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Review

Neuroactive steroid effects on cognitive functions with a focus on the serotonin and GABA systems

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ABSTRACT

This article will review neuroactive steroid effects on serotonin and GABA systems, along with the subsequent effects on cognitive functions. Neurosteroids (such as estrogen, progesterone, and allopregnanolone) are synthesized in the central and peripheral nervous system, in addition to other tissues. They are involved in the regulation of mood and memory, in premenstrual syndrome, and mood changes related to hormone replacement therapy, as well as postnatal and major depression, anxiety disorders, and Alzheimer's disease. Estrogen and progesterone have their respective hormone receptors, whereas allopregnanolone acts via the $GABA_A$ receptor. The action of estrogen and progesterone can be direct genomic, indirect genomic, or non-genomic, also influencing several neurotransmitter systems, such as the serotonin and GABA systems. Estrogen alone, or in combination with antidepressant drugs affecting the serotonin system, has been related to improved mood and well being. In contrast, progesterone can have negative effects on mood and memory. Estrogen alone, or in combination with progesterone, affects the brain serotonin system differently in different parts of the brain, which can at least partly explain the opposite effects on mood of those hormones. Many of the progesterone effects in the brain are mediated by its metabolite allopregnanolone. Allopregnanolone, by changing $GABA_A$ receptor expression or sensitivity, is involved in premenstrual mood changes; and it also induces cognitive deficits, such as spatial-learning impairment. We have shown that the 3beta-hydroxypregnane steroid UC1011 can inhibit allopregnanolone-induced learning impairment and chloride uptake potentiation in vitro and in vivo. It would be important to find a substance that antagonizes allopregnanolone-induced adverse effects.

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Contents

1. Neurosteroids

Neurosteroids (a term introduced by Baulieu in 1981) are steroids synthesized in the central and peripheral nervous system, in myelinating glial cells, astrocytes, and neurons (Baulieu and Robel, 1990; Compagnone and Mellon, 2000). The precursor, cholesterol, can be supplied by peripheral sources or biosynthesis, or it can be derived from low-density lipoproteins in many cells of the nervous system (Hu et al., 1989; Jung-Testas et al., 1992b; Jurevics and Morell, 1995). The cytochrome P450 side-chain cleavage enzyme (P450scc) is involved in the conversion of cholesterol to pregnenolone (Le Goascogne et al., 1987). Pregnenolone can be oxidized to progesterone by the 3β-hydroxysteroid dehydrogenase/isomerase (3βHSD), see Fig. 1. 3βHSD mRNA expression has been determined in the adult rat brain by in situ hybridization, and types I and II are the major isoforms in the brain (Guennoun et al., 1995; Kohchi et al., 1998). Estradiol can also be classified as a neurosteroid. It can be synthesized de novo or converted from testosterone in the brain by aromatase P450. This conversion is possible because it has been shown that the aromatase inhibitor formestane decreases the estradiol concentration in the cortex and in the hippocampus of female rats (Amateau et al., 2004). In addition, the enzymes needed for estradiol synthesis, P45017alpha and P450 aromatase, are localized in hippocampal neurons—in pyramidal cells of the CA1–CA3 regions as well as in the granule cells of the dental gyrus (Hojo et al., 2004). The brain can also take up the same steroids from the blood, and an accumulation compared to serum concentrations occurs. This fact indicates that the brain concentrations are related to the peripheral production in the endocrine organs. The distribution in the brain is, however, not even because certain regions accumulate more than others and time differences in concentration peaks have been shown—for example, after stress (Barbaccia et al., 1994; Bixo et al., 1997; Bixo et al., 1995; Bixo et al., 1986; Purdy et al., 1991).

Estradiol and progesterone are the major human female sex hormones. In the adult women, the principal sources of estradiol are the granulosa cells of the developing follicle and the corpus luteum (Speroff et al., 1999). The adrenal gland can produce androstenedione, which can be converted to estrone and estradiol, or to testosterone, which in fat, placenta and endometrium, the liver, intestines, skin, muscle, and brain can be converted to estradiol. Conversion of testosterone to estradiol is mediated by the aromatase cytochrome P450 enzyme. Progesterone is mainly synthesized in granulosa cells of the corpus luteum, but also in the placenta and the adrenals (Speroff et al., 1999). Following synthesis, most of the estradiol and progesterone are bound to plasma proteins (sex hormone-binding globulin, albumin, transcortin) (Speroff et al., 1999). Bound hormones are relatively inactive, although the albumin-bound fraction may be available for cellular action as this binding has low affinity.

Estrogens are required for the normal female phenotype, sexual maturation, female genital function, as well as for skeleton maintenance and are probably protective for the cardiovascular system (Baker et al., 2003; Riggs et al., 2002; Speroff et al., 1999). Progesterone is a key hormone for conception and pregnancy maintenance. Ovarian steroids have profound effects on brain function, including regulation of the reproductive neuroendocrine system, mood and cognition, as well as neuroprotective effects on neurons (Behl, 2002; McEwen, 2001; Speroff et al., 1999). Since steroid hormones are lipophilic and have a low molecular weight, estradiol and progesterone readily cross the blood–brain barrier and become available for their actions on the brain. The brain is also a significant site for progesterone metabolism. Steroid hormone concentrations in plasma and the brain vary throughout the menstrual cycle.

Many effects of progesterone are mediated through its metabolite allopregnanolone (3alpha-hydroxy-5alpha-pregnan-20-one). See Fig. 2A. The enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase needed for the production of allopregnanolone from progesterone are in neurons and glial cells present in many areas of the brain, notably in the cortex and the hippocampus (Compagnone and Mellon, 2000). allopregnanolone is a neurosteroid that accumulates in the brain and increases in plasma during the luteal phase of the