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.

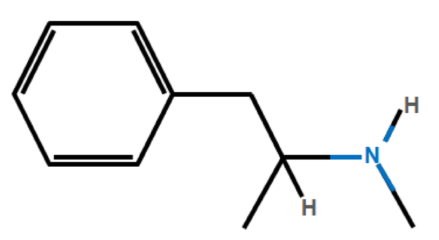

Figure 1. Methamphetamine chemical structure
Monoamine (lipophilic compound).

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 psychotic 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.

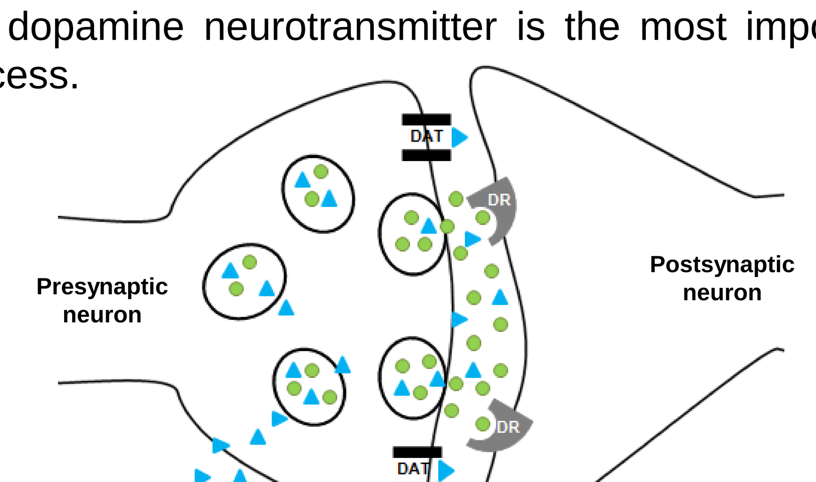

Figure 2. Methamphetamine action mechanism
Methamphetamine *(blue triangles)* enters the presynaptic neuron, replacing the dopamine that is in the cells or its vesicles. Then, it substitutes for dopamine *(green dots)* in the dopamine transporter (DAT), functioning as a substrate. In this way, the DAT endogenous function is reverted, resulting in the release of dopamine from its vesicles. This stimulates the dopamine receptor (DR) in the postsynaptic neuron.

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.

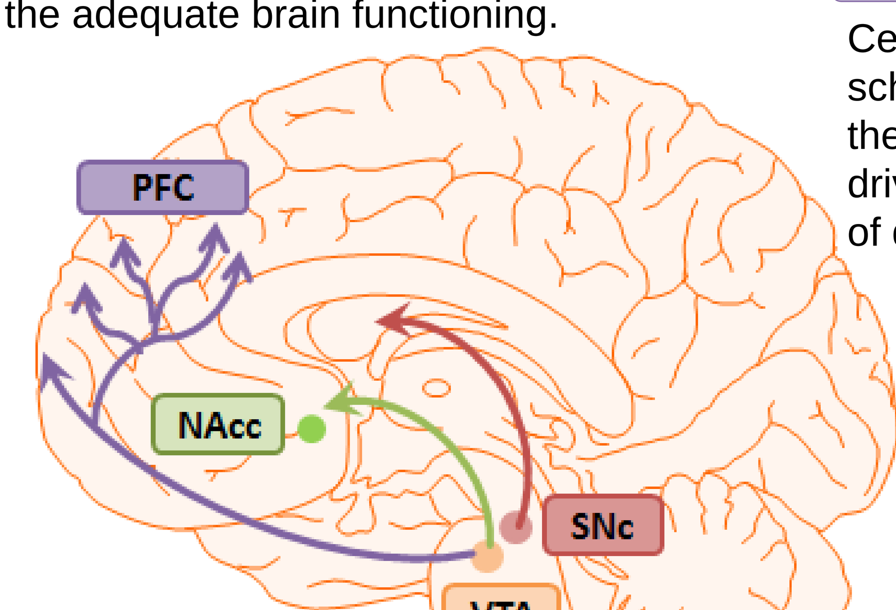

Figure 3. Dopaminergic pathways in brain
The nigrostriatal pathway *(red)* consists in dopamine release from the substantia nigra pars compacta (SNc) to the striatum. The mesolimbic pathway *(green)* includes projections from the ventral tegmental area (VTA) to the nucleus accumbens (Nacc). In the mesocortical pathway *(purple)* dopamine release is from the VTA to the prefrontal cortex (PFC).

Nigrostriatal pathway	• Behavior control
Mesolimbic pathway	• Reward processing
Mesocortical pathway	• Cognitive functions

Figure 4. Functions of dopaminergic pathways

Disturbances in these pathways produce changes that are linked to drug addiction.

Dopamine also modulates other structures' functioning , like the hippocampus, the amygdala, and the dorsal striatum, related to memory, conditioning, and habit formation.

Methamphetamine effects

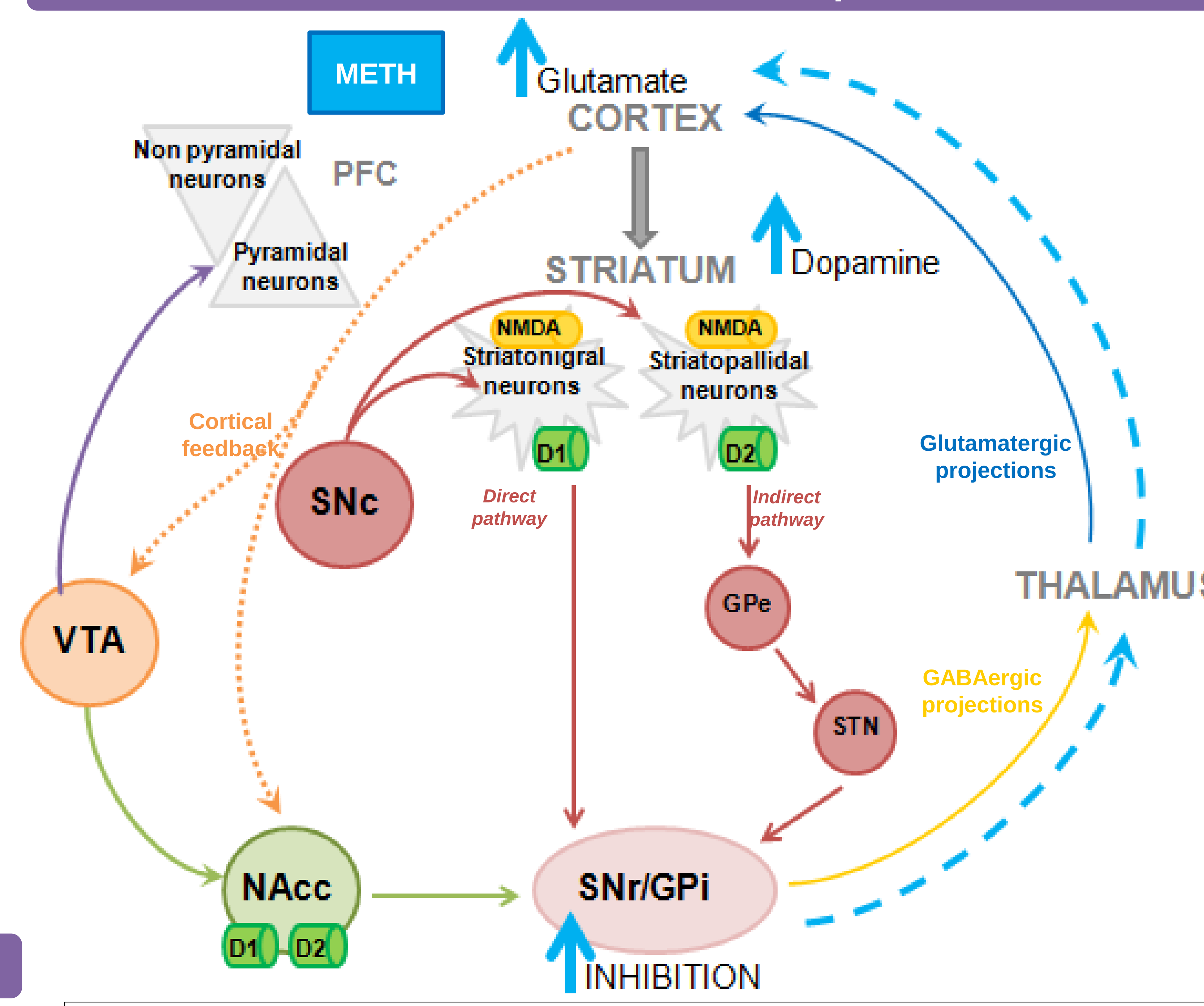

Figure 5. Detailed dopaminergic pathways
Different colors represent the diverse dopamine projections in circuits where it is involved. The nigrostriaral pathway *(red)* is subdivided in a direct and an indirect pathway that send respectively activating and inhibitory signals to SNr/Gpi, driven by dopamine release. The mesolimbic pathway *(green)* sends inhibitory signals to SNr/GPi by GABA projections. Cortical feedback is also important in the regulation of processes.
PFC: prefrontal cortex; VTA: ventral tegmental area; SNc: substantia nigra pars compacta; NAcc: nucleus accumbens; GPe: globus pallidus externa; STN: subthalamic nucleus; SNr: substantia nigra reticulata; GPi: globus pallidus interna. D1,D2: dopamine receptors. The purple arrow indicates the mesocortical pathway. Blue discontinued and continued arrows correspond to the effect of meth action in the system.

The methamphetamine effects on dopaminergic pathways are primarily mediated by the notable increase of dopamine levels in the brain involved circuits. This finally produces an inhibition increase of SNr/GPi from the three paths, leading to an increase of thalamocortical signals. The result is a dopamine increase in the striatum and a glutamate excess release in the cortex.

Due to meth presence, dopamine is released from the mesolimbic and the mesocortical pathways and it is increased in the striatum by the nigrostriatal path.

The meth interference with normal functioning of the dopaminergic system, produces a variety of effects that involve changes in behavior and cognition.

Beyond dopamine, cortical GABAergic interneurons are also important to maintain the signal tone, providing correct cognitive functioning in the brain.

Dopamine, glutamate, and GABA perform an important role in synaptic plasticity modulation, also related to drug addiction.

Acute effects

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

Block of dopamine reuptake → ↑**Dopamine** release in CNS (Mesocortic limbic regions)

↓ **REWARD AND EUPHORIA** ← Enhanced dopaminergic neurotransmission → Reinforcement properties

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.

↑ Glutamate
- Cortex damage → Attentional disturbances
- Frontostriatal regions' dysfunction → Cognitive deficits
- → **CRAVING**

Methamphetamine and schizophrenia

SCHIZOPHRENIA

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

Mesolimbic system overactivation → Positive delusional symptoms

Mesocortical system dysfunction → Negative and cognitive symptoms

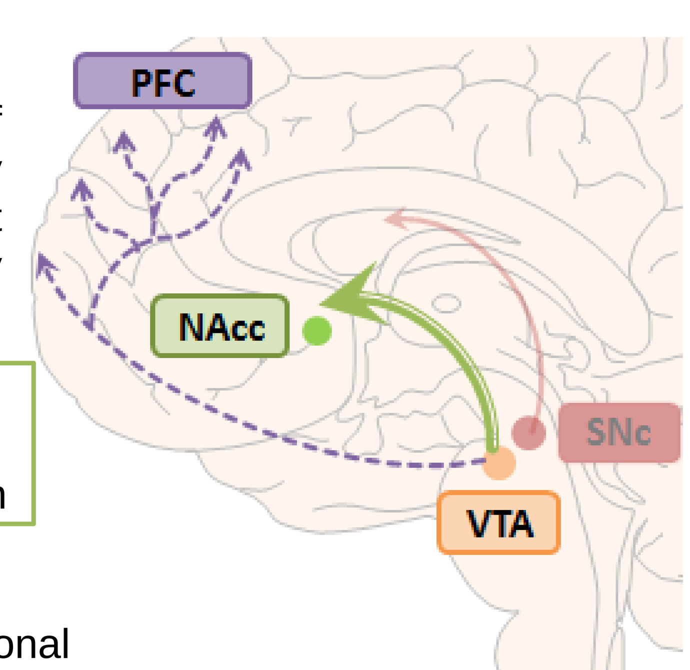

Figure 6. Disruption of dopaminergic pathways in schizophrenia

COMMON EFFECTS

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

Dopamine and GABA neurotransmission's dysregulation	• Diminished abilities in selective attentional responses • Disruption of normal information processing • Selective impairment in declarative memory
PFC dysfunction	• Deficits in functional outcome of cognitive control

Figure 7. Particularities. Different brain disturbances are observed in both types of patients affected by methamphetamine effects or schizophrenia.

Repeated meth use involves psychotic effects that could constitute a manner to reflect the same symptoms and cognitive deficits seen in schizophrenia.

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 psychosis 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.