# New perspectives and directions in schizophrenia therapeutics: advances related to non-dopaminergic systems

## *Novas perspectivas e indicações na terapêutica da esquizofrenia: avanços relacionados com os sistemas não-dopaminérgicos*

The dopamine hypothesis of schizophrenia first emerged in relation to the ability of anti-dopaminergic compounds to reverse psychotic symptoms. Antipsychotics are still the gold standard for treating schizophrenia, despite their limited success in the management of negative symptoms and their side effect profile. Several non-dopaminergic hypotheses have emerged based on a variety of studies. We will focus on these non-dopamine systems and their therapeutic implications for the management of schizophrenia.

### Glutamate and NMDA receptor hypofunction

The N-methyl-D-aspartic acid receptor (NMDAR) hypofunction hypothesis developed from the finding that drugs which block glutamate NMDARs, such as phencyclidine (PCP), induce effects almost identical to the positive and negative symptoms seen in schizophrenia. Animals given chronic doses of NMDAR antagonists developed loss of grey matter similarly reported in schizophrenia, while a relative deficit in NMDAR binding has been found in the left hippocampus of schizophrenic patients using SPECT imaging.[1] Although studies on glutamate have focused on NMDA receptors, it must be kept in mind that other glutamate receptors, both ionotropic and metabotropic, may also play a role in schizophrenia.

### γ-Aminobutyric acid (GABA)

Patients with schizophrenia have evidence of reduced GABAergic neurotransmission in the prefrontal cortex. Drugs enhancing GABAergic function would be expected to be useful by reducing excessive cortical glutamate release. Currently, there is little or no evidence that any drugs enhancing GABA-A receptor function, such as benzodiazepines, carbamazepine or valproate are useful in schizophrenia. However, no alpha-2 subunit-selective drugs have been developed to our knowledge, and no trial of GABA-A enhancing drugs in the very early stages of the illness has yet been performed.[1]

### Glycine

Glycine is an amino acid that is inhibitory in the spinal cord and brain stem but also acts as a co-agonist at glutamate NMDARs. Genetic and pharmacologically-induced deficiencies in glycine binding in mice produce behavioral changes that model the negative and cognitive symptoms of schizophrenia. Several studies have tested the effects of combining glycine with certain antipsychotics or using glycine transport inhibitors with promising results. There is evidence supporting the administration of glycine and Gly-T1 transport inhibitors in order to enhance NMDAR-mediated neurotransmission for the treatment of schizophrenia.[2]

### D-Serine

D-Serine is the main NMDAR co-agonist and it potentiates NMDAR function. Daily administration of large quantities of D-serine alone or as an adjunct to atypical antipsychotics has been reported to improve schizophrenic symptoms. D-Serine is metabolized by D-amino acid oxidase (DAO) and inactivation of DAO in mice has been reported to improve behavioral deficits which are similar to the negative and cognitive symptoms in schizophrenia. Some DAO inhibitors currently under study show increased D-serine bioavailability when co-administered with D-serine, allowing for the administration of a lower dose of D-serine to patients in treatment.[2,3]

### Nitric oxide (NO) and arginine

Interfering with NO production in rodents has been reported to reverse PCP-induced effects. Pretreatment with nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase (NOS) inhibitor, counteracted PCP's behavioral effects and NO levels were reduced. However, there is also evidence from animal studies with PCP that the underproduction of NO may be linked with schizophrenia. Some studies suggest that NO donors (e.g. sodium nitroprusside) can block the behavioral effects of PCP and improve cognitive deficits. Postmortem studies have identified disrupted cellular migration and functioning involving NO-producing neurons in schizophrenia, supporting the neurodevelopmental theory and suggesting that a decrease in the production of NO in cortical areas could perhaps contribute to altered neuronal development, disrupted circuitry, hypofrontality, and poor cognitive functioning.[3,4]

### Homocysteine, folate deficiency, and the neurodevelopmental hypothesis

Studies have reported both positive and negative findings in relation to folate deficiency in schizophrenia. Hyperhomocysteinemia has been more consistently found in patients with schizophrenia. One meta-analysis concluded that the homozygous MTFHR 677TT polymorphism is associated with an elevated risk of schizophrenia. Animal studies have shown that the impact of folate deficiency is not restricted to the embryo. Consequently, abnormal C1 metabolism might impair cortical and hippocampal neurogenesis during development, and might contribute to the decreased brain volume consistently seen in patients with schizophrenia. Folate deficiency could be associated with schizophrenia acting either through hyperhomocysteinemia and/or through homocysteine-independent effects on neuronal progenitor division. Studies have shown that homocysteine-reducing strategies contribute to symptom reduction in patients with schizophrenia.[5]

### Acetylcholine receptors (nicotinic and muscarinic receptors)

Acetylcholine has been implicated in schizophrenia because of its modulation of neurotransmission at both dopamine and NMDA receptors and due to its central importance to cognitive functions. However, cholinesterase inhibitors have generally not been found to be helpful as an add-on therapy to antipsychotics.[1]

**Nicotinic receptors**: postmortem studies with schizophrenic patients have found abnormalities in the alpha-7 nicotinic receptor subtype expression, and a gene locus harboring the alpha-7 nicotinic receptor has been linked with schizophrenia. Animal studies suggest that nicotine transiently normalizes similar sensory gating deficits as seen in schizophrenia (manifesting as an inability to appropriately pay attention to sensory stimuli). A double blind, placebo-controlled trial of galantamine, a combined cholinesterase inhibitor and allosteric potentiator of nicotinic receptors, was found to enhance cognition. A trial of a selective alpha-7 agonist has also shown cognitive enhancement in schizophrenia.[1]

**Muscarinic receptors**: a postmortem study with schizophrenic patients has found reduced levels of muscarinic receptors in the caudate-putamen. Non-medicated schizophrenic patients were found to have reduced muscarinic receptor availability on SPET imaging. Furthermore, clozapine clearly acts as a partial agonist at the muscarinic M1 and M4 receptors, and its affinity for these receptors is several-fold higher than for the dopamine D2 receptor. Therefore, muscarinic partial agonists might be potential therapeutic agents in schizophrenia, as well as add-on treatments to improve the efficacy of atypical antipsychotics. Some preclinical evidence exists supporting this hypothesis,[1]

### Cannabinoid receptors

The study of the cannabinoid system has advanced greatly over the past few years and investigations have shown that this system might be involved in the manifestation of psychiatric symptoms to a greater extent than previously thought. Recent evidence suggests that cannabinoids can provoke schizophrenia-like symptoms in healthy individuals, including cognitive impairment. Also, the use of substances acting in the cannabinoid system has been shown to exacerbate symptoms and to trigger relapse, in addition to having other negative consequences on the course of the illness.[6] The induction of transient psychotic symptoms by cannabinoids seems to be the result of the modulation, by the cannabinoid system, of dopamine, GABA, and glutamate pathways, but these associations are not yet clear. Conversely, studies with other *cannabis*-derived substances such as cannabidiol have shown that these compounds may also have antipsychotic properties.[7]

These lines of investigation show that there is much more to be discovered in relation to schizophrenia and that dopamine, important as it certainly is, is far from being the only pathway involved in the clinical presentation of the disorder. The future treatment of schizophrenia will likely be based on a multiple-pathway approach, with different drugs and doses targeting specific neural networks and the symptoms associated with them.

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