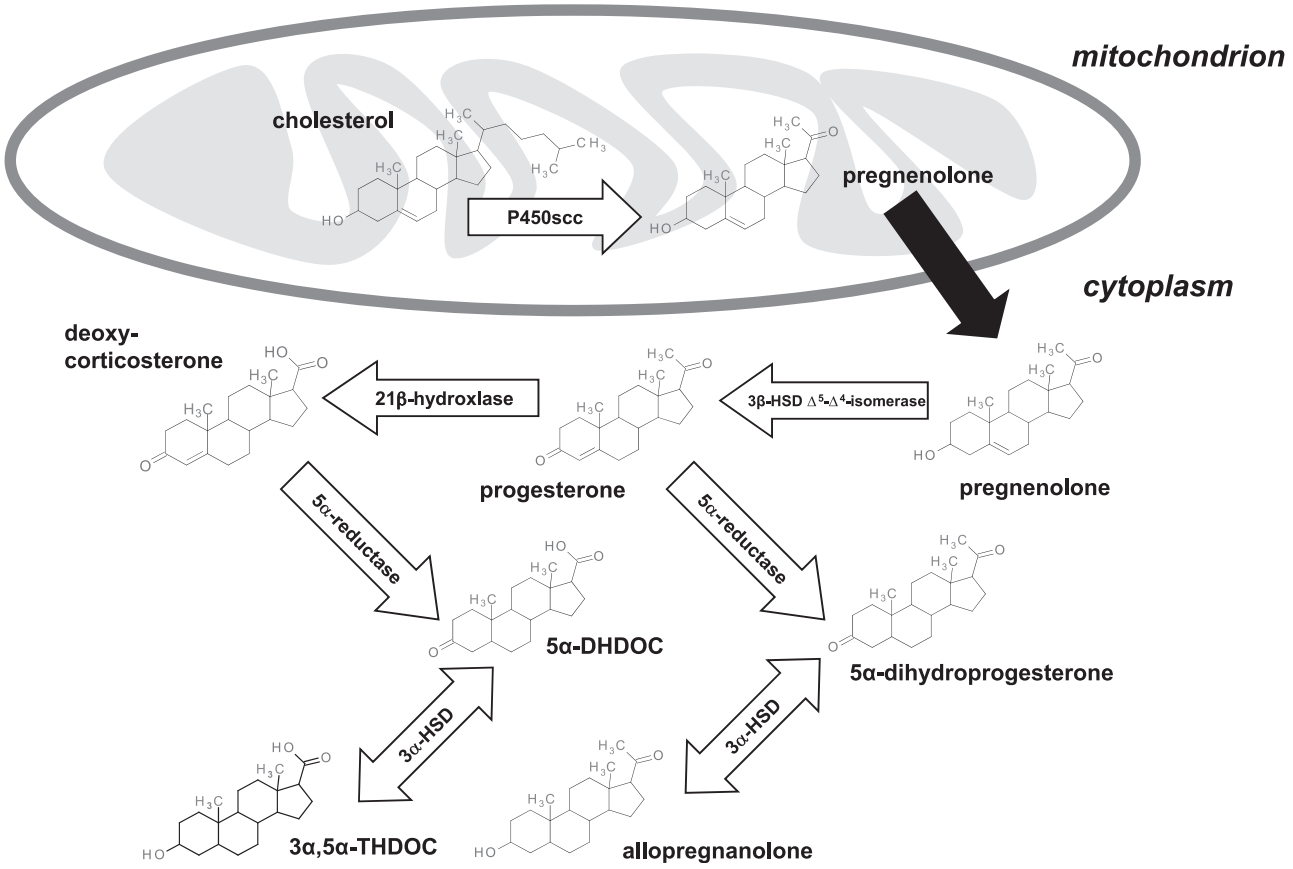

Fig. 1. Synthesis of neurosteroids (Nothdurfter et al., 2012a). The cholesterol side-chain-cleaving cytochrome-P-450 enzyme (P-450scc, CYP11A1) is located at the inner mitochondrial membrane and converts cholesterol to pregnenolone. In the cytoplasm (diffusion marked by black arrow), pregnenolone is metabolized to progesterone by the microsomal 3β-dehydrogenase/Δ^5–Δ^4 isomerase. Progesterone is further converted to deoxycorticosterone by the 21-hydroxylase (CYP21B). The reduction of progesterone and deoxycorticosterone by the 5α-reductase leads to 5α-dihydroprogesterone and 5α-dihydrocorticosterone (5α-DHDOC). The neurosteroids allopregnanolone and allotetrahydrodeoxycorticosterone (3α, 5α-tetrahydrodeoxycorticosterone, 3α, 5α-THDOC) are formed by further reduction through 3α-hydroxysteroid dehydrogenase (3α-HSD).

mitochondrial membrane, thereby promoting neurosteroidogenesis (Papadopoulos et al., 2006; Rupprecht et al., 2010). Pregnenolone is further converted into an array of different steroids (Fig. 1). Progesterone may be formed by the 3β-hydroxysteroid dehydrogenase and serves as the main precursor molecule for 3α-reduced neuroactive steroids. Progesterone and deoxycorticosterone (DOC) are irreversibly reduced by the 5α-reductase into 5α-dihydroprogesterone (5α-DHP) and 5α-dihydrodeoxycorticosterone (5α-DHDOC). These pregnane steroids may be further reduced to 3α,5α-tetrahydroprogesterone (3α,5α-THP; 3α-hydroxy-5α-pregnan-20-one; allopregnanolone), 3α,5β-tetrahydroprogesterone (3α,5β-THP; 5β-pregnan-3α-ol-20-one; pregnanolone) and 3α,5α-tetrahydrodeoxycorticosterone (3α,5α-THDOC; 3α,21-dihydroxy-5α-pregnan-20-one; allotetrahydrodeoxycorticosterone) by the 3α-hydroxysteroid dehydrogenase (3α-HSD).

In particular, certain 3α-reduced metabolites of progesterone such as 3α,5α-THP (allopregnanolone) and 3α,5β-THP (pregnanolone) are potent positive allosteric modulators of the $GABA_A$ receptor complex, whereas 3β,5α-THP or DHEA exert an inhibitory modulation of the $GABA_A$ receptor (Paul and Purdy, 1992; Rupprecht and Holsboer, 1999). In preclinical studies at the molecular level, selective serotonin reuptake inhibitors (SSRIs) were able to enhance the formation of 3α-reduced neuroactive steroids (e.g. allopregnanolone) via shifting the activity of the cytosolic 3α-HSD type 3 toward the reductive direction; only sertraline also inhibited the reverse oxidative reaction. The tricyclic antidepressant imipramine had no effect on the formation of allopregnanolone (Griffin and Mellon, 1999). The authors of this study hypothesized that these results may explain the rapid amelioration of dysphoria and anxiety symptoms associated with major depression and late luteal phase dysphoria by SSRIs. However, another study, which did not find any change in the activity of this enzyme after administration of various SSRIs, came to the conclusion that the interference with the 3α-HSD type 3 might not be the crucial mechanism by which SSRIs increase allopregnanolone concentrations (Trauger et al., 2002).

In our research group we examined the effects of the antidepressant drug mirtazapine (α_2-, 5-HT_2-, 5-HT_3- and H_1-antagonist) on the reduction of 5α-DHP (into 3α,5α-THP = allopregnanolone) catalyzed by the cytosolic 3α-HSD type 3 and on the oxidation of 3α,5α-THP (into 5α-DHP) catalyzed by the microsomal 3α-HSD (Schule et al., 2006b). Pure recombinant human cytosolic 3α-HSD type 3 protein was expressed in *Escherichia coli*, whereas the cDNA for human microsomal 3α-HSD was stably expressed in HEK-293 cells. Our in vitro investigations demonstrated a dose-dependent inhibitory effect of mirtazapine on the activity of the microsomal 3α-HSD in the oxidative direction (conversion of 3α,5α-THP into 5α-DHP); however, in contrast to SSRIs no effect of mirtazapine on the cytosolic 3α-HSD catalyzing the reductive pathway (conversion of 5α-DHP into 3α,5α-THP) was observed. Nevertheless, these in vitro investigations support the view that both SSRIs and mirtazapine may enhance the formation of 3α-reduced neuroactive steroids such as allopregnanolone thereby potentiating the GABAergic tone in the brain. The effects of psychotropic drugs on neurosteroidogenesis in humans, in particular depressed patients, are summarized in Table 1.