

Modulation of Central Nitric Oxide as a Therapeutic Strategy for Schizophrenia

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ÖZET:

Şizofreni için yeni tedavi stratejileri olarak nitrik oksit modülasyonu

Antipsikotik ilaç geliştirilmesindeki son ilerlemelere rağmen, şizofreninin farmakolojik yönetimi görece yetersiz kalmaktadır. Santral nitrik oksit modülasyonuna dair artan kanıtlar şizofreni tedavisi için yeni bir tedavi stratejisi sunabilir. Bu nedenle, bu editöryal yazıda şizofreni ve antipsikotik ilaçların mekanizması ile santral nitrik oksit patofizyolojisi ilişkisi anlatılmaya çalışılmaktadır. Nitrik oksit modülasyonunun yeni stratejileri şizofreni için potansiyel bir farmakoterapi yöntemi olarak karşımızda durmaktadır.

Anahtar sözcükler: Şizofreni, nitrik oksit, farmakoterapi

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ABSTRACT:

Modulation of central nitric oxide as a therapeutic strategy for schizophrenia

Despite recent advances in antipsychotic drug development, pharmacological management of schizophrenia remains relatively unsatisfactory. There is growing evidence that modulation of central nitric oxide may offer a novel therapeutic strategy for the treatment of schizophrenia. Therefore, this editorial presents pathophysiology of central nitric oxide relevant to schizophrenia and mechanism of antipsychotic drugs. Novel strategies of modulating nitric oxide as a potential pharmacotherapeutic strategy for schizophrenia are presented.

Key words: Schizophrenia, nitric oxide, pharmacotherapy

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The search continues to identify precise neurobiological mechanisms into the pathophysiology of schizophrenia. It is a complex heterogeneous syndrome which impairs social, occupational, and individual functioning and often results in a considerable decline in the quality of life. Although existing treatments are successful in many cases in reducing psychotic symptoms, they are not always effective and are often accompanied by significant side effects which themselves impact on the quality of life (1). The burden of schizophrenia extends beyond the individual affected to close relatives and caregivers and to society at large. The annual cost to Canada alone has been estimated at \$7 billion (2). The disease is progressive in the sense that full blown symptoms often develop from a prodromal period with nonspecific symptoms that themselves may cause discomfort and treatment-seeking behavior. There is increasing evidence that this evolution of symptoms is accompanied by subtle loss of cortical grey matter (3), and this may account for the well established finding that the longer the period of untreated symptoms, the poorer the prognosis. Therefore, effective and safe treatments at

the earliest phases of the illness may change the outcome and the disease progress (4,5).

Up to 1% of the population will develop schizophrenia and perhaps 3% will develop a psychosis. Treatment of the disorder is hampered by patients' lack of acceptance of antipsychotic drugs, with resultant poor adherence and delays in presentation of symptoms. About 50% of first episode cohorts stop medication over any 6 month period and non-adherence increases odds of relapse 5 fold. Improving treatment in the early stages may improve the later course when options for refractory illness are limited (5,6). One of the principal predictors of non-adherence from the earliest stages onwards is lack of perceived or actual benefit from medication (7,8,9), so increasing the efficacy of treatment using an acceptable drug with minimal side effects is likely to reduce this problem.

The development of an effective adjunctive therapy to antipsychotic treatment in schizophrenia is needed. Current antipsychotics have little effect on the main causes of impaired social functioning, negative symptoms and cognitive deficits. This type of disability is not only a

huge economic burden but one of the primary concerns of patients. Moreover, although clozapine is the most effective treatment for refractory schizophrenia (10,11), it produces a heavy burden of adverse effects that sometimes preclude its use (1) and is relatively expensive to administer. Despite being the most effective treatment for refractory schizophrenia, it has limited effectiveness (10,11). The evidence for other existing adjunctive treatments is much weaker and their efficacy appears limited (e.g. 12, NICE Clinical Guidelines 82, 2009).

Dysfunction of connectivity of the neuroregulators glutamate and nitric oxide (NO) has been implicated in mechanisms not only of neurodegeneration but also of psychosis itself (13). Glutamate NMDA receptors have functional connections via the PSD-95 protein to the NO system in the brain. Nitric oxide, a soluble gas, has many different functions in the body. The significance of its physiological role has recently been realized, and indeed in 1998 the Nobel prize was awarded to Robert Furchgott, Louis Ignarro, and Ferid Murad for their discovery of NO (http://nobelprize.org/nobel_prizes/medicine/laureates/1998/illpres/). It is produced by nitric oxide synthase (NOS), a NO-producing enzyme found in neurons, endothelial cells, and macrophages in the body. Three separate isoforms of the nitric oxide synthase (NOS) enzyme exist, and they are encoded by three separate genes. The endothelial form e(NOS) is responsible for vasodilation, the inducible form i(NOS) is produced in macrophages in response to an inflammatory insult, and the neuronal form n(NOS) is responsible for neuronal signaling (14,15).

In the brain, NO functions as a neuromodulator or second messenger (15). As a lipophilic soluble gas, it is able to diffuse across the cell membrane to alter neuronal response without direct connection to the synapse. Nitric oxide is known to be able to diffuse a few hundred micrometers, and so it is able to influence a large number of neighboring neurons at the same time (16). Several neurotransmitters such as acetylcholine, dopamine, norepinephrine and GABA have all been reported to be modulated by NO (16,17) and all have been implicated in schizophrenia.

The synthesis of NO in the brain is dependent on a fully functional NMDA receptor and its pathway involves many intracellular components (see Figure 1). When glutamate binds to the NMDA receptor, the neuron depolarizes causing an influx of calcium (Ca^{++}) into the

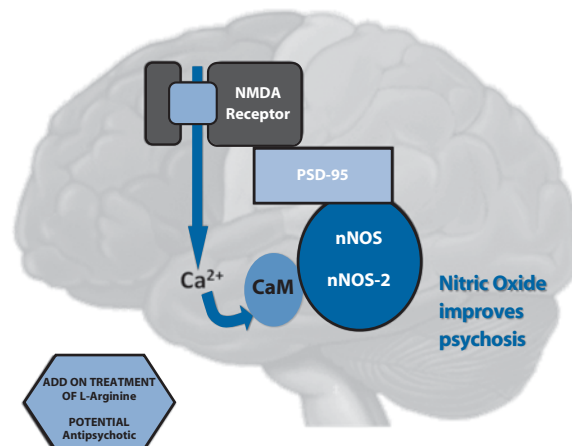


Figure 1: Proposed mechanism of action of L-arginine in schizophrenia. Stimulation of nNOS by the Ca^{++} calmodulin complex promotes the conversion of L-arginine to NO in the brain. Increased NO production may reverse downstream effects of disrupted NMDA receptors in schizophrenia.

cell. The influx and binding of Ca^{++} to calmodulin activates nNOS. Activation of nNOS stimulates it to use its substrate L-arginine, converting this amino acid to L-citrulline and NO. Nitric oxide then binds to soluble guanylate cyclase, which increases the production of the second messenger cyclic GMP (cGMP). Increases in cyclic GMP activate various kinases, which phosphorylate proteins, and promote the desired physiological response in the target cell (14,18).

The role of NO in the pathophysiology of schizophrenia remains unclear. From the various studies that have been published, there are conflicting reports about whether there is more or less NO synthesis in the illness (17,19). Due to the heterogeneity of schizophrenia and the inability to quantify NO levels directly in the human brain, its mechanisms in schizophrenia remain unknown. Most studies have relied on the measurement of various biomarkers and metabolites produced via the NO pathway as indirect measures of its presence in the illness, and so it is unclear whether NO plays a neuroprotective or cytotoxic role.

The use of NOS inhibitors in preclinical studies has been helpful to determine the behavioral effects of NO in pharmacological models of schizophrenia. There have been studies demonstrating that perhaps an overproduction (20-22) of NO may be responsible for PCP-induced psychotic symptoms. However, it has also been shown that an underproduction of NO may be linked

to the behavioral effects and the neurobiology of schizophrenia. The use of L-NAME, a NOS inhibitor, was found to increase PCP-induced behaviors as well as increase PCP-induced c-fos expression in cortical regions in rats. The conflicting behavioral results may be explained by the ataxia that was produced in the animals by similar doses of PCP and reduced doses of PCP and L-NAME used in the Bujas-Bobanovic et al. study (23,24). Ataxia is a reliable measure of drug intoxication due to cerebellar impairment. Ataxia in the Bujas-Bobanovic et al. study impaired the ability of the animals to engage in hyperlocomotor activity and stereotyped behaviors, which may lead to opposing conclusions in studies where locomotor activity and stereotyped behaviors are measured alone (20-24).

There is also preclinical evidence to suggest that NO donors such as sodium nitroprusside and molsidomine have the ability to block behavioural and neurobiological markers of psychosis in animals induced by PCP (23,24) and improve cognitive deficits in animals induced by MK-201 (25). By increasing NO production, the ability to bypass the blocked NMDA receptor is achieved and the behavioral effects of psychosis in these animals can be reversed.

Nitric oxide donors have never to our knowledge, been used as a therapeutic augmenting strategy in schizophrenia. However, clinical studies have suggested that there may be reduced production of NO in the illness. Postmortem studies have identified disrupted cellular migration and functioning involving NO-producing neurons in schizophrenia. Altered distribution of cells containing nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd), a cofactor needed in NO synthesis, have been found in frontal and temporal lobes of patients with schizophrenia (26). Abnormalities have also been found in NOS-containing neurons in the striatum (27), and a decrease of NOS activity, but not of protein expression, was also found in the prefrontal cortex of patients with schizophrenia (28). These findings support the neurodevelopmental theory of schizophrenia and suggest that a decrease in production of NO in cortical areas could perhaps contribute to altered neuronal development, disrupted circuitry, hypofrontality, and poor cognitive functioning that are all characteristic of the illness (29-31).

Studies measuring the NO metabolites nitrite and

nitrate in both plasma (32) and cerebrospinal fluid (33) have also been helpful in increasing our knowledge of the function of NO in schizophrenia. Nitrite and nitrate concentrations are accepted measures of NO production and can be used as a marker for CNS NO metabolism. In plasma, nitrate levels of patients with a cognitive deficit syndrome were significantly lower than non-deficit patients, suggesting a decreased production of NO in this subset of patients (32). Similar results have been found in patients with depression (34). These findings may suggest that deficient NO production could be responsible for the negative and depressive symptoms of the illness and that the use of a NO donor may benefit these particular features. Similar NO metabolite findings in cerebrospinal fluid are also of particular interest as this implies a direct reduction of NO in the CNS (33).

The modulation of the NO pathway continues to gain considerable interest as a possible therapeutic target in the treatment of schizophrenia. Nitric oxide donors could improve NMDA receptor dysfunction as any downstream effects could be corrected by NO at the cellular level. L-Arginine a semi-essential amino acid, is the precursor of NO. If so, using L-arginine to increase NO production could bypass the blocked NMDA receptors and reverse the functional effects. As an augmenting strategy, we are interested in whether L-arginine can further improve and enhance the therapeutic efficacy (positive, negative, and depressive) symptoms and effectiveness of antipsychotic therapy (see Figure 1 for an illustration of possible antipsychotic potential of L-arginine). For details please refer to (<http://clinicaltrials.gov/ct2/show/NCT00718510>). Other studies are exploring possible augmenting strategies in schizophrenia with L-lysine, an amino acid that competes for the same transporter as L-arginine. (<http://clinicaltrials.gov/ct2/show/NCT00996242>).

Because of the relatively disappointing therapeutic efficacy and adverse side effect profiles of currently available antipsychotics, augmentation therapy is of considerable interest. L-Arginine may offer a safe and effective add-on therapeutic approach to improve the symptoms of the illness.

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