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Review

The role of nitric oxide donors in schizophrenia: Basic studies and clinical applications

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ABSTRACT

Schizophrenia is a complex and chronic mental health disease that affects nearly 1% of the population worldwide. While the current antipsychotic medications have profoundly impacted the treatment of schizophrenia over the past 50 years, the newer atypical antipsychotics have not fulfilled initial expectations, and enormous challenges remain in long-term treatment of this debilitating disease. In particular, improved treatment of the negative symptoms and cognitive dysfunction in schizophrenia which greatly impact overall morbidity is required. Nitric oxide (NO) is considered as an intra- and intercellular messenger in the brain. The implication of NO in the pathogenesis of schizophrenia is documented. Specifically, underproduction of NO is linked to this pathology. This, in turn, indicates that enhancement of nitrergic activity might be beneficial in this disease. Therefore, novel molecules aiming to increase NO production such as NO donors might constitute potential candidates for the treatment of schizophrenia. Here I intended to critically review advances in research of these emerging molecules for the treatment of this psychiatric disorder. Present analysis suggests that NO donors might be a promising class of compounds for the treatment of schizophrenia. However, the potential neurotoxicity and the narrow therapeutic window of NO donors would add a note of caution in this context.

Contents

1. Schizophrenia

Schizophrenia is a serious mental disorder that affects up to 1% of the population worldwide. It is a complex heterogeneous

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syndrome which impairs social, occupational and individual functioning and results in a remarkable decline in the quality of life of patients. Its etiology and pathophysiology remain unknown. Schizophrenic patients suffer from enduring and persistent psychotic symptoms, which can be divided in three major types: positive symptoms (f.i., hallucinations, delusions, disordered thought processing, catatonic behavior), negative symptoms (social withdrawal, anhedonia, avolition) and cognitive disturbances (deficits in attention and memory) (Freedman, 2003).

Abnormalities in a number of neurotransmitter systems, most notably the dopamine, glutamate, cholinergic, the serotonergic and the γ-aminobutyric acid (GABA) systems are thought to be important for the appearance of this disease (Steeds et al., 2015). In particular, positive symptoms of schizophrenia are associated with an excess of dopaminergic neurotransmission, in striatal brain regions, while negative symptoms and cognitive deficits are linked to dopaminergic hypofunction in prefrontal brain regions.

Moreover, consistent experimental evidence proposes a role for glutamate hypofunction in the pathophysiology of schizophrenia. NMDA receptor dysfunction is linked to secondary dopaminergic dysregulation in striatal and prefrontal brain regions. In addition, clinical observations have demonstrated that pharmacological blockade of NMDA receptor produced the component symptoms—negative symptoms and cognitive impairments—that were neither affected by antipsychotics nor produced by dopaminergic agonists (Javitt, 2007). Further, inhibitory GABAergic neurotransmission appears to be impaired in schizophrenia patients (Pratt et al., 2012). In this context it is important to underline that GABAergic firing regulates dopamine transmission in the prefrontal cortex and a GABA interneuron deficit in schizophrenia has been proposed to underlie some of the clinical symptoms (Lewis et al., 1999).

Although traditional antipsychotic drugs have demonstrated utility in treating the positive symptoms of schizophrenia, current treatments are limited in their ability to alleviate the negative and cognitive symptoms clusters and often are accompanied by significant side effects which themselves impact the quality of life (Field et al., 2011). Finally, one third of patients are resistant to currently available medication. Therefore, there is an urgent requirement to develop new molecules for the treatment of schizophrenia.

2. Nitric oxide (NO)

Nitric oxide (NO), a soluble, short-lived and freely diffusible gas, is an important intercellular messenger in the brain (Garthwaite et al., 1988). NO originally was identified as endothelium-derived relaxing factor mediating relaxation of blood vessels (Furchgott and Zawadski, 1980). NO plays essential roles in the regulation of a wide range of physiological processes, including cellular immunity (Hibbs et al., 1988), vascular tone (Palmer et al., 1987), and neurotransmission (Garthwaite et al., 1988).

2.1. Synthesis of NO

NO is originated by the conversion of L-arginine to L-citrulline, with the release of NO. The enzymatic oxidation of L-arginine to L-citrulline occurs in the presence of oxygen (O_2) and nicotinamide adenine dinucleotide phosphate with flavin adenine dinucleotide, flavin mononucleotide, henme, thiol and tetrahydrobiopterin as cofactors (Palmer et al., 1987; Knowles and Moncada, 1994).

The enzyme responsible for the generation of NO is NO synthase (NOS). Three NOS isoforms encoded on different distinct genes have been described: neuronal NOS (nNOS, NOS type I) being the isoform found in neuronal tissues, inducible NOS (iNOS, NOS type II) being the isoform which can be synthesized following induction by pro-inflammatory cytokines or endotoxin and endothelial (eNOS, NOS type III) being the isoform expressed in endothelial cells (Bredt, 1999). nNOS and eNOS are constitutively expressed and dependent on the presence of calcium (Ca^{2+}) ions and calmodulin to function, whereas the activity of iNOS is Ca^{2+} independent (Calabrese et al., 2007a).

NO is formed following activation of glutamate receptors, mainly the NMDA subtype. After this activation, Ca^{2+} is transiently increased in the cytosol and forms a complex with calmodulin that binds to and activates nNOS (Knowles and Moncada, 1994). Glial cells (astrocytes and microglia) synthesize NO after the transcriptional expression of a Ca^{2+} independent iNOS isoform (Merrill et al., 1993). By contrast to conventional transmitters, which are water soluble and cannot cross lipid membranes, NO is both water and lipid soluble, and so after it is synthesized, it freely diffuses to adjacent neurons and acts directly to intracellular components from cell to cell (Garthwaite, 2008).

2.2. Main physiological targets of NO

The most prominent natural target of NO is soluble guanylyl cyclase (sGC) (Arnold et al., 1977), whose activation produces cyclic guanosine monophosphate (cGMP) when NO binds to a heme group in the enzyme (Bredt and Snyder, 1989). cGMP, in turn, activates cGMP-dependent protein kinase (PKG), which may affect additional second messenger systems. cGMP can also directly activate other protein kinases, such as the cyclic adenosine monophosphate (cAMP)-dependent kinase (PKA) (Muller, 2000). Metabolism of cGMP by phosphodiesterase suppresses or terminates NO/sCG signaling (Kleppisch, 2009). Thus, NO is similar to conventional transmitters that act via second messengers to activate protein kinases which may in turn affect transcription factors and protein synthesis (Susswein et al., 2004).

In this context, current literature indicates that the sGC should probably no longer be considered the only target of the action of NO (Edwards and Rickard, 2007). Alternative sGC-independent mechanisms have recently been proposed. One reaction which is gaining prominence is the *S*-nitrosylation of various proteins. Depending upon the protein species, *S*-nitrosylation can either inhibit or upregulate activity. Three cation channels opened by *S*-nitrosylation, the cyclic nucleotide-gated (CNG) channels; the large conductance Ca^{2+}-activated potassium (BK_{Ca}) channels; the ryanodine receptor Ca^{2+} release (RyR) channels; and the enzyme mono(ADP-ribosyl) transferase are amongst of the cGMP-independent mechanisms by which NO may exert its action (Edwards and Rickard, 2007).

NO is involved in synaptic activity, neural plasticity and cognition (for review see Prast and Philippu (2001)). It promotes also survival and differentiation of neurons and exerts long-lasting effects through regulation of transcription factors and modulation of gene expression (Calabrese et al., 2007a). NO potentially acts via the above described mechanisms, depending on the concentration, with low concentrations being neuroprotective and mediate physiological signaling (e.g., neurotransmission or vasodilatation), whereas higher concentrations mediate immune/inflammatory actions and are neurotoxic (Calabrese et al., 2007a, 2007b).

Because of its mobility, unconstrained by cell membranes, NO can act across a broad volume and its actions are limited by inactivation (e.g., scavenging or degradation). It has long been postulated that NO can also could act as a retrograde messenger at the synapse, mediating transmission from target neurons back onto the synapse and regulating synaptic plasticity, but the same properties also enable NO to signal to any local compartment and to cells that lack synaptic activity or NOS expression (Steinert et al., 2010).