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Review

Sexual neurosteroids and synaptic plasticity in the hippocampus

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ABSTRACT

Sexual neurosteroids (SN), namely 17β-estradiol (E2) and 5α-dehydrotestosterone (DHT), are synthesized in the hippocampus, where they induce circuit modifications by changing the number of excitatory spine synapses in a paracrine and sex-specific manner. The mechanisms of this sex-specific synapse turnover, which are likely to affect cognitive functions, are poorly understood. We found that hippocampal neurons synthesize estradiol, which maintains LTP and synapses in females but not in males. In females, inhibition of estradiol synthesis results in impairment of LTP and synapse loss. These effects were not seen in males. The essential role of local estrogen on the stability and maintenance of connectivity in the hippocampus is consistent with age-related cognitive decline in women after menopause. In male animals the regulation of synaptic stability and plasticity by locally synthesized sexual steroids remains to be clarified.

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1. Sexual steroids effect synaptic plasticity in the hippocampus

Gonads are the main source of sexual steroids in serum, and these steroids can easily enter the brain from the peripheral circulation. The varying densities of spines along dendrites of hippocampal CA1 pyramidal neurons during the estrus cycle of females strongly support the idea that estrogen of ovarian origin regulates spinogenesis in the hippocampus (Woolley et al., 1990); for review see Spencer et al. (2008). In addition, the removal of gonads has been shown to result in reduced hippocampal dendritic spine density in males and females (Gould et al., 1990; Leranth et al., 2004; Li et al., 2012). A rescue of spine loss after ovariectomy, however, could be achieved by injections of E2 into females, but not into males. In gonadectomized males, injections of DHT restored reduced spine density after removal of the testes (Leranth et al., 2004; Li et al., 2012). Together, the results point to the sex-specific roles of sexual steroids from the gonads (E2 in females and DHT in males) played by spine density in the hippocampus. In addition, it has frequently been shown that E2 enhances LTP, a widely accepted cellular model for learning and memory, in the hippocampus (for review, see Spencer et al. (2008)). E2 treatment increases the magnitude of LTP at hippocampal CA3-CA1 synapses (Foy et al., 1999; Smith and McMahon, 2005; Kramár et al., 2009) in acute hippocampal slices. In this context, the role of glutamatergic receptors has not yet been clarified. In females, E2 increases the number of NMDA receptor binding sites with no effect on AMPA receptor binding sites, as shown by autoradiography (Woolley et al., 1997). Gazzaley et al. (1996) reported that E2 increases immunofluorescence of the NMDA receptor subunit NR1 in females. Blockade of the NR2B NMDA receptor subunit abolishes E2-induced enhancement of LTP (Smith and McMahon, 2005), while Snyder et al. (2011) did not find any changes in NR2B protein expression upon E2 treatment. Similar studies on the effects of DHT on glutamatergic receptors are lacking so far.

Both phenomena, increased spine density and enhanced LTP, have been related to the memory-enhancing effects of sexual steroids. Data on E2-regulated cognitive abilities in women originate predominantly from studies on E2 replacement therapy in pre- and postmenopausal women. Many reports point to a beneficial function of E2 with respect to memory (Sherwin, 1988; Phillips and Sherwin, 1992; Duka et al., 2000; Maki et al., 2001) and risk of dementia (Yaffe et al., 1998; Nelson et al., 2002). In men, it has been shown that spatial memory is improved in response to androgen treatment (Cherrier et al., 2005). In tests for cognitive impairment, pharmacological inhibition of E2 synthesis did not influence cognitive performance in boys (Hero et al., 2010). DHT replacement reverses altered synaptic transmission after gonadectomy in male mice (Sakata et al., 2000). Recently, androgens have been shown to be important in achieving optimal results in working memory tests on male animals (McConnell et al., 2012).

A major concern in most studies cited above is that the effects of sexual steroids on spine and spine synapse density and LTP were commonly shown by using gonadectomized animals, which had been systemically treated with E2 or DHT (Gould et al., 1990; Warren et al., 1995; Cordoba Montoya and Carrer, 1997; Smith and McMahon, 2005, 2006; Kramár et al., 2009). The vast majority of results from these studies show that exogenous application of sexual steroids is effective after the gonads, as a major source of these steroids, have been removed. These experimental approaches leave the question open as to whether application of E2 or DHT actually causes major alterations of previously non-affected neuronal networks (Mendez et al., 2011), or simply restores effects of estradiol and testosterone depletion, respectively. Other studies have used hippocampal slice cultures indifferently prepared from neonatal male and females (Mendez et al., 2011; Foster, 2012) which ignores the possibility of intrinsic sex-specific differences of the hippocampal tissue. Regarding LTP, E2 was applied to acute slices of mostly male rats (Foy et al., 1999; Kramár et al., 2009; Micevych and Dominguez, 2009; Srivastava et al., 2013) Finally, it appears questionable to draw conclusions from treatments using supraphysiological doses of E2 and DHT, which were commonly used in the studies, for the *in vivo* situation.

1.1. *Sexual steroid receptors in the hippocampus*

The hippocampus expresses both ERs and ARs, irrespective of gender. For E2-signaling, two ER subtypes have been identified, ERα and ERβ, which are considered to be both cytosolic/nuclear and membrane-bound receptors, and GPR30 as a further membrane-bound receptor. ERα and ERβ are transcription factors and can function in a genomic way, but also in a non-genomic manner *via* membrane-initiated effects (Micevych and Dominguez, 2009; Foster, 2012; Srivastava et al., 2013). This also holds true for androgen receptors (Sarkey et al., 2008). Thus, ERs and also ARs, are able to induce rapid, membrane-bound effects in addition to longer-lasting genomic effects. The role of membrane-bound *versus* genomic receptors with respect to turnover of glutamatergic synapses is highly controversial (Zhou et al., 2014). As to differences between genders in the equipment of sexual steroid receptors, it appears that AR protein expression is lower in the female hippocampus than in age-matched males (Xiao and Jordan, 2002; Feng et al., 2010) and that sex differences in the expression of estrogen receptors exist during hippocampal development (Zuloaga et al., 2013). This was shown, however, on the light microscopical level and by Western blot analysis, which does not allow for the quantification of cytosolic/nuclear *versus* membrane-bound sites of steroid receptors. At the ultrastructural level, several attempts have been made to localize ERs and ARs in the hippocampus using conventional electron microscopy and primarily diffusible immunoperoxidase labeling (Milner et al., 2005; Tabori et al., 2005; Mitterling et al., 2010), which does not allow for precise receptor localization. A comparative quantitative analysis of ERs and ARs in male and female hippocampal neurons on an ultrastructural level, using immunogold labelling, is so far lacking. The knowledge of the precise quantities of membrane-bound and cytosolic/nuclear sites, however, would be important for understanding the signalling of sexual steroids in the hippocampus.