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DISSERTATION SUMMARY

Neurosteroid induced synaptic plasticity in the hypothalamus: the role of the locally synthesized estradiol

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Neuronal plasticity is the remarkable ability of the nervous system to modify the number, morphology and activity of synapses and in such a way the response of a neuron to given inputs. Plastic changes occur both naturally and under experimental conditions, they have been shown to be involved in such phenomena as learning, memory, aging and response to injury. During the last decades it became clear that the gonadal steroids are among those factors, which are able to induce certain adaptive modification of the synaptic connections.

The sex hormones are playing important organizatory role during the development of the nervous system and their action results in sexually dimorphic brain regions. These dimorphic areas differ in size, number of neurons, and synaptic connectivity, all these alterations may serve as a basis for different functioning and for sexually dimorphic behaviour. The hormonal effects, however, are not limited to developmental stages *i.e.* they are influencing the plastic changes in the adult brain, too.

In female rodents a continuous cycling synaptic remodeling is taking place in the hypothalamus that are linked to hormonal variations during the ovarian cycle. Experimental data show that the synapse remodeling in the hypothalamic arcuate nucleus is driven by 17ß-estradiol, because in ovariectomized rats the hormone substitution resulted in reversible decline of synapses. It has also been demonstrated that the hormonally induced changes of axo-somatic inputs to arcuate neurons is specific, because not all of the synapses are affected. To better understand the hormonally induced synaptic remodeling, it would be necessary to describe the changes in the number and/or in the structure of synapses in different areas of the nervous system.

In the present study the anteroventral periventricular nucleus (AvPv) of adult rats was chosen for analysis, due to its abundant estrogen- and progesterone-receptive neurons and its critical role in the control of gonadotrophin secretion.

12 female rats were ovariectomized (OVX) at age of 2 months and sacrificed 4 weeks later. Six animals were injected sc. with 17ß-estradiol (100g / 100g body weight), the rest was used as controls injected with sesame oil.

The combination of pre- and postembedding immunostaining was used to investigate the synaptic connections of estrogen receptor-immunoreactive (ER-ir) and non-ER-ir neurons in the AvPv.

Ultrastructural analysis revealed that the AvPv neurons of OVX animals receive approximately the same number of GABA-immunoreactive (inhibitory) and non-immunoreactive (probably excitatory) axo-somatic synapses. In contrast with the arcuate nucleus, 17ß-estradiol treatment of OVX rats did not result in changes of GABAergic axo-somatic synapses, but we observed a significant increase of non-GABAergic contacts and a decrease of all types of axo-dendritic synapses. The innervation patterns of ER-ir and non-ER-ir neurons were different.

To study the hypothesis that the locally synthesized estradiol has an effect on synaptic connectivity we treated the animals with the precursor of 17ß-estradiol dehydroepiandrosterone (DHEA). This neurosteroid could also induce changes in AvPv synapses, but its effect was blocked by the aromatase inhibitor letrozol. This observation suggests that the conversion of DHEA into estradiol is involved in the mechanism of action of this neurosteroid on synaptic remodeling.

Our data indicate that 17ß-estradiol induces synaptic remodeling in the AvPv nucleus and may play a decisive role in the regulation of gonadotrophin secretion. On the other hand the present study shows that the molecular mechanisms responsible for the hormonally induced synaptic remodeling in AvPv and arcuate nucleus are different, which may reflect the fact that these two nuclei are responsible for different functions.

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