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Dopamine Dysfunction in Schizophrenia and its Significance

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About the Study

Current Antipsychotic Drugs (APDs) operate on D2 receptors, and preclinical studies show that D2 antagonist injection consistently downregulates spontaneously activated DA neurons by causing overexcitation-induced inactivation of firing (depolarization block). Animal models of schizophrenia based on Moderate Acute Malnutrition injection during pregnancy yield offspring with adult characteristics compatible with schizophrenia, such as ventral hippocampus hyperactivity and DA (dopamine) neuron overactivity. The MAM model demonstrates that APDs behave differently in a hyperdopamineregic system than in a normal one, including rapid onset of depolarization block in response to acute D2 antagonist administration and downregulation of DA neuron population activity in response to acute and repeated D2 partial agonist administration, which are not observed in normal rats.

On the basis of the hypothesis that glutamatergic dysfunction is key to schizophrenia pathophysiology, several target drugs have been designed. Despite showing promise in preclinical studies, none of the innovative medications made it through clinical trials. However, preclinical research is often conducted in normal, drug-free rats, whereas models with disease-relevant pathology and past APD exposure may increase prediction validity. Indeed, continuous D2 antagonist therapy causes permanent DA hypersensitivity in MAM animals, interfering with the response to medicines that address upstream pathophysiology. Furthermore, MAM rats demonstrated that the peri-pubertal phase is a stress-sensitive window that may be targeted to avoid MAM disease in adulthood.

Neurodevelopmental models, such as the MAM model, can thus be used to evaluate possible pharmacotherapies for treating schizophrenia in its early phases. The DA hypothesis of schizophrenia proposes that psychotic symptoms are caused by activation of the DA system. Patients with schizophrenia who respond to current therapies consistently have higher levels of presynaptic DA function than healthy controls. Early crucial investigations in patients examined radio-ligand displacement from DA receptors as a marker of DA release using Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging. Patients with schizophrenia had more DA release in the striatum at rest and in response to amphetamine than healthy controls. Furthermore, greater DA signal is associated with increasing symptom severity. Patients with schizophrenia also have a higher potential for striatal DA production, as determined by fluorodopa absorption into DA terminals. Individuals at Ultrahigh Risk For Psychosis (UHR) have enhanced DA system response capacity, with additional increase related with the development of psychosis. Although measurements of DA function are good predictors of psychosis in individuals, there are difficulties in selecting adequate animal models to examine DA impairment in schizophrenia. The action of medicines that elicit psychotic states is studied in pharmacological models of schizophrenia. NMDA receptor antagonists, such as Phencyclidine (PCP) and ketamine, cause psychotomimetic effects in healthy persons while exacerbating symptoms in schizophrenia patients. Acute ketamine and PCP treatment raises striatal DA levels in rats and healthy human volunteers. Chronic administration of an NMDA receptor antagonist, on the other hand, has been demonstrated to have no effect on striatal DA levels. Based on clinical data that acute treatment might enhance DA efflux and aggravate symptoms in patients, amphetamine has also been investigated as a schizophrenia model. Prolonged amphetamine usage in the general population can result in paranoid psychosis, however by the time an individual becomes addicted to amphetamine, the substance produces a comparatively tiny amount of DA compared to the original dose. Both NMDA receptor antagonists and amphetamine exhibit considerable variances in their acute and chronic effects, which influence the conclusions that may be derived from their usage in animal models.

Neurodevelopmental animal models are founded on the idea that aberrations from normal maturation might result in long-term brain alterations. The structural and functional defects caused by early-life insults frequently do not manifest themselves fully until maturity. As a result, developmental models are useful for identifying processes by which a triggering event might proceed into a pathological state and assessing preventative measures that could be used in the prodromal stage. Environmental manipulations that cause early-life stress, like as social isolation or mother separation, can have developmental implications. Adversity in childhood and adolescence can affect the development of circuits that underpin emotional function, and the consequent hyper-responsivity to stress is a key component of many mental diseases.

A substantial amount of research points to stress as a risk factor in the development of schizophrenia. The relationship between early life stress and the degree of positive feelings may be explained in part by the interplay between stress and the DA system. When compared to healthy controls, both UHR persons and schizophrenia patients have increased DA release in response to stress. Furthermore, peri-pubertal stress in rats has been demonstrated to enhance DA neuron activity in adulthood, suggesting that stress before or during puberty has a special influence on the DA system's responsiveness.

The Neonatal Ventral Hippocampal Lesion (NVHL) model was the first to test the notion that abnormal development of the Ventral Hippocampus (vHPC), a key location of pathology in the schizophrenia,

might mirror schizophrenia's developmental history. The model demonstrated that a vHPC lesion in the early postnatal period causes the adult emergence of behavioural impairments and DA dysfunction associated with schizophrenia. Developed by the NVHL model's findings and research establishing the role of immune activation during pregnancy as a risk factor for schizophrenia, another significant neurodevelopmental model of schizophrenia, the Methylazoxymethanol Acetate (MAM) model, was established.