PSYCHOSIS AND DEPRESSION – A NEUROBIOLOGICAL VIEW

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SUMMARY

Psychosis and depression are syndromes that affect the most basic human processes of perception and judgment. Traditional dichotomous classification of psychotic and affective disorders resolved in strict separation between schizophrenia on one hand and bipolar disorder and recurrent depressive disorder on the other hand. However, it is not uncommon that depression and psychosis as syndromes are expressed together in the course of the same mental disorder. According to recent knowledge on the molecular level there are probably many multiple susceptibility genes involved in the pathogenesis of both psychotic and affective disorders, each of small effect, which act in conjunction with environmental factors. Research data indicates a significant overlap in genetic susceptibility across the traditional classification categories of psychotic disorders and affective disorders. It seems that a new classification and research approach will provide better understanding of severe mental disorders and explain the usefulness of some medications in different groups of these disorders.

Key words: psychosis – depression – schizophrenia – genes - neurobiology

Introduction

Psychosis and depression are syndromes that affect the most basic human processes of perception and judgment. Psychotic disorders, with schizophrenia as the most researched, are a group of disorders characterized by psychotic symptoms, by a disruption of cognitive and integrative mental functions, by affective changes and by a severe lack of insight. On the other hand depression is the most frequent syndrome observed in affective disorders. Traditional dichotomous classification by Krepelin of the so-called “functional” psychoses resolves in strict separation between schizophrenia and bipolar disorder (Krepelin 1919). However, it is not uncommon that depression and psychosis as syndromes are expressed together in the course of the same mental disorder. From the neurobiological point of view, mental disorders could be evaluated on molecular, cellular, and systems-level. According to recent knowledge on the molecular level there are probably multiple susceptibility genes involved in the pathogenesis of psychotic and affective disorders, each of small effect, which act in conjunction with environmental factors (Berrettini 2003, Badner & Gershon 2002). These genes could influence synaptic plasticity, neurodevelopment and neurotransmission. However, new data from genetic studies do not fit well in the dichotomous model of psychoses (Craddock et al. 2006). Genetic studies of schizophrenia, major depressive disorder and bipolar disorder are beginning to identify proteins of candidate genetic risk factors for these disorders. However significant overlap in genetic susceptibility across the traditional classification categories has been reported (Craddock et al. 2006).

Schizophrenia and brain dysfunction

Pathogenesis of schizophrenia is among the most examined mental disorders. It is known that schizophrenia is influenced both by genes and the environment (Frangos et al., 1985). However, the genetic influence seems to be predominant. Current neurobiological data suggest the hypothesis that schizophrenia is characterised by hypoglutamatergic and hyperdopaminergic neurotransmission. It is assumed that the disease is related to over stimulation of subcortical type 2 dopamine receptors, hypoactivity of frontal cortical type 1 dopamine receptors and reduced prefrontal glutamatergic activity (Goldman-Rakic et al. 2004; Laruelle et al. 2003). A meta-analysis of 13 in-vivo studies which revealed 12% elevated type 2
dopamine receptor density in drug-naïve and in drug-free schizophrenia patients (Laruelle 1998) supports the type 2 dopamine receptor hyperactivity hypothesis. However, not only neurotransmitter activity but also synaptic changes were observed in the prefrontal and temporal cortex, hippocampus and caudate nucleus. Reductions in dendritic length, spine density and arborisation of receptive cells were reported (Garey et al. 1998, Glantz & Lewis 2000, Rosoklija et al. 2000). It seems that not only neurons per se but also other systems are involved in the pathogenesis of schizophrenia. It was reported that decreases in oligodendrocyte density of ~20-30% was found in various frontal cortical regions in schizophrenia (Hof et al. 2002, Hof et al. 2003, Uranova et al. 2004, Vostrikov et al. 2004). Another important issue seems to be increased oxidative stress reported in schizophrenia. Large reduction in cerebral and CSF glutathione levels was reported in schizophrenia (Do et al. 2000). Numerous publications support the involvement of free radicals and oxidative stress in the pathogenesis of schizophrenia (Mahadik & Shafer 1996, Reddy & Yao 1996, Yao et al. 2001, Carter 2006). Regarding these data, it was suggested that genes associated with schizophrenia tend to cluster in families that can be related to some of the key pathological processes of this disease (glutamatergic and dopaminergic dysfunction, synaptic plasticity, oligodendrocyte cell loss and oxidative stress) (Carter 2006).

Dopaminergic dysfunction is not restricted only to the synaptic cleft but involves also post-dopamine receptor signalling (Amar et al., 2008). Activation of the type 2 dopamine receptor leads to down-regulation of cyclic AMP production resulting in decreased phosphorylation of proteins including GSK-3beta (Li et al. 2000). It was also reported, that GSK-3beta enzyme is not regulated only at transcriptional level but also by phosphorylation which seems to be involved in antipsychotic drug action (Beaulieu et al. 2004, Beaulieu et al. 2005, Emamian et al. 2004, Svenningson et al. 2003). Further it was reported that atypical antipsychotics inhibit GSK-3 activity (Li et al. 2007) and haloperidol and clozapine elevate the levels of inactive phosphorilated GSK-3beta (Kang et al. 2004, Kozlovsky et al. 2006).

Overlapping of genetic factors

Numerous genes have been connected with the pathogenesis of schizophrenia, including dysbin-
susceptibility between schizophrenia and bipolar disorder (McGuffin et al. 1982, Cardno et al. 2002).

Conclusions

Research data indicates a significant overlap in genetic susceptibility across the traditional classification categories of psychotic disorders on the one hand and affective disorders on the other. It seems that new classification and research approaches will provide a better understanding of severe mental disorders and explain the usefulness of some medications in different groups of these disorders.

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