Pharmacological Models of Psychosis – Amphetamine and Ketamine

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Introduction

Although substance abuse disorder is a common comorbidity of mental illness, it is particularly prevalent in patients with schizophrenia1. One of the most widely held explanations for this phenomenon is the self-medication hypothesis2,3 which is based on the negative reinforcement theory; that is the behaviour is reinforced by the purposeful removal of aversive experience, which could be disease symptoms and/or side effects of the medication. However recent studies on the neuropathology of schizophrenia and addiction behaviour have provided an alternative hypothesis. It has been suggested that there is a common neuropathological substrate independently causing the manifestation of symptoms of schizophrenia and addiction disorder. There are substantial literature suggesting that the mesolimbic dopamine (DA) system is a major substrate for reinforcement effects of substance and involving in mediating drug craving. The mesolimbic DA system is also an important system involved in the neuropathology of schizophrenia1. In fact, studies of pharmacological models of psychosis using different psychoactive substances have provided further evidence on this hypothesis and also improve our understanding of the biological basis of psychotic symptoms and the disorder as a whole. This article aims at providing further understanding of the dopamine hypothesis of schizophrenia through brief discussions on two commonly studied pharmacological models of psychosis – Amphetamine and Ketamine.

Dopamine Hypothesis of Psychosis – Amphetamine Model of Psychosis

It was first proposed that the hyperactivity of dopamine transmission is responsible for the psychotic symptoms3. This was supported by the correlation of the clinical dose of antipsychotic drugs and their potency in blocking the dopamine D2 receptors6,7 mainly in the subcortical regions. Further evidence has been accumulated using amphetamine challenge. Amphetamine is an indirect-acting dopamine agonist which increases dopamine levels in the synaptic cleft by inhibiting the action of the dopamine transporter8. High dose repeated administrations of amphetamine to normal volunteers result in paranoid symptoms and formal thought disorders9. More recently, studies using imaging techniques such as PET and Single Photon Emission Computed Tomography (SPECT) during amphetamine challenge have shown that there is an elevation in the binding of dopamine at the D2 receptors after amphetamine challenge in schizophrenic patients compared to age-matched controls, and the elevation is associated with positive psychotic symptoms10,12.

However, there is little indication that amphetamine psychosis provides a model of negative symptoms. Some studies have shown a decreased dopamine turnover13,14 and hence raised a possibility of hypoactive dopamine system involvement. This has led to the revision of the classical hypothesis of schizophrenia. The hyperactive subcortical mesolimbic dopamine projection (hyperstimulation of the D2 receptors) is associated with positive psychotic symptoms; while hypoactive mesocortical dopamine projection (hypostimulation of D1 receptors) is associated with negative and cognitive symptoms15,16. Consistent with this, pre-clinical studies have demonstrated that a deficit of dopamine transmission at the D1 receptors in the prefrontal cortex might be implicated in cognitive impairments and negative symptoms of schizophrenia17.

The possibility of coexistence of both hypodopaminergic and hyperdopaminergic states in the same condition has raised the possibility of involvement of other neurotransmitters as modulators. Consistent with this is the observation that in addition to amphetamine, many other psychoactive agents can produce similar disturbances in thought process and perception, including PCP/Ketamine.

Dopamine and Glutamate - Ketamine Model of Psychosis

Ketamine is a structural analogue of phencyclidine (PCP). Both PCP and ketamine are dissociative anaesthetic agents and are non-competitive antagonists of the N-methyl-D-aspartic acid (NMDA) subtype of glutamate receptors. It was observed that a subanaesthetic dose of PCP (0.1 mg/kg) could induce a schizophrenic-like psychotic state in healthy human subjects18. The symptoms include positive psychotic symptoms (such as hallucinations, delusions and thought disorder), negative symptoms (such as apathy), and cognitive symptoms (such as inability to maintain cognitive sets, planning deficits and concrete ideation).

PCP non-competitively blocks the ion flow through the NMDA-sensitive glutamate receptor ionophore19. Because of the neurotoxic effects of PCP determined by studies in rodents20,21, the use of PCP in studies in humans is considered unethical. The structural analogue of PCP, ketamine, provides an alternative model of...
psychosis for use in human subjects. Further studies have been carried out in recent years both in healthy volunteers and schizophrenic patients to examine this model of psychosis. In schizophrenic patients, ketamine briefly exacerbated existing symptoms that patients had experienced before and some of them had delayed or prolonged effects; patients did not experience new symptoms that they had not previously encountered as part of their illness

In healthy volunteers, ketamine transiently produces a range of dose-related psychotomimetic and cognitive effects that include positive symptoms, negative symptoms, mood changes and thought disorders. Dissociative symptoms are prominent and these may be important early features of the illness. Cognitive dysfunction, consistent with the impairments seen in patients with schizophrenia, are also evident in healthy subjects following exposure to ketamine, including impairment in attention, memory, abstract thinking, planning and judgement.

The NMDA receptor is one of the receptors present on the GABAergic interneurons which modulate the excitatory pathways. The antagonistic effect of ketamine on these NMDA receptors reduces the GABAergic inhibitory action and hence disinhibits the excitatory pathways, including dopamine, glutamatergic, serotonin and norepinephrine, and cholinergic systems. The understanding of the psychogenic effects of ketamine and neuropathological process supports the hypothesis that endogenous hypo-function of the NMDA receptor may be a key component of the pathophysiology of psychosis.

This hypothesis has received further supports from the preclinical studies. It was shown that acute administration of NMDA receptor antagonists increased the release of dopamine in striatum and nucleus accumbens. PET imaging of 11C-raclopride binding in human subjects showed ketamine increased striatal dopamine release and the magnitude of its increase correlated with ketamine induced psychosis. Preclinical studies also showed acute administration of NMDA antagonists increased dopamine transmission in the prefrontal cortex. It was found that ketamine increased cortical dopamine levels particularly in the posterior cingular and dorsolateral prefrontal cortex in human subjects.

The above evidence supports the idea that changes in dopaminergic function are closely associated with changes in the glutamate system, particularly via the NMDA receptors: this is a dynamic and reciprocal relationship, with evidence of glutamatergic modulation of dopamine, as described above, but equally, dopaminergic influences on glutamate: D2 receptor stimulation inhibits NMDA-mediated glutamate transmission whereas D1 receptor stimulation facilitates it.

**Conclusion**

The study of the amphetamine model of psychosis supports the role of dopamine in the neuropathological process of psychosis. Studies of ketamine model of psychosis further suggest the modulatory role of glutamate in this process. It is clear that studying the psychogenic effects of different substances and their associated neuropathological changes, the pharmacological models of psychosis, provides us with a window to further explore the complex neuropathological process of psychosis. One of the other pharmacological models being studied actively is the delta-9-tetrahydrocannabinol (THC) model, which is a major component of cannabis. These different models have provided us with more detailed insight into the interaction of other neural substrates with dopamine and the relationship with the symptom formation. This would be an important tool to enhance our understanding of the neuropathological process of psychosis.

**References**


