SES06.3

Hypoestrogenism in schizophrenic women: implications for research

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Estrogens seem to have a neuroleptic-like effect in schizophrenia and therefore a beneficial influence on the course of illness in schizophrenic patients. Therefore, the impact of hypoestrogenism in women with schizophrenia is of high clinical interest. While the precise mechanism of low estrogen levels in schizophrenic women is unclear, there is evidence that hypoestrogenism in schizophrenic women is not exclusively the consequence of hyperprolactinemia-inducing neuroleptics, but connected with schizophrenia itself.

To test this hypoestrogenism hypothesis the levels of estradiol, prolactin, LH, FSH, progesterone, and testosterone of 75 women with schizophrenia were determined in the follicular, periovulatory and luteal phases of the menstrual cycle.

Hypoestrogenism was found in about 60% of the patients and anovulatory cycles were assumed in most of the women. To rule out a possible effect of hyperprolactinemia on the gonadal axis and the subsequent effect on the estrogen level due to conventional neuroleptics, estradiol serum levels of patients treated with atypical neuroleptics known to induce only a mild increase in prolactin, or no increase at all, were compared with those from patients treated with conventional neuroleptics. The data clearly indicate high prolactin levels in the latter, but low levels in the group treated with atypical neuroleptics. In both groups, however, low levels of estradiol were measured.

The findings provide evidence that hypoestrogenism in schizophrenia occurs in women with and without neuroleptic-induced hyperprolactinemia. Because of the clinical consequences of hypoestrogenism in schizophrenic women further research should be conducted to clarify the cause of this endocrinological abnormality.

SES06.4

Estrogen therapy in women with depression

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Objectives: Summarize the present evidence regarding the impact of estrogen decline on mood disorders in the postpartum period, in peri and postmenopausal women and in women suffering from PMDD. Develop a practical model of integrated care for patients with depressive disease

Methods: Review of the literature regarding biological, epidemiological, clinical evidence. Review of the methods applied. Critical evaluation of research concepts. Qualitative longitudinal studies performed at our department.

Results: Biological evidence supports the link of estrogens with affective disorders. Epidemiological data are however controversial. The methodological difficulties include the lack of longitudinal studies, endocrine status, variation in measures etc. Theories include the domino effect of estrogen induced vegetative disturbances on affective symptoms, the developmental crisis theory and the psychosocial stress hypothesis. Pathogenetic studies point to the importance of psychosocial stressors. Intervention studies have frequently shown the positive effect of estrogens on non psychiatric classified mood disorders. Our own longitudinal studies show the intraindividual variation of effective interventions.

Conclusion: An individualized clinical model emerges, in which the the patient with a mood disorder during specific life span changes (endocrine and psychosocial) is evaluated not only using psychiatric diagnostic scales but also determining the gynecological-endocrine status including somatic symptoms and risks as well as psychosocial stressors. The model of practice in Basel will be presented.

SES06.5

Cerebrospinal fluid estradiol and β-amyloid levels in female patients with Alzheimer's disease

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Objective: Recent epidemiological studies demonstrated that estrogen replacement therapy may delay onset and progression of AD. Experiments in cell cultures indicated that estrogens such as 17β-estradiol (E2) may decrease the production of β-amyloid 1–42 (Aβ42), a peptide central for the formation of senile plaques in Alzheimer's disease (AD).

Method: To test this finding in a clinical study, cerebrospinal fluid levels of E2 were investigated in 33 female AD patients and 14 patients with depression with respect to β-amyloid 1–40 (Aβ40) and Aβ42 levels. In a second step, we compared E2 levels in a larger sample of 59 AD patients with 13 healthy controls.

Results: E2 levels were significantly ($p<0.05$) lower in the AD group compared to both depressed and healthy controls. Within the AD group, low E2 levels were inversely correlated with Aβ42 concentrations.

Conclusions: Our study revealed a slight E2 deficit in female AD patients which may influence Aβ42 metabolism. This observation corresponds to the beneficial effects of estrogen replacement therapy on the development and course of AD.

SES07. AEP Section Epidemiology & Social Psychiatry – Gender differnces in major mental disorders – Part II

Chairs: J. Kulkarni (AUS), R.K.R. Salokangas (FIN)

SES07.1

Psychosis after childbirth

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The rate of psychosis after childbirth is about 1–2/1000 and has been remarkably consistent over 150 years and across countries. Most illnesses are affective in nature and have an onset within 2 weeks of childbirth.

In bipolar women the occurence of episodes in the puerperium has recently been shown to be partially genetically determined. It is likely therefore that the rapid steroid decline after childbirth can highlight an otherwise latent neurotransmitter dysfunction in predisposed subjects. Interactions of oestrogens and progestins with neurotransmitter systems are numerous and complex. Recent findings have suggested several possible sites for such an interaction, for example within the serotonin and the dopamine systems.

Although pregnant women with a history of severe affective disorder are at a high risk of recurrence after delivery there are no

https://doi.org/10.1016/S0924-9338(02)80186-9 Published online by Cambridge University Press

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.

Supported by the UK Medical Research Council

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SES07.3

Estrogen – a possible role in the treatment of schizophrenia?

J. Kulkarni. *Australia*

No abstract was available at the time of printing.

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.

https://doi.org/10.1016/S0924-9338(02)80186-9 Published online by Cambridge University Press