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Review

Interactions between hormones and epilepsy

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ABSTRACT

There is a complex, bidirectional interdependence between sex steroid hormones and epilepsy; hormones affect seizures, while seizures affect hormones thereby disturbing reproductive endocrine function.

Both female and male sex steroid hormones influence brain excitability. For the female sex steroid hormones, progesterone and its metabolites are anticonvulsant, while estrogens are mainly proconvulsant. The monthly fluctuations in hormone levels of estrogen and progesterone are the basis for catamenial epilepsy described elsewhere in this issue. Androgens are mainly anticonvulsant, but the effects are more varied, probably because of its metabolism to, among others, estradiol.

The mechanisms for the effects of sex steroid hormones on brain excitability are related to both classical, intracellularly mediated effects, and non-classical membrane effects due to binding to membrane receptors. The latter are considered the most important in relation to epilepsy. The different sex steroids can also be further metabolized within the brain to different neurosteroids, which are even more potent with regard to their effect on excitability. Estrogens potentiate glutamate responses, primarily by potentiating NMDA receptor activity, but also by affecting GABA-ergic mechanisms and altering brain morphology by increasing dendritic spine density. Progesterone and its main metabolite 5α-pregnan-3α-ol-20-one (3α-5α-THP) act mainly to enhance postsynaptic GABA-ergic activity, while androgens enhance GABA-activated currents.

Seizures and epileptic discharges also affect sex steroid hormones. There are close anatomical connections between the temporolimbic system and the hypothalamus controlling the endocrine system. Several studies have shown that epileptic activity, especially mediated through the amygdala, alters reproductive function, including reduced ovarian cyclicity in females and altered sex steroid hormone levels in both genders. Furthermore, there is an asymmetric activation of the hypothalamus with unilateral amygdala seizures. This may, again, be the basis for the occurrence of different reproductive endocrine disorders described for patients with left-sided or right-sided temporal lobe epilepsy.

1. Introduction

There is a complex interaction between hormones and epilepsy that is manifest in many different ways. Firstly, hormones influence epilepsy, while secondly, epilepsy affects hormones. In addition, antiepileptic drugs (AEDs) can interact both with the epilepsy itself and with hormones. The focus of this review is hormones and gender, addressing the interactions between epilepsy and sex steroid hormones. Interactions with AEDs are described elsewhere in this issue of Seizure, which is a special issue based on presentations held at the Second Gender Issues in Epilepsy Meeting in Oslo, 28–29 August 2014.

The male and female peripheral sex steroid hormones, estradiol, progesterone, and testosterone, are all derived from cholesterol and are closely linked as seen in Fig. 1. Cholesterol, having been metabolized to progesterone, can be further metabolized to androstenedione and testosterone. These, in turn, through aromatization can be transformed to estradiol. Furthermore, progesterone is metabolized through the action of the enzymes 5α-reductase and 3α-hydroxysteroid to 3α-5α-THP, a very powerful antiepileptogenic substance. Steroids that are synthesized in the brain are also called neurosteroids; they are precursors and metabolites of steroid hormones influencing neuronal

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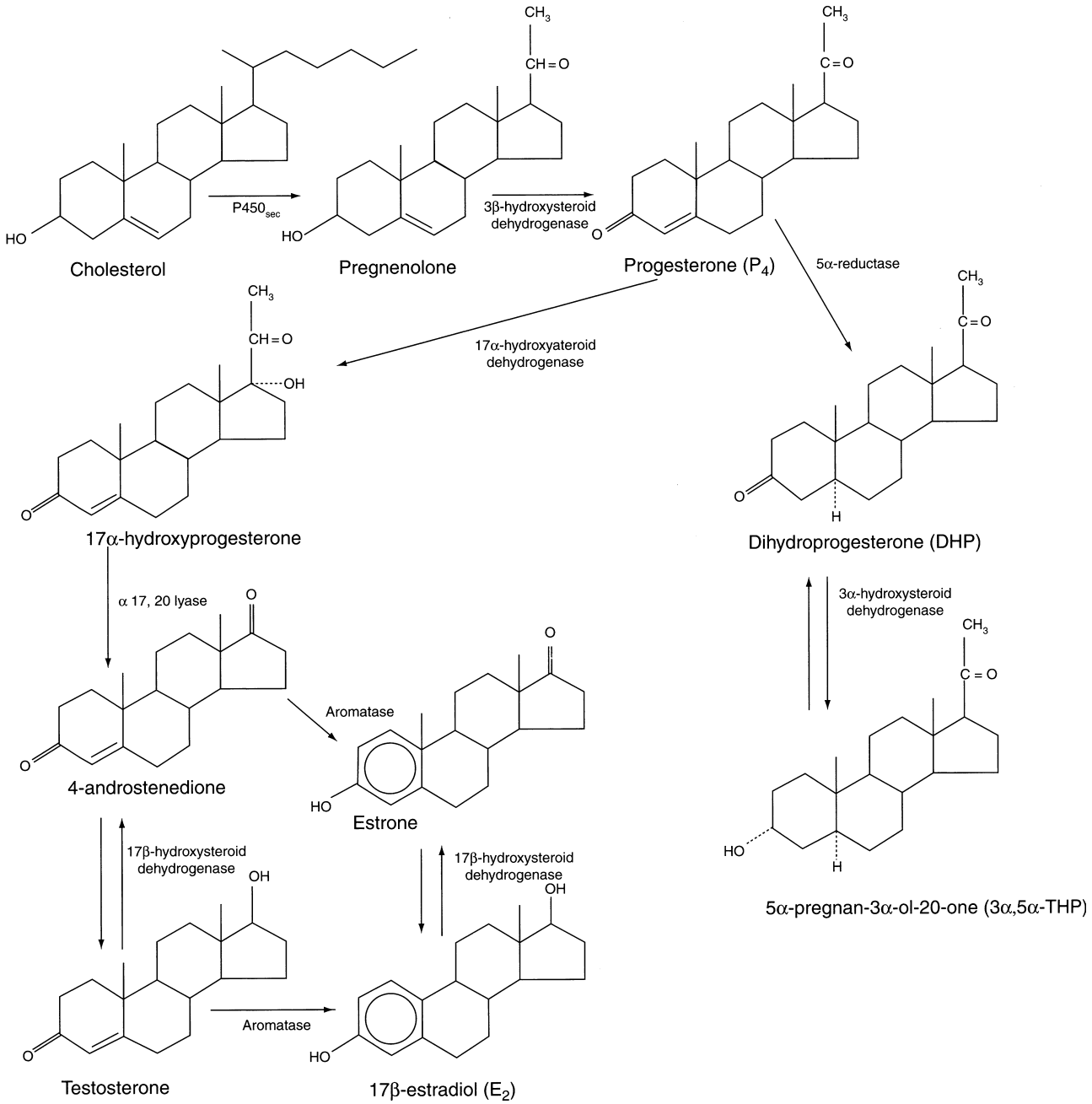

Fig. 1. Formation of progesterone and its metabolites, estrogens, and testosterone from cholesterol.
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excitability, mainly through non-genomic mechanisms. The enzymes 5α-reductase and 3α -hydroxysteroid, the most important enzymes enabling the brain to produce neurosteroids, are widely distributed in the brain.

Clinically, the effect of hormones on brain excitability appear as fluctuations in seizure frequency in relation to changes in hormone levels. This is most typically seen in catamenial epilepsy [1,2], where seizure frequency varies with fluctuations in estrogen and progesterone levels (Fig. 2). The phenomenon of cyclical changes in seizure frequency in relation to menstruation was first properly studied by Gowers [3] in 1885, who found a relationship between menstrual phases and seizure frequency in 46 of 82 patients. This finding was later confirmed in numerous studies, like that of Laidlaw [4] who monitored 50 institutionalized patients and demonstrated seizure exacerbation in relation to menstruation in 72% of the women. The phenomenon of catamenial epilepsy demonstrates the clinical relevance of hormonal effects on brain excitability.

2. The effect of hormones on epilepsy

Female sex steroid hormones have repeatedly been shown to affect neuronal excitability, with estrogens being mainly proconvulsant and progesterone and its metabolites being anticonvulsant.

Clinically, a direct excitatory effect of estrogen was convincingly demonstrated by Logothetis et al. in 1959 [5]. Intravenous (i.v.) injections of the estrogenic substance, Premarin, were