Methamphetamine effects on dopamine as model of schizophrenia pathogenesis

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Introduction

Methamphetamine (also known as meth or crystal) is a potent amphetamine-type stimulant drug that interacts with the dopaminergic brain system, producing an overactivation, and exerting significant excitation on the central nervous system.

The dopamine function in the brain involves structures that are related to reward, motivation, judgment, the experience of pleasure, motor function, and inhibitory control of behavior. These structures maintain the brain functioning. Acute effects of methamphetamine intake produce euphoria, due to rapid dopamine release in reward regions that are stimulated. Furthermore, repeated methamphetamine use can lead to drug addiction, with chronic effects that produce important changes in brain circuits in which dopamine is involved. This produces psychotomimetic symptoms, similar to those produced in schizophrenia. Therefore, understanding interactions between neurotransmitter systems and their relationship with symptoms will be an important step towards building a coherent hypothesis for schizophrenia pathogenesis.

Dopaminergic pathways

Methamphetamine acts as an agonist of different monoamine receptors, binding to its membrane-bound transporters. It increases the amount of neurotransmitters in the brain (Figure 2). The dopamine neurotransmitter is the most important in this process.

In this way, the increased dopamine signals due to methamphetamine action, stimulate the three main pathways in which it is involved.

To exert its function, methamphetamine interferes with the three main dopaminergic brain pathways (Figure 3), located in the cortex and the basal ganglia. These carry out diverse functions related to the adequate brain functioning.

Acute effects

After meth exposure, persistent adaptive changes are produced in those brain regions that modulate mechanisms involved in drug addiction.

Chronic effects

To define drug addiction, chronic methamphetamine intake is necessary. Then, neurochemical changes and alterations in the brain circuits are produced, predominantly in the striatum. Due to better ability of dopamine release in the Nacc and the dorsal striatum, there is also an increase of glutamate levels. Both factors result in consequent brain alterations.

Methamphetamine and schizophrenia

Central physiopathology of schizophrenia is defined by the psychotic element driven by increased ability of dopamine release.

COMMON EFFECTS

The main comparison point between methamphetamine effects and those produced in schizophrenia is the dopaminergic system alteration, resulting in a cortical and subcortical function imbalance.

Conclusions

Methamphetamine abuse induces a hyperdopaminergic state by altering the different brain pathways where dopamine is involved. Chronic methamphetamine abuse triggers the appearance of psychotic symptoms that can be associated with typical psychoses developed in schizophrenia.

The effects of methamphetamine intake and schizophrenia share similar biological mechanisms that allow the establishment of a coherent hypothesis to understand how schizophrenia is developed, by studying neurochemical and general changes in the brain. Representation models of the dopaminergic and the GABA systems dysfunction, may help to unify the understanding of schizophrenia’s physiopathogenesis. This is the reason why the development of drug models may serve as an important source in this area of study.

The involved changes in behavior and cognition by methamphetamine effects provide a promising approach for studying many aspects of schizophrenia.

The utility of these models cannot only help to understand dysfunctional pathways that lead to psychopathology, but it can also allow the prediction of therapeutic efficacy for the treatment of these types of alterations, and which types of compounds may be developed.

Different colors represent the diverse dopamine projections in circuits where it is involved. The nigrostriatal pathway (red) is involved in a direct and an indirect pathway that send respectively activating and inhibitory signals to the SNr/GPi, driven by dopamine release. The mesolimbic pathway (green) sends inhibitory signals to the SNr/GPi by GABA projections. Cortical feedback is also important in the regulation of dopamine signaling. Certain colors help to understand the brain circuit in which methamphetamine interactions are involved.