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Review

Sex steroids and neurogenesis

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ABSTRACT

The brain has long been known as a dimorphic organ and as a target of sex steroids. It is also a site for their synthesis. Sex steroids in numerous ways can modify cerebral physiology, and along with many processes adult neurogenesis is also modulated by sex steroids. This review will focus on the effects of the main steroids, estrogens, androgens and progestogens, and unveil some aspects of their partly disclosed mechanisms of actions. Gonadal steroids act on different steps of neurogenesis: cell proliferation seems to be increased by estrogens only, while androgens and progestogens favor neuronal renewal by increasing cell survival; differentiation is a common target. Aging is characterized by a cognitive deficiency, paralleled by a decrease in the rate of neuronal renewal and in the levels of circulating gonadal hormones. Therefore, the effects of gonadal hormones on the aging brain are important to consider. The review will also be expanded to related molecules which are agonists to the nuclear receptors. Sex steroids can modify adult neuronal renewal and the extensive knowledge of their actions on neurogenesis is essential, as it can be a leading pathway to therapeutic perspectives.

Contents

1. Introduction

The brain is both a target for gonadal hormones [1], and a site for de novo steroid synthesis. Sex steroids can have different origins which are often interlinked and difficult to sort out. They are synthesized in the gonads: ovary for 17β estradiol (E2) and progesterone (P), and in the Leydig cells of testes for testosterone (T). They enter the circulation from where they are distributed to all the organs. Yet, in the brain, they can also be produced locally: their synthesis can take place in the central nervous system and therefore they are named "neurosteroids" [2,3]. The concentrations of some steroids can be higher in the brain than in plasma: such is the case for dehydroepiandrosterone (DHEA) for instance [2]. Indeed, the whole enzymatic equipment has been localized in neu-

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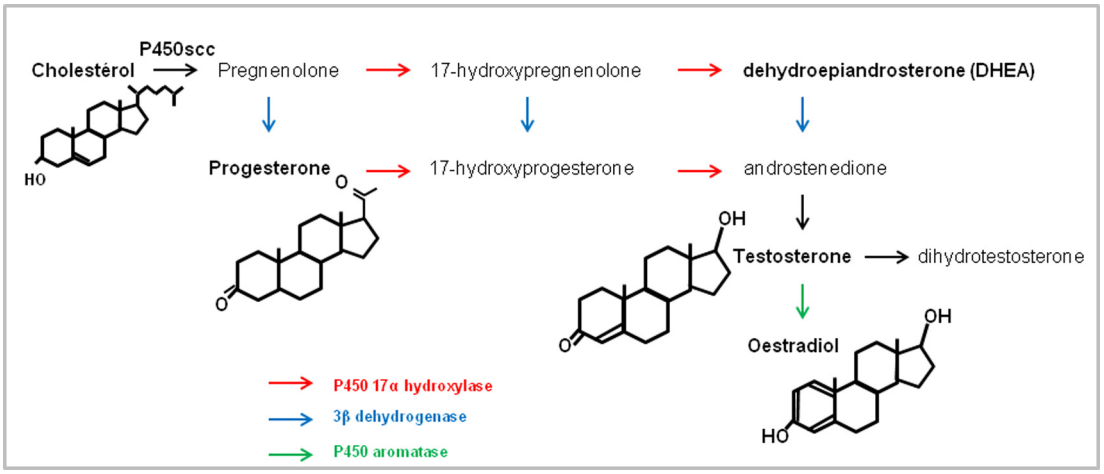

Fig. 1. Main gonadal steroids metabolism. Steroids are synthetized in different organs. The brain possesses the whole enzymatic equipment for the synthesis, present in the neurons and the astrocytes [4].

rons and astrocytes [4]. Both cell types can synthetize E2, but astrocytes are considered a major source of E2 since global ischemia can induce their P450 aromatase activity [5]. E2 is synthetized particularly in the hippocampus [6] and E2 levels in the brain are different from the serum levels [6,7]. Whether from paracrine, or endocrine origin, E2 plays an important role on neural development and cognition. Local E2 is involved in the development and evolution of the connectivity in the hippocampus [8]. Several studies, using ovariectomized animals, cultured cells, or transgenic models concur to the conclusions that E2 synthesized in the brain is essential for synaptogenesis, modifies spine density, and favors long-term potentiation [8,9].

Neurogenesis is a process easily modified by internal or external cues, and steroids- which are master regulators of cerebral functions- can reshape neuronal renewal [10]. This review will focus on the effects of the preponderant gonadal steroids, i.e. E2, T and P, with a special attention to E2, since it has probably been studied the most. Indeed, T is transformed in E2 via the action of P450 aromatase, and P has been studied most of the time in conjunction with E2, as explained below. The mechanisms involved in these effects will be described, and the review will expand to E2-related molecules.

2. Synthesis of sex steroids and the identity of their receptors

Steroids all derive from cholesterol through its conversion into pregnenolone by the cholesterol cytochrome P450 side-chain cleavage enzyme in the mitochondria (P450scc). Fig. 1 schematizes the synthesis of the main sex steroids. Corticoids originate also from this synthesis pathway, either from progesterone or from 17-hydroxy-progesterone. The main enzymes are cytochrome P450 17α-hydroxylase and 3β-dehydrogenase, which are active

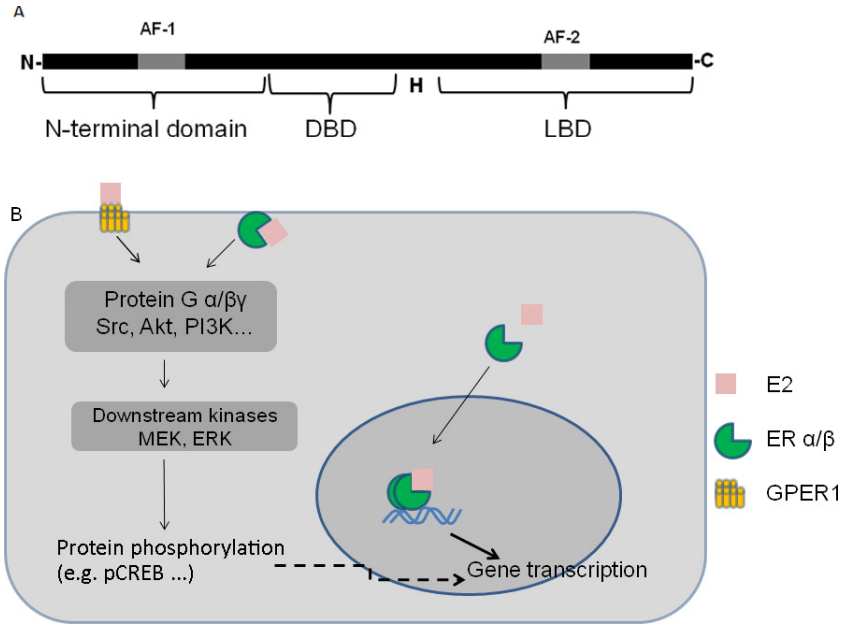

Fig. 2. A: Structure of the nuclear receptors. The super-family of nuclear receptors is highly conserved and characterized by 4 domains: DBD: DNA-binding domain; H: Hinge; LBD: Ligand-binding domain; AF-1 or -2: activation function -1 or -2. B: E2 receptors and intracellular mechanisms. The classical receptors, ERα and ERβ are located in the cytoplasm and in the membrane. They induce, upon E2 binding, genomic effects; binding to the proteins located in the membrane triggers rapid, non-genomic effects, mainly through kinase activation. GPER1 is a seven transmembrane receptor coupled to protein G. it has been localized in the plasma membrane of neurons [12,13].