EDITORIAL

Special Issue: Molecular Mechanisms of Schizophrenia

Schizophrenia has been one of the most elusive brain disorders to understand. Part of the problem lies in the complexity of its presentation, which cannot be defined by any single symptom or pathophysiological brain change. Equally perplexing is the identification of the genes and their products that serve as vulnerability factors for schizophrenia. Despite a number of promising candidate genes identified there is no single gene whose association with schizophrenia has been replicated in every study population, although there are a number of candidates that are increasingly being implicated in the disease. Indeed, the diversity of molecular mechanisms presented in this issue of *Biological Psychiatry* illustrates how difficult it has been to elucidate a comprehensive pathophysiology of schizophrenia.

Since we have moved beyond the dopamine hypothesis of schizophrenia in favor of more sophisticated models based on the many biological abnormalities identified, how do we reconcile such a diversity of proposed causes? Moreover, can we completely abandon the dopamine hypothesis in light of the fact that some symptoms common amongst all patients with schizophrenia (hallucinations, delusions, disorganized speech and behavior) respond, albeit variably, to dopamine D2 receptor antagonists in the majority of patients? Furthermore, the supersensitivity of most schizophrenic patients to dopamine agonists supports dopaminergic dysfunction in schizophrenia as a common feature of the illness. Given all this it seems reasonable to speculate that the numerous distinct neurodevelopmental, neural circuitry, genetic and biochemical processes identified thus far all contribute to the development of schizophrenia by ultimately converging on dopamine neurotransmission to produce dysregulation in that system. Moreover, it may be the interplay of genetic, environmental and stochastic factors during development which determines if the pathophysiological processes mediating between predisposing genes and the clinical manifestations of schizophrenia will ultimately result in the full phenotype of schizophrenia, or will end in an intermediate phenotype.

While this may seem an oversimplification of a comprehensive pathophysiologic process associated with schizophrenia, as may be argued by those proponents of a disconnection hypothesis for schizophrenia, the cellular and molecular mechanisms of dopamine influenced cortical network activity is more complex than that depicted by the original and even revised dopamine hypothesis (Davis et al 1991). Dopamine appears to be critically involved in maintaining the balance of excitatory-inhibitory synaptic interactions between elements of the prefrontal cortex, thalamus and striatum in order to achieve stability of cortical network activity.

Indeed, there is growing evidence of the convergence of a number of diverse biological abnormalities associated with schizophrenia on to a dopamine abnormality in schizophrenia. For example, neurgulin-1 which has a role in dendritic morphogenesis and the expression and activation of multiple neurotransmitter receptors is being increasingly recognized as a susceptibility gene for schizophrenia (including data presented by Walss-Bass et al 2006, in this issue). A significant reduction in the number of N-methyl-D-aspartate (NMDA) receptors has been observed in neuregulin-1 mutant mice (Stefansson et al 2002) which also exhibit disruptions of prepulse inhibition (characteristic of the sensory motor gating abnormalities of schizophrenia). Moreover, neuregulin-1 induced suppression of NMDA receptor activation is increased in the prefrontal cortex of schizophrenic patients (Hahn et al 2006). Given that D1 dopamine and NMDA receptors interact bi-directionally in the prefrontal cortex it is not unreasonable to predict an indirect D1 effect by neuregulin-1 in the prefrontal cortex. Indeed, there are data indicative that neuregulin directly modulates the activity of mesostriatal dopaminergic neurons (Yurek et al 2004).

These data lend support to the NMDA receptor hypofunction hypothesis of schizophrenia and further demonstrate the convergence of these biological abnormalities to a dopaminergic common pathway. While phencyclidine (PCP) and ketamine are known NMDA glutamate receptor antagonists, these drugs have a dopamine altering effect. When administered to healthy humans, PCP produces symptoms resembling schizophrenia. The subchronic administration of PCP to rats produces synaptic pathology (Hajszan et al 2006, in this issue) and a sustained reduction of dopamine utilization in the prefrontal cortex (Jentsch et al 1997) associated with impairment of spatial working memory task performance characteristic of the cognitive impairment of schizophrenia (Jentsch et al 1997).

The elucidation of NMDA's putative role in the pathophysiological pathway of schizophrenia has been helpful in the elucidation of novel treatments. Indeed, pharmacological agents that enhance NMDA function through either the glycine modulatory site directly (D-serine, glycine, or D-cycloserine) or through inhibition of the glycine transporter 1 (sarcosine) seem to improve positive, negative and cognitive symptoms of patients with schizophrenia. Interestingly, these glycine modulatory site agents have proven effective when given as adjunctive treatment to other antipsychotics except for clozapine. A similar negative interaction between the glycine transporter 1 inhibitor sarcosine and clozapine is demonstrated by Lane and colleagues (2006) in this issue. Furthermore, intracellular recordings demonstrate that clozapine produces greater NMDA-induced currents in pyramidal cells of the medial prefrontal cortex than risperidone, and that sarcosine potentiates NMDA-induced currents produced by risperidone but not by clozapine (Konradsson et al 2006). These data may explain the lack of beneficial clinical results when using agents which enhance NMDA function as adjuvant treatment to clozapine and may explain, at leat partially, clozapine's superior efficacy as an antipsychotic.

While abnormalities of the prefrontal cortex seem to be a principal component of the pathology of schizophrenia, hippocampal pathology has been reported as well. Through a series of interactions this hippocampal pathology may produce the observed prefrontal pathology of schizophrenia and ultimately the dopamine dysregulation of schizophrenia as well. Neonatal ventral hippocampal lesions to rats has been proposed as a developmental model of schizophrenia because of numerous similarities between this model and schizophrenia. Excitotoxic ventral hippocampal lesions in neonatal rats produces abnormalities in dopamine mediated behaviors including exaggerated locomotor responses to amphetamine, increased stereotypies, deficits in prepulse inhibition and impaired working memory. Interestingly, these behaviors emerge only postpubertally and some are ameliorated by antipsychotic medication. These neonatal ventral hippocampal lesions also lead to molecular and functional changes in the prefrontal cortex such as altered

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dendritic morphology of pyramidal neurons and altered neurophysiologic properties such as hyperexcitability and a reduced ability to further increase activity with increasing stimulation of the ventral tegmental area (Tseng et al 2006, in this issue). Consistent with the timing of the behavioral changes reported in the neonatal ventral hippocampal lesioned rats is altered expression of the nuclear orphan receptor gene Nur77 (reduced in prefrontal and cingulate cortices). Interestingly, the pattern of distribution of Nur77 is closely related to dopamine systems. In this issue Gilbert and colleagues (2006) demonstrate that genetic disruption of Nur77 alters dopamine activity such that Nur77 deficient mice display increased locomotor activity and increased sensitivity to dopamine agonist. Moreover, the expression of catechol-o-methyl transferase (COMT) is significantly reduced in these Nur77 deficient mice. Finally, the growing evidence of a DISC1 (disrupted in schizophrenia) association with susceptibility to schizophrenia (including the work of Liu et al 2006, in this issue) is relevant to this discussion because it may confer susceptibility to schizophrenia via structural and functional alterations in the hippocampal formation (Callicott et al 2005).

Given the heterogeneity of the genetic and pathophysiological components of schizophrenia it is becoming clear that schizophrenia will not be amenable to traditional genetic linkage approaches assuming inheritance of a single major gene will result in the expression of schizophrenia as if it were a binary trait. Instead, evidence points to multiple genes of small effect contributing to increasing risk for schizophrenia, which will only result in expression of the disorder when, in combination with other liability factors, some putative threshold is crossed. A promising approach to overcome this complexity is to dissect schizophrenia into its more discretely determined neurobehavioral sub-components, termed intermediate phenotypes. The expression of these intermediate phenotypes vary quantitatively among at risk individuals according to their genetic liability for schizophrenia (eg. genetic proximity of unaffected individuals to persons with schizophrenia). Therefore, clinically unaffected relatives of patients with schizophrenia are very informative for genetic linkage studies. The utility of this approach is demonstrated in studies using neurocognitive deficits as intermediate phenotypes. For example, spatial working memory deficits worsen with increasing genetic loading for schizophrenia among twins discordant for schizophrenia and control twins (Glahn et al 2003). Paralleling these findings Cannon and colleagues (2002) show that structural abnormalities of dorsolateral prefrontal regions is associated with genetic proximity to schizophrenic patients. Winterer and colleagues (2006, in this issue) show that another intermediate phenotype characterized by increased variability of stimulus induced prefrontal electrophysiological activity (prefrontal noise) is increasingly associated with lower activity genotypes for COMT via increased dopamine signaling.

The cortical auditory processing abnormalities studied by Ahveninen and colleagues (2006, in this issue) represent another promising intermediate phenotype to study the molecular genetic basis of schizophrenia. These cortical auditory processing abnormalities are present in schizophrenic patients and in their unaffected co-twins, and the magnitude of this abnormality is correlated with the genetic resemblance of the unaffected subjects to the schizophrenic subjects (Ahveninen et al 2006, in this issue). Moreover, functional polymorphisms of the schizophrenia susceptibility gene encoding the alpha 7 neuronal nicotinic acetylcholine receptor are associated with cortical auditory processing abnormalities (Leonard et al 2002). Given the relationship of this neurobiological deficit to broader neuropsychological deficits in schizophrenia, the alpha 7 nicotinic receptor has been identified as a potential pharmacological target to address the cognitive impairment of schizophrenia as is tested in the paper by Schubert and colleagues (2006) in this issue.

Given the considerable challenges psychiatric investigators have had to face in their attempts to unravel the complex molecular mechanisms of schizophrenia it is becoming evident that the field has evolved from an earlier atmosphere of pessimism to an environment in which the pursuit of multiple, yet convergent, molecular pathways is enabling rapid progress in our understanding of the illness and the development of new treatments.

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