

PHARMACOGENOMICS OF MENTAL ILLNESSES: DO SEX-SPECIFIC DIFFERENCES MATTER?

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SUMMARY

Objectives: Genetic factors are extensively studied in respect to drug response in psychiatric disorders. Recent evidence suggests that action of reproductive steroid hormones in brain may also have a role.

Methods: Sex-specific differences in terms of illness onset, duration, severity of symptoms and treatment response are well documented. It is believed they result from different brain morphology and function between sexes, factors being highly influenced by sex hormones.

Results: The synergistic effects of the genetic background and potential prenatal stressors may influence the processes of sexual brain maturation, the most vulnerable period for developing susceptibility for psychiatric disorders. A resulting neuroendocrine dysfunction implies inadequate response of brain structures to pubertal flow of circulating sex hormones.

Conclusion: Steroid sex hormones, at least estrogen, are major parts of the communication system in the brain. For that reason, estrogen receptors could be attractive targets in development of new treatment strategies. Potential benefits from compounds mimicking estrogen should be also considered in clinical practice.

Key words: mental illnesses - limbic system – estrogen - estrogen receptors - pharmacogenomics

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INTRODUCTION

The project of human genome sequencing (HUGO) and resulting data about the genetic polymorphisms in humans gave basis for a development of pharmacogenomics, a new area in medicine. Pharmacogenomics uses genetic information to improve patients' treatment outcome assuming that genetic variation between individuals contribute to disease susceptibility and drug response toxicity or efficacy (Pinsonneault & Sadée 2003). Pharmacogenomics appeared to be promising in the context of psychiatric illnesses. It is well known that many patients react adversely to pharmacotherapy with, for instance antidepressants, or do not respond to medication after completing an adequate treatment period. This

means the treatment for patients is being selected in „trial and error“ fashion, since therapists offer different pharmacological agents endeavoring to select the best treatment (Morley & Hall 2004). Information from pharmacogenomic testing may help in selecting the most beneficial drug and dosage for individual patients (Aitchison et al. 2005, Gupta et al. 2006, Tsapakis et al. 2004, Zdemir et al. 2002). Kirchheiner et al. (2001), for instance, made preliminary genetic-based dose recommendations for tricyclic antidepressants and selective serotonin reuptake inhibitors for some of the cytochrome P450 genes. In spite of the fact that genetic polymorphisms in different neurotransmitter receptor and transporter genes, neurotrophic genes and neurotransmitter signaling-related enzymes have already been identified and

correlated to clinical expression of psychiatric illnesses and/or better or worse drug response (Bertolino et al. 2006a, Bertolino et al. 2006b, Bolonna et al. 2004, Bozina et al. 2006a, Bozina et al. 2006b, Contini et al. 2006, Hariri & Holmes 2006, Inada et al. 2003, Kendler et al. 2003, Weickert et al. 2004), pharmacogenomic testing is still far from routine use in clinical practice. Limitations are numerous: many relevant genetic polymorphisms have not yet been found, our knowledge of mechanisms of action of different psychopharmacotherapeutic drugs is obscure and influenced not only by individual genetic make-up but also by non-genetic factors such as drug-drug interactions, physiological and environmental factors (Dorado et al. 2006, Kendler et al. 2005, Sadée 1999). This work will focus on sex-specific differences in clinical presentation and treatment outcome of mental diseases, as well as differences in brain development, structure and function originating from different physiological conditions that the actions of steroid sex hormones in females and males account for. The term „sex“ used in this article refers to biological sex, represented by carriers of the XX or XY chromosomal constitution.

CLINICAL IMPLICATIONS OF SEX DIFFERENCES IN MENTAL ILLNESSES

Sex differences are recognized for different mental illnesses and disorders in the age of onset, severity of the illness, co-morbidity and risk, and can be traced through childhood, adolescence and adulthood. During their lifetime females are twice as likely as men to have panic disorder (5% vs. 2%), agoraphobia (7% vs. 3.5%), posttraumatic stress disorder (PTSD, 10.4% vs. 5%) or general anxiety disorder (6.6% vs. 3.6%). Other disorders such as social anxiety disorder (15.5% vs. 11.1%) and obsessive-compulsive disorder (3.1 vs. 2%) are also more common in females but differences in prevalence are less pronounced. During childhood, conduct disorders with aggressive and antisocial behavior have a higher prevalence among boys than girls. During adolescence, girls are at higher

risk of developing depression and eating disorders, and engage more in suicidal ideation and attempts than boys. Boys, on the contrary, engage more in high-risk behavior and commit suicide more frequently than girls. In adulthood, antisocial behavior and substance use are higher in men (Lynch et al. 2002). Adult women suffer more from depression and anxiety (Kessler 1993) where females outnumber males at a rate 2:1, but these sex differences come to light only after onset of puberty (Pinsonneault & Sadée 2003). Sex differences in affective functioning are also pronounced in schizophrenia (Goldstein & Link 1988).

In schizophrenia, lifetime prevalence is approximately 1-1.5% worldwide in both sexes. However, the illness peaks at ages 15-25 in men and 25-35 in women (Malhotra 2001) with a second peak at a time that coincides with the menopause (after age 44). Furthermore, premorbid adjustment and treatment outcome are more favorable in women. Women respond to antipsychotics faster and at lower doses than men. The symptomatic expression of schizophrenia also differs between the sexes: it is characterized by apathy, flat affect, higher level of cognitive impairment, paucity of speech and social isolation in men, and more often depression in women. Concerning treatment outcome, depressed women were found to have a superior response to monoamine oxidase inhibitors (MAOIs) than men (Quitkin et al. 2002).

All mentioned sex-differences in mental diseases could be, at least partly, attributed to the female reproductive steroid hormone estrogen actions. Estrogen is known to exert neuroexcitatory and neuroprotective actions, and to interfere with neurotransmitter systems in the brain (Goldstein 2007, Greenwood & Parasuraman 2003, Stevens 2002). Estrogen has been proposed as an influencing factor for sex differences in drug abuse (Carroll et al. 2004). Mood swings in women were found to be related to the cyclic rise and fall of estrogen. Infertility or hysterectomy has been found to increase the risk for affective/neurotic syndromes. Women experience premenstrual

dysphoria, postpartum depression, and perimenopausal depression. Thus, reproductive effectiveness in females might be connected to their mental health. Less literature is available on the contribution of the men's reproductive functioning to mental health. However, lower levels of total gonadotropins and testosterone, as well as, abnormal growth hormone response to luteinizing hormone-releasing hormone and thyrotropin-releasing hormone, were reported in unmedicated male schizophrenic patients, relative to age-matched controls (Gil-Ad et al. 1981, Van Cauter et al. 1991), suggesting a possible relationship between reproductive and mental health also in the male sex. This relationship is further supported by the instance of a hypogonadal depression in men.

The limitation in pharmacogenomic studies may further support the fact that the impact of the genetic polymorphisms (e.g. expression of the genes) may differ between males and females due to hormonal influence. An example can be traced to the differences in the developing brain anatomy during the middle and late period of human pregnancy.

SEXUAL DIFFERENTIATION IN THE HUMAN BRAIN

A comparison between schizophrenic patients and control healthy individuals revealed significant brain anatomy differences: larger than normal third and lateral ventricles, and lower than normal volume and number of neurons in one or more thalamic nuclei in the 25-50% patients. In the 10-15% of them a lower than normal volume of the fronto-temporal cerebral gyri and cortex was found (Stevens 2002). Furthermore, the significant sex-dimorphism differences were found in brain areas recognized to be dimorphic in healthy men and women: orbitofrontal cortex, anterior cingulate gyrus, hypothalamus, hippocampus and amygdala (Goldstein 2006, Swaab & Fliers 1985). Hippocampus, anterior cingulate gyrus and orbitofrontal cortex have larger volumes in women while amygdala, hypothalamus, paracingulate gyrus and medial frontal cortex are larger in men. The

cerebrum is larger in men than women by 8-10%, but the difference can not be solely attributed to larger body size. A body of evidence suggests that sex differences in the human brain arise during fetal development in brain regions functionally associated in the arousal circuitry (orbitofrontal cortex, anterior cingulate gyrus, hypothalamus, hippocampus and amygdala) (Swaab et al. 2002), by an interaction of sex hormones and developing neurons, with probable involvement of genetic (mutations and polymorphisms in the sex hormone receptors) and environmental factors (the action of environmental endocrine disrupters). Recent findings of a greater sexual dimorphism in those brain regions having the highest expression of sex steroid receptors during critical periods of brain development argue in favor of this hypothesis. The study in rats showed disruption in the period of sexual differentiation of the brain (last week of rat pregnancy) to cause changes in behavior associated with schizophrenia. Therefore, it was concluded that the period of sexual differentiation of the brain coincides with the period of the highest brain vulnerability for development of susceptibility for schizophrenia (Goldstein 2006). This implies that physiological developmental processes in brain regions showing sexual dimorphism and involving sex hormone actions might have a key role in the etiology of vulnerability for schizophrenia.

A role for both estrogen and testosterone has been established in sexual differentiation of human brain although the effects of estrogen are much better characterized. The primary sites of testosterone action in the brain might be the amygdala and anterior hypothalamus, since RNA metabolism in these two regions of the newborn female rat, responded to testosterone administration quite differently from the rest of the brain (Clayton et al. 1970). These brain regions express both estrogen and androgen receptors (Stevens 2002). The effects of testosterone supplementation in older men were reported to improve certain types of memory (working, verbal and spatial memory), or even limit the death of brain cells. However, it is yet to be determined whether such positive effects are intrinsic to

testosterone since testosterone can be converted to estrogen by the aromatase enzyme in the brain, and it is claimed that testosterone effects overlap with those of estrogen. A role for androgen in the pituitary secretion has been suggested in female rats (Handa et al. 1986). Data from the studies in rats suggest that the structure of the brain is not fixed during fetal development, and not set permanently at birth. It is more probable that sex hormones promote sexual differentiation in female's and male's brains and help maintain sex-specific brain structure and function throughout the whole life (McEwen 1999).

SEX DIFFERENCES IN LIMBIC ACTIVITY AND IMPLICATIONS FOR NEUROENDOCRINE FUNCTION

Limbic system (amygdala, hippocampus, cingulate gyrus and posterior orbitofrontal cortex) integrates arousal, affective stimuli and emotions. Volumetric sex-specific differences in limbic structures may be associated with sex steroid activity early in development and imply significant functional differences of these brain regions between males and females. Sex differences and laterality in the activation of the limbic regions were demonstrated in response to aversive affective stimuli. Women demonstrated greater memory for negatively valenced emotional material and greater responses to aversive cues than men (Bradley et al. 2001, Cahill et al. 2001). The Amygdala, for instance, show a laterality effect in emotion processing in general: 1) The right amygdala shows a more temporally dynamic pattern of response which is associated in men with enhanced declarative memory and induction of negative emotions (Cahill et al. 2001, Schneider et al. 2000). 2) The left amygdala shows a more temporally stable response which in women is associated with enhanced declarative memory and induction of negative emotions (Cahill et al. 2001, Schneider et al. 2000). There are differences in negative emotions and mood induced sex-specific neuronal activity: There is a greater extent of activity in the anterior cingulate gyrus, left insula,

and right orbitofrontal cortex in women than men (George et al. 1996). Sex-specific laterality in brain function may be related to differential distribution of gonadal hormone receptors in the two brain hemispheres i.e. laterality effects in brain activity may vary by sex and hormonal status. Indeed, neuroendocrine activity of limbic regions showed significant differences during the two points in the menstrual cycle in women suggesting hormonal regulation (Goldstein 2005). The study of Herzog (1989) has previously shown a strong reciprocal relationship between limbic regions and the endocrine system. Limbic structures showed neuroprotective or neurotoxic responses to steroids. Other clinical studies have further implicated the amygdala and hippocampus in reproductive endocrine dysfunction in men (Herzog 2002). In conclusion, the limbic structures have an important role in modulating neuroendocrine secretion depending on the specific distribution of the sex steroid receptors in the brain and the level of circulating sex steroid hormones.

THE MULTIPLE ROLES OF ESTROGEN IN THE BRAIN

The role of estrogen in the brain has been recognized in the 1970s, when researchers found evidence of specific estrogen receptors (ERs) in rat brain cells. The primary site of estrogen synthesis are the ovaries but small amounts of estrogen are also synthesized in the brain. Enzymes for steroid synthesis were found primarily in glial cells (Scharfman & MacLusky 2006). Estrogen has a potent neurotransmitter-modulating role and neurotrophic effects (Stahl 1997, Taber et al. 2001). It affects dopaminergic, serotonergic, cholinergic and glutamatergic neurotransmission, it has a role in synaptogenesis and tearing synapses apart, in neuroprotection, modulating neuronal apoptosis, cognitive performance, and affecting gene expression (Scharfman & MacLusky 2006, Stahl 1997, Taber et al. 2001). Estrogen upregulates levels of dopamine and acetylcholine and downregulates levels of serotonin and norepinephrine in the prefrontal cortex (Taber et al.

2001). The neuroprotective effect of estrogen is probably exerted by a mechanism involving genes containing an estrogen response element (ERE), for instance, brain-derived neurotrophic factor (BDNF) gene in chromosome 11p13 (Scharfman & McLusky 2006). The presence of ERE enables direct binding of estrogen and avoiding secondary messenger mechanisms in cell signaling. Thus, estrogen appears to directly induce expression of neurotrophic gene: BDNF. A role of BDNF protein has been extensively studied in hippocampus, the brain region critical for memory. BDNF has a role in maintaining hippocampal neuroplasticity, a process underlying long-term potentiation associated with memory formation (Greenwood & Parasuraman 2003). The BDNF role in the neuroplasticity may also affect brain morphology, as shown for its allelic variants (Agartz et al. 2006). Both steroid and BDNF protein exert their variable effects (neuroprotective or the opposite) in parallel, which is consistent with the mechanism presented above.

Besides having direct effects on gene expression, estrogen acts through its ERs (ER α and ER β). Steroid and BDNF protein seem to induce the same cellular signaling mechanisms via ERs and other receptor complexes, for instance, insulin-like growth factor 1 (IGF-1). ER α appeared to be an integral part of the IGF-1 receptor complex, suggesting that both estrogen and IGF-1 are needed to activate IGF-1 signaling pathway in the cell (Pinsonneault & Sadee 2003).

THE DISTRIBUTION AND ROLE OF ESTROGEN RECEPTORS IN THE BRAIN

ERs are mainly located in several limbic regions implicated in social behaviour, cognition, emotional interpretation and emotional processing. There are at least two forms of estrogen receptors: ER α and ER β , whose distribution covers not only neurons, but also astrocytes, oligodendrocytes and microglia. ERs are recognized as transcriptional factors belonging to the nuclear transcription factor superfamily. Their distribution in cholinergic, serotonergic, dopaminergic, GABAergic, and

glutamatergic neurons and interneurons imply involvement in the interplay between estrogen and neurotransmitter systems. Different studies showed a preferential limbic-related expression of ERs (Östlund et al. 2003). ER α 's locations are primarily amygdala and hypothalamus, while ER β dominates in the hippocampus, entorhinal cortex and thalamus. A role of ER α has been recognized in inflammatory pathways in the brain, as well as in neuronal differentiation and neurite outgrowth, all mediated by estrogen (Mérot et al. 2005; Vegeto et al. 2003). ER α also mediates the estrogen's protective effect against neurodegeneration after endogenous brain injury or during oxidative shock (Mérot et al. 2005). Although, the neuroprotective effect of estrogen is seen in the better recovery of women compared with men after brain injury (Greenwood & Parasuraman 2003), there was no reported difference in the distribution of ER α in the brains of males and females. On the contrary, ER β showed sexually dimorphic distribution in neonatal mice (Kudwa et al. 2005). In their recent study Kudwa et al. (2005) demonstrated the critical role of ER β in the process of defeminization (suppression of female behavior and cyclic pattern of gonadotropins secretion) of the male brain. During late gestation and the first two weeks after birth male mice had significantly higher expression of ER β in the medial basal hippocampus than females. This event coincides with the period of sexual differentiation in the mammalian brain. A role for ER α has been proposed in brain masculinization. Both brain defeminization and masculinization are supposed to arise through fetal brain exposure to testosterone that is aromatized neurally to estrogen. These findings indicate a critical role of ERs and, possibly, the impact of their genetic variation, on sexual differentiation of mammalian brains.

THE IMPLEMENTATION OF ESTROGEN EFFECTS IN PHARMACOGENOMIC RESEARCH

Antipsychotic drugs have variable affinity for different neurotransmitter receptors. A number of

pharmacogenetic studies trying to define the association of dopamine receptors' polymorphisms and response to typical and atypical antipsychotic medication, connected few dopamine receptor 2 (DRD2) and dopamine receptor 3 (DRD3) polymorphisms with a favorable response (Scharfetter 2004). Anttila et al. (2004) reported an interaction between polymorphisms in NOTCH4 and catechol-o-methyl transferase (COMT), potential schizophrenia-susceptibility genes, to poor response to neuroleptics.

Alteration of the gene expression, a known long-term effect of antipsychotic medication implies involvement of transcriptional factors. It is interesting that estrogen colocalizes with some neurotransmitters. ERs are, for instance, placed in the serotonergic neurons of the dorsal raphe nucleus (having role in facilitating neurotransmission), in numerous cholinergic terminals in the amygdala projecting from the basal forebrain, and in GABAergic hippocampal interneurons promoting formation of new dendritic spines and synapses (Taber et al. 2001). If we assume a sharing or close relationship of binding sites between particular antipsychotic drugs and ERs, the modifying role of estrogen to antipsychotic treatment outcome may be postulated.

In the etiology of major depression, an association was found for the serotonin transporter promoter polymorphism (short/long allele) in individuals with a history of stressful early life events (Caspi et al., 2003; Kendler et al., 2005). The same polymorphism was found to affect the clinical response to a class of antidepressants, the selective serotonin reuptake inhibitors. Polymorphisms of the cytochrome P450 (CYP) family genes CYP2D6 and CYP3A affected antidepressant drug plasma level and were shown to have clinical importance in treatment response to a large number of neuroleptic drugs (Berecz et al. 2004, Jung et al. 2005, Vandel et al. 2007). A few studies investigated polymorphisms in multidrug resistant protein (MDR1) gene and treatment response, with opposite results, probably reflecting ethnical differences in allelic frequencies (Bozina et al. 2006, Yasui-Furukori et al. 2006). Recent

evidence showed polymorphisms in genes regulating the hypothalamic-pituitary-adrenal axis to have an important impact on response to antidepressant therapy (Binder and Holsboer 2006). Licinio et al. (2004) suggested a role of polymorphism in corticotrophin-releasing hormone receptor 1 (CRHR1) and other genes in stress-inflammatory pathways to be involved in response to antidepressant treatment. These findings directly incorporate estrogen into mediating antidepressant treatment response. A new evidence of involvement of ER β in the hippocampus in the anti-anxiety and anti-depressive effects of estrogen comes from the study of Walf and Frye (2007), making ER β an attractive target for antidepressant therapy. Potential benefits from compounds mimicking estrogen should be also considered in clinical practice.

CONCLUDING REMARKS

The causal relationship between the action of estrogens and neuroendocrine hormones, and sex-specific brain morphology and function has been established. Hormonal interaction with different brain structures is achieved by their direct action on ERE containing genes or mediated by ERs expressed preferentially in the limbic area in the brain. The middle to late period of pregnancy was shown to be critical for sexual brain differentiation. The effects of potential prenatal stressors during that time may be expressed as abnormalities of the sexual maturation of a specific brain region (preferentially amygdala and hippocampus involved in the regulation of behavior, emotion and affect), and consequently neuroendocrine dysfunction. Neuroendocrine dysfunction including gonadotropin-releasing and corticotropin-releasing hormones and morphological changes in the sexually dimorphic brain regions were found in schizophrenic patients, suggesting that abnormalities of the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes, established during the prenatal period of high brain vulnerability, may represent a part of the susceptibility for schizophrenia, depression,

anxiety and other psychiatric disorders. The effects of abnormalities of the HPG and HPA axes appear during the period of life characterized by dramatic endocrine changes such as pubertal maturation. In this context, especially in pharmacogenomic studies, morphologic and functional sex-specific differences, resulting from actions of sex steroid hormones in the brain, must be always considered.

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