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PSYCHOSIS AND DEPRESSION – A NEUROBIOLOGICAL VIEW

Peter Pregelj

University Psychiatric Hospital, Studenec 48, Ljubljana, Slovenia

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*

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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

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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).

Dopamineric 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 phosporylation 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 dysbindin, neuregulin 1, DAOA, COMT, BDNF and DISC1, and neurobiological studies of the normal and variant forms of these genes are now well justified (Carter 2006). However, many of these candidate genes have been found connected also with affective disorders suggesting overlap in genetic susceptibility (Craddock et al. 2006). Probably the best example of one gene involvement in different severe mental disorders is the DISC 1 gene. A Scottish family with a high loading of major mental disorders which cosegregates with a t (1; 11) was reported (St Clair et al. 1990). Long term follow up of this family has reported 87 family members, of whom 37 carry the translocation (Blackwood et al. 2001). Out of 29 family members carrying the translocation, for whom psychiatric assessment was possible, 7 have a diagnosis of schizophrenia, 1 has a diagnosis of bipolar disorder and 10 individuals has recurrent major depressive disorder (Blackwood et al. 2001). On the contrary, none of 38 individuals without translocation have a diagnosis of serious mental disorder (Blackwood et al. 2001). These data provide a strong link between the t (1;11) and the psychiatric liability in this family. No evidence for schizophrenia susceptibility at the breakpoint on chromosome 11 was found (Devon et al. 1997, Millar et al. 1998). The investigation of chromosome 1 component of the translocation has revealed the DISC 1 and DISC 2 genes (Millar et al. 2000, Millar et al. 2001). A very large number of potential DISC 1 interactions have been identified and the majority can be loosely classified into the following groups: cytoskeleton, cell cycle, signal transduction, intracellular transport/exocythosis, golgi and central nervous system development (Chubb et al. 2008). It seems that in some cases were DISC 1 is not directly implicated, variants acting on its binding partners and other risk factors may act instead to confer risk of schizophrenia and depression (Chubb et al. 2008).

Also some studies have shown that bipolar disorder occurs at increased rates in relatives of probands with schizophrenia (Tsuang et al. 1980) and that schizophrenia occurs at increased rates in relatives of probands with bipolar disorder (Vales et al. 2000). The same was true for shizoaffective disorders which occur at increased frequencies in families of probands with bipolar disorder (Rice et al. 1987) and schizophrenia (Kendler et al. 1998). Also some twin studies unconstrained by the diagnostic hierarchy revealed an overlap in genetic

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 approachs 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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Correspondence:

Peter Pregel
University Psychiatric Hospital
Studenec 48, Ljubljana, Slovenia
E-mail: peter.pregelj@psih-klinika.si