Psychiatria Danubina, 2009; Vol. 21, Suppl. 1, pp 128–131 *Conference paper*

NEUROBIOLOGICAL ASPECTS OF PSYCHOSIS AND GENDER

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SUMMARY

In comparison to female schizophrenia patients male patients have more impaired premorbid functioning, earlier onset of disorder, more severe symptomatology, less favourable outcome, different structural brain abnormalities and cognitive deficits. It has been hypothesized that estrogen, with effects on both neurodevelopment and neurotransmission, could play a protective role in women with schizophrenia and account for some of the gender differences observed in the disorder. On the other hand, it is known that altered promoter DNA methylation could play a critical role in mediating differential regulation of genes and in facilitating short-term adaptation in response to the environment. This data could indicate that environmental factors have gender specific influence on DNA methylation changes in schizophrenia. Recent data support the epigenetic theory of major psychosis and suggest that DNA-methylation changes are important to the etiology of psychosis in a gender specific pattern. Clinically observed gender differences in schizophrenia are probably influenced by genetic and environmental factors. The interplay between those two sets of factors is mediated by estrogen and epigenetic mechanisms.

Key words: *psychosis - gender- differences – schizophrenia – estrogen - epigenetic factors*

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Introduction

The close link between the life-course and the propensity to generate schizophrenia as the most researched psychotic disorder, probably betrays an underlying neurobiological phenomenon, such as the maturation of certain connections through normal or abnormal myelination (Jones & Buckley 2006). Schizophrenia is rather more common in men when it is tightly defined in terms of excluding affective symptoms. Most studies with modern criteria include as few as half as many women as men in the first half life, with the balance being restored later on (Jones & Buckley 2006). Male patients have impaired premorbid functioning, earlier onset of schizophrenia, more severe symptomatology, less favourable outcome, different structural brain abnormalities and cognitive deficits (reviewed by Leung & Chue 2000, Canuso & Pandina 2007). These clinically observed differences could be connected with some neurobiological gender differences, with the most obvious being found in different hormonal status.

Schizophrenia and the estrogen hypothesis

It has been hypothesized that estrogen, with effects on both neurodevelopment and neuro-transmission, may play a protective role in women with schizophrenia and account for some of the gender differences observed in the disorder (Canuso & Pandina 2007). The estrogen hypothesis has been proposed to explain these gender differences and suggests that estrogen provides protection from the development of schizophrenia and decreased the severity of negative symptoms (Seeman 1982, Lang Seeman & Lang 1990). The role of estrogen in the pathogenesis of schizophrenia was supported by several clinical observations. Reduced levels of plasma estrogen in both male (Huber et al. 2005) and female (Riecher-Rossler et al. 1994, Huber et al. 2004, Bergemann et al. 2005, Huber et al. 2001) schizophrenia patients were found. Further, fluctuations of psychotic symptoms in female schizophrenia patients during their menstruation cycle were reported (Bergemann et al. 2005, Huber et al. 2001, Huber et al. 2004, Riecher-Rossler et

Paper presented at ISPS Slovenia meeting, Bled, September 2008

al. 1994). There were also some indications of a higher efficacy of antipsychotic treatment in schizophrenia in women than in men, however in females after the age of the menopause, there was no consistent increase in daily doses of antipsychotics observed (Salokangas 1995).

It is well established that estrogen has pleiotrophic effects on a variety of processes in the developing and adult brain (Boulware & Mermelstein 2005, Huber et al. 2004, McEwen 2002, Garcia-Segura et al. 2001), and therefore estrogen-mediated signalling cascades rather than estrogen itself are candidate pathways that may affect the risk of or modify the manifestation of schizophrenia (Olsen et al. 2008). This implies that while estrogen varies enormously between and within gender, the putative schizophrenia risk genes downstream of estrogen need not differ between men and women. However, the findings for several gene variants, e.g. in glycolysis, are weak and not resistant to correction for multiple testing, which may indicate that they are either spurious or may relate to a particular subtype or aspect of schizophrenia (Olsen et al. 2008).

There are two possibilities of estrogen involvement in the pathogenesis of schizophrenia. Beside direct influence on neurotransmission, estrogen may play a role in schizophrenia susceptibility gene regulation (Olsen et al. 2008). The rationale behind this indirect estrogen involvement rests on the growing evidence that estrogen affects a variety of processes in the developing and adult brain, including neuronal differentiation, survival and excitability (reviewed by Boulware & Mermelstein 2005, Garcia-Segura et al. 2001) as well as on glial proliferation and synaptic plasticity (Reviewed by Garcia-Segura 2001, Olsen et al. 2008). Preclinical data supports the involvement of estrogen in the regulation of several neurotransmitter systems (dopamine, serotonin, noradrenalin and glutamate) (McEwen 2002, Cyr et al. 2002). However, despite the potential benefit of estrogen, women with schizophrenia appear to be at risk for hypoestrogenism, either as a consequence of antipsychotic-induced hyperprolactinemia or, possibly, as a manifestation of the illness itself (Canuso & Pandina 2007).

Environment and epigenetic factors

It seems that not only hormonal factors but also psychosocial factors could have influence on the gender differences. Because of the overwhelming evidence for the role of environmental factors in psychotic disorders comprehensive approaches that examine both genetic and epigenetic factors are required. It was shown that, the central reversible but covalent epigenetic modification to DNA derived from methylation of the cytosine residues, that is potentially heritable, can affect gene expression and downstream activities in mental disorders (Abdolmaleky et al. 2008). It is known that environmental factors can influence DNA methylation patterns and hence alter gene expression. Such changes can in individuals with genetic susceptibilities to specific mental disorder increase the risk for disorder expression. Recent reports provided compelling evidence that both hyper- and hypo-DNA methylation changes of the regulatory regions play critical roles in defining the altered functionality of genes in schizophrenia (Abdolmaleky et al. 2008).

It is also known that altered promoter DNA methylation could play important role in mediating differential regulation of genes and in facilitating short-term adaptation in response to the environment. Recent studies found evidence in the frontal cortex for psychosis-associated DNA-methylation differences in numerous loci, including several involved in dopaminergic, glutamatergic and GABA-ergic neurotransmission, brain development, and other processes functionally linked to disorder etiology (Mill et al. 2008). DNA-methylation changes in a significant proportion of these loci correspond to reported changes of steady-state mRNA level associated with psychosis (Mill let al. 2008).

Changed activity of membrane-bound catechol-O-methyltransferase (MB-COMT) due to altered promoter methylation and the nature of the contribution of COMT Val158Met polymorphism as risk factors for schizophrenia and bipolar disorder was reported (Abdolmaleky et al. 2006). These data reveal that the MB-COMT promoter DNA is frequently hypomethylated in schizophrenia and bipolar disorder patients, compared with controls, particularly in the left frontal lobes. Further quantitative gene-expression analyses showed a corresponding increase in transcript levels of MB-COMT in schizophrenia and bipolar disorder patients compared with the controls (Abdolmaleky et al. 2006). These findings suggest that MB-COMT over-expression due to promoter hypomethylation and/or hyperactive allele of COMT may increase dopamine

degradation in the frontal lobe providing a molecular basis for the symptoms of psychosis (Abdolmaleky et al. 2006).

Another study demonstrated the role epigenetic modulations of the GABA-ergic system. Cortical dysfunction in schizophrenia and related disease is associated with changes in GABAergic circuitry, including altered expression of glutamic acid decarboxylase (GAD), a key enzyme for GABA synthesis in cortical interneurons (Benes & Berretta 2001). It was shown that in controls, the methylation frequencies at CpG dinucleotides, while overall higher in repressive as compared to open chromatin, did not exceed 5% at the proximal GAD1 promoter and 30% within intron 2 (Huang & Akbarian 2007). On the contrary subjects with schizophrenia showed a significant, on average 8-fold deficit in repressive chromatin-associated DNA methylation at this promoter (Huang & Akbarian 2007). It was concluded that chromatin remodelling mechanisms are involved in dysregulated GABA-ergic gene expression in schizophrenia (Huang & Akbarian 2007).

Gene-ontology analysis highlighted epigenetic disruption to loci involved in mitochondrial function, brain development, and stress response (Mill et al. 2008). Methylome network analysis uncovered decreased epigenetic modularity in both the brain and the germline of affected individuals, suggesting that systemic epigenetic dysfunction may be associated with major psychosis. It was also reported that frontal-cortex DNA methylation in the brain derived neurotrophic factor (BDNF) gene is correlated with genotype at a nearby nonsynonymous single nucleotide polymorphism (SNP) that has been previously associated with major psychosis (Mill et al. 2008).

Epigenetic mechanisms could be involved, because for a limited number of genes, the alterations of mRNA levels have been linked to inverse DNA methylation changes at sites of the corresponding promoters. However, results from independent studies have been inconsistent, and when expressed in quantitative terms, disease-related methylation changes appear to be comparatively subtle (Connor & Akbarian 2008). A recent study identified approximately 100 loci with altered CpG methylation in schizophrenia or bipolar disorder, the majority of which were gender-specific (Connor & Akbarian 2008).

This data could indicate that environmental factors have gender specific influence on DNA methylation changes in schizophrenia. However, additional research will be necessary to clarify the origin and timing of these methylation changes in psychosis and to localize the specific cell types. Recent data support the epigenetic theory of major psychosis and suggest that DNA-methylation changes are important to the etiology of psychosis in a gender specific pattern (Connor & Akbarian 2008).

Conclusions

In comparison to female schizophrenia patients male patients have more severely impaired premorbid functioning, earlier onset of the disorder, more severe symptomatology and less favourable outcome. Clinically observed gender differences in schizophrenia are probably influenced by genetic and environmental factors. The interplay between those two sets of factors is mediated by estrogen and epigenetic mechanisms.

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