Bridging pharmacology and neurodevelopment in schizophrenia

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A brief history of schizophrenia research

At the beginning of the 20th century, when neuropathologists had long searched without success for the neural basis of schizophrenia, this field was called a ‘graveyard for neuropathologists’. This disappointment opened the door for psychiatrists to focus on psychopathology.

The discovery of antipsychotic agents in the 1950s provided a clue to understanding the pathology of this difficult disease. The anti-dopaminergic effect of antipsychotics, together with the induction of psychotic symptoms by psychostimulants, supported the dopamine hypothesis. On the other hand, phencyclidine (PCP) was found to cause symptoms resembling both positive and negative symptoms of schizophrenia. Since PCP inhibits the NMDA-type glutamate receptor, a glutamatergic hypothesis for schizophrenia was proposed.

Starting in the 1970s, neuroimaging studies showed that patients with schizophrenia have ventricular enlargement and reduced hippocampal volume (Suddath et al., 1990). These studies revived the research focus on neuropathology; reduced hippocampal volume without gliosis was thought to reflect a neurodevelopmental abnormality that leads to schizophrenia.

Genetic factors are well-established risk factors for schizophrenia. Initial genetic association studies focused on pharmacology-related candidate genes, such as the dopamine D2 receptor gene (Arinami et al., 1994). However, recent candidate genes derived from whole genome linkage analysis, such as DTNBP1 (Straub et al., 2002) and NRG1 (Stefansson et al., 2002), do not seem to have a direct relationship to dopaminergic or glutamatergic neurotransmission. Now, researchers are trying to combine these genetic findings into a pharmacological hypothesis. One of the most established genetic factor for schizophrenia, DISC1 (Millar et al., 2000), is thought to be directly related to neurodevelopment (Ozeki et al., 2003), but its relevance to a pharmacological hypothesis awaits further elucidation.

Thus, a neurodevelopmental hypothesis is now emerging from the integration of genetic, neuroimaging and post-mortem brain findings in schizophrenia. However, it is not well understood how a pharmacological hypothesis of schizophrenia can be integrated with a neurodevelopmental hypothesis.

Is there a critical period for schizophrenogenic agents?

Nishikawa has long been trying to answer this important question with special attention to the developmental features of schizophrenia and its pharmacological models (Nishikawa et al., 1993). The repeated administration of psychostimulants such as amphetamines and cocaine is known to cause an enduring enhancement of their psychotomimetic effects in humans and experimental animals (Sato et al., 1992). This phenomenon is referred to as behavioural sensitization or ‘reverse tolerance’ and has widely been accepted to be a model for the onset and/or relapse of schizophrenia, because (1) the abuse of these psychostimulants often results in schizophrenia-like hallucinations and delusions, and (2) a subpsychotomimetic dose of a psychostimulant has been described to reactivate these positive symptoms in remitted schizophrenic patients (Lieberman et al., 1987). Interestingly, a long-lasting behavioural sensitization is not observed when the psychostimulants are repeatedly administered during the pre-weaning period of the rodents (Fujiwara et al., 1987; Nishikawa...
et al., 1993). Moreover, amphetamine and methylphenidate are less psychotomimetic before than after puberty, as is evidenced by widespread use of psycho-stimulants in children for the treatment of attention deficit hyperactivity disorder (Rapoport et al., 1978).

In other words, there seems to be a critical period for the development of behavioural sensitization. The importance of this finding is highlighted by the fact that the onset of schizophrenia is always after puberty. This implies that the neural circuit responsible for the sensitization phenomenon and schizophrenia matures during puberty. Based on this evidence, Nishikawa invented his original research strategy to identify the neural circuit responsible for schizophrenia.

Nishikawa and colleagues found marked developmental changes in the patterns of psychotomimetic-induced c-fos gene expression especially in the neocortex, indicating the late-developing nature of the schizophrenia-related neural circuits (Nishikawa et al., 1993; Sato et al., 1997). They further searched for genes induced by methamphetamine (MAP) ‘after puberty’ [postnatal day (PD) 50] in rats, but not altered by MAP ‘before puberty’ (PD 8). Using an RNA arbitrarily primed PCR (a differential cloning) technique, they identified such a new transcript, and named it methamphetamine responsive transcript 1 (mrt1).

The other story: d-serine

Nishikawa and colleagues first demonstrated that d-serine is present in the mammalian brain at a high content throughout life with the NMDA receptor-like distribution (Hashimoto et al., 1992), which overturned the presumption that D-amino acids are uncommon in mammalian tissues. This discovery originated from Nishikawa’s efforts to find a new treatment strategy for schizophrenia by enhancing NMDA receptor function (Nishikawa et al., 1991). He focused on d-serine and D-alanine, as agonists of the glycine site of NMDA receptors (Nishikawa et al., 1991; Tanii et al., 1994). According to his idea to develop a ‘lipophilic D-serine or D-alanine compound’ that could penetrate into the brain as a potential antipsychotic agent (Nishikawa et al., 1991), Nishikawa and associates synthesized N-myristoyl-d-serine (NMD-Ser) (Tanii et al., 1991). They subsequently found attenuating effects of NMD-Ser on PCP-induced abnormal behaviour as an animal model of schizophrenia (Tanii et al., 1991). Nishikawa attempted to validate the possible accumulation of d-serine following the expected penetration of externally administered NMD-Ser into the brain and planned to measure the brain d-serine concentrations in the rats treated with these agents. Surprisingly, d-serine was detected in the control rats that were not treated with these myristoyl-D-amino acids and Nishikawa hypothesized the close correlation between the distribution of the brain d-serine and NMDA receptor during development and ageing. This serendipitous finding that d-serine exists in the brain provoked a new area of research on d-serine in neuroscience (Martinou et al., 2006; Nishikawa, 2005), as most of the readers of this journal will be aware of.

Agonists of the NMDA glycine site, or inhibitors of glycine transporters, are promising candidate antipsychotics (Lindsay et al., 2006). Moreover, the role of d-serine in the pathophysiology of schizophrenia is attracting attention. Whereas the glycine-binding site of the NMDA receptor was reported to be increased (Ishimaru et al., 1992), there was no significant alteration of d-serine levels in the post-mortem brains of patients with schizophrenia (Kumashiro et al., 1995). On the other hand, decreased levels of d-serine in the serum of patients with schizophrenia were reported (Hashimoto et al., 2003). G72, a promising candidate gene identified on 13q34, encodes D-amino acid oxidase activator (DAOA) (Detera-Wadleigh and McMahon, 2006). D-serine is thought to be synthesized by serine racemase, and metabolized by D-amino acid oxidase. Whereas association of the serine racemase
gene with schizophrenia is debatable (Yamada et al., 2005), PICK1, which encodes a serine racemase-binding protein, was found to be associated with schizophrenia (Fujii et al., 2006).

Although the relationship between genetic deficits in the D-serine system and neurodevelopment in schizophrenia is still unknown, Nishikawa points out that, during the postnatal development, brain D-serine and the NMDA receptor R2B subunit show similar distribution patterns that mature around the critical period for the schizophrenenogens (Nishikawa, 2005). Together with the involvement of the R2B subunit and D-serine in the neuronal network formation, these findings allow him to postulate that the maldevelopment of the D-serine–NMDA receptor system could also be connected to the age-dependent onset of schizophrenia. To obtain insight into the molecular basis of this possibility as well as D-serine metabolism, schizophrenia. To obtain insight into the molecular function of such a molecule will facilitate understanding of the relationship between altered D-serine metabolism and the neurodevelopmental hypothesis of schizophrenia.

Conclusion

There are several research approaches to understanding the pathophysiology of schizophrenia, such as pharmacological, neuropathological, neuroimaging, and genetic studies. The unique approach by Nishikawa’s group integrates these lines of evidence into one picture. Their studies show promise as a remedy for the ‘disorganization’, and chronic lack of coherence, in the field of schizophrenia research.

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Statement of Interest

None.

References


