randomized controlled trials as to its prevention. However, results from retrospective and uncontrolled treatment trials with lithium or oestradiol are encouraging.

SES07.2

Hormones and mental disorders – focus on estrogen–serotonin interactions

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Clinical observations suggest that sex steroids may exert potent effects on mood, mental state and cognition in the human. In particular, changes in the concentration of plasma estradiol have been implicated in depressive symptoms experienced by some women at the time of menstruation (premenstrual syndrome), the perimenopause and the puerperium. Estrogen has also been implicated in schizophrenia, and several observations suggest that estrogen may be neuroprotective with respect to Alzheimer's Dementia, age-related cognitive changes and ischemic brain damage including stroke.

Basic studies of the neuroprotective and psychoprotective action of estrogen are currently centered on two complementary themes – (i) estrogen effects on nerve growth and synapse formation, and (ii) estrogen effects on central neurotransmission. Focused on the latter, our studies in female rats show that estradiol, in its positive feedback mode for gonadotropin release in the female rat, increases the expression of the genes for the 5-hydroxytryptamine 2A (5-HT2A) receptor and the serotonin transporter (SERT) in the dorsal raphe nucleus (DRN), the location of serotonergic neurons that innervate the forebrain. This increase in gene expression is associated with an increase in the density of 5-HT2A receptors in the frontal, cingulate and piriform cortex, nucleus accumbens, caudate-striatum and olfactory tubercule, and an increase in SERT density in the basolateral nucleus of the amygdala, lateral septum and the ventromedial nucleus of the hypothalamus [I,2]. Testosterone and estrogen have similar effects on the 5-HT2A receptor and the SERT in the male as estrogen in the female – the action of testosterone is mediated by its conversion to estradiol [3]. Studies in intact male and female rats suggest that the estrogen-induced increase in the density of 5-HT2A receptors in cerebral cortex is dependent on the concentration of estrogen to which the brain is exposed. The similar action of testosterone and estrogen on serotonin mechanisms in higher brain centers contrasts markedly with their opposite actions on the hypothalamic control of gonadotropin release. The effects of estrogen on the 5-HT2A receptor and the SERT are blocked completely by tamoxifen and raloxifene, suggesting that the action is mediated by estrogen receptors, even though they may not necessarily be located in the serotonergic neurons of the DRN or in serotonin target neurons [4].

Since the 5-HT2A receptor has been implicated in depression and psychosis, and the SERT in depression, these experimental data provide a possible rational basis for estrogen effects on mood and mental state.

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SES07.3

Estrogen – a possible role in the treatment of schizophrenia?

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SES07.4

Future perspectives of gender hormones in neuroprotection

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Gender hormones modulate brain development and may interfere with a wide variety of psychiatric disorders. They influence brain maturation, neurodegenerative processes and alter recovery from brain injury. For example, cultured hippocampal neurons display a clear gender difference in vulnerability to hypoxia (vulnerability of male hippocampal neurons >> female neurons). Epidemiological and experimental studies indicate estrogens as important neuroprotective factors in Alzheimer disease and schizophrenia. Estrogens inhibit neuronal cell death, axonal and dendritic pruning, promote synaptic plasticity and enhance synaptic transmission. They are strong antioxidants and activate protective antiapoptotic genes. Other gender hormones may play a role in neuroprotection as well. Testosterone, for example, can in the brain be enzymatically converted to estradiol. Gender hormones as a neuroprotective add-on therapy may in the future complement the traditional drug therapies in psychiatric disorders, in particular, in schizophrenic psychoses to counteract the progressive worsening of cognitive / mental performance.

SES07.5

Gender differences in the genetics of anxiety disorders

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Epidemiological and clinical data demonstrate gender differences as regards frequency, age of onset, severity and symptomatology of anxiety disorders. Even self-reports on anxiety seem to be influenced by gender. The reasons are complex and include psychosocial as well as genetic factors.

In panic disorder, clinical genetic studies indicate that the role of genetic factors is different between genders. Separation anxiety as a precursor syndrome has been suggested to be genetically determined only among women. Agoraphobia segregates predominantly among the female relatives of patients with panic disorder. Molecular genetic studies have provided first gender-specific results. Associations with the higher expressing alleles of monoamine oxidase A and the more active allele of catechol-O-methyltransferase have been found significantly only among women in independent European samples.

These studies in humans are supported by studies in knock-out mice. As part of the genetic background gender is a major factor for the contribution of a knock-out to the development of anxiety.

The role of gender effects therefore will be a necessary focus of future genetic studies to contribute to the development of novel and individual therapies for anxiety disorders.