Letter to the Editor

**Sodium nitroprusside, a nitric oxide donor for novel treatment of schizophrenia, may also modulate dopaminergic systems**

“Schizophrenia is arguably the worst disease affecting mankind, even AIDS not excepted”. Since this statement in 1988 (Editors, 1988), schizophrenia still remains a major challenge to medicine, with up to 60% of patients not responding adequately to treatment despite the relatively large arsenal of antipsychotics currently available. By modulating the nitric oxide (NO) pathway, a new paradigm for schizophrenia treatment apparently involving modulation of nitric oxide (NO) has been proposed (Oliveira et al., 2011). After a preclinical study which showed that sodium nitroprusside (SNP) infusion abolished the psychosis-like behavior and c-fos cerebral expression in rats induced by phencyclidine (PCP) (Bujas-Bobanovic et al., 2000), our group designed a translational trial to evaluate the effects of this NO donor in acute schizophrenia in humans and found that SNP infusion improved the symptoms of schizophrenia patients already taking antipsychotics in a matter of hours (Hallak et al., 2013).

The rationale for this experiment was based on the glutamatergic hypothesis of schizophrenia. Drugs, such as ketamine and PCP, that block NMDA receptors induce positive, negative, thought disorder and cognitive symptoms closely resembling schizophrenia. NMDA receptors are activated by a complex interaction of glutamate and the co-agonists α-serine and glycine, resulting in calcium influx into the cell. Calcium binds to calmodulin and stimulates neuronal nitric oxide synthase (nNOS), which produces NO in the central nervous system. NO activates soluble guanylate cyclase that increases the production of cyclic GMP (cGMP), which in turn influences the activity of kinase cascades, mRNA stability and translation, transcription factors and primary gene products. Blockade of NMDA receptors by drugs such as ketamine and PCP reduces NO production (Oliveira et al., 2011).

In recent studies in which we were investigating the effects of SNP on the circadian rhythm of mice presenting with ketamine-induced psychosis, it was found that ketamine or saline produced standard sleep–wake cycle state maps, showing the usual clusters of waking, REM (rapid eye movement) sleep and SWS (slow wave sleep). However, in the group treated with SNP, the state map method used was not able to produce the clusters separation, and a strange break in the pattern of the sleep–wake cycle was found (Fig. 1).

Dzirasa et al. (2006) had previously reported this same break pattern of the sleep–wake cycle in DAT-KO transgenic mice (knock-out for the dopamine transporter) treated with α-methyl-p-tyrosine (αMT), an inhibitor of the tyrosine hydroxylase enzyme, which inhibits the synthesis of dopamine. Because the DAT-KO mice are unable to recycle dopamine, their dopamine levels are dependent exclusively on new synthesis. Treatment of such animals with αMT inhibits the new dopamine synthesis, leaving them with a striatal dopamine concentration reduced to 0.2% of the levels found in regular animals. When these animals were subsequently treated with L-dopa, a precursor of dopamine, their REM sleep cluster was restored (Dzirasa et al., 2006).

Therefore, the question arises whether SNP, a NO donor, is able to affect dopaminergic neurotransmission in such way of causing a break in the pattern of the sleep–wake cycle similar to that found in animals depleted of dopamine.

Interactions between dopamine and NO have been described. Lee and colleagues reported decreased serum NO in schizophrenic patients compared with a control group, and found that a six-week treatment with the dopamine antagonist antipsychotic risperidone increased NO levels and that this increase was associated with improvement of symptoms (Lee and Kim, 2008). A recent meta-analysis found that patients taking antipsychotics have higher levels of plasma/serum NO than controls (effect size g = 0.663, 95%CI = 0.365 to 0.961, p < 0.001) (Maia-de-Oliveira et al., 2012). There are also studies that showed increased cGMP levels in the cerebrospinal fluid of schizophrenia patients after treatment with antipsychotics (as previously reported, NO induces increases in cGMP concentrations) (Ebstein et al., 1976). Indeed, it has been speculated that NO exerts a tonic inhibitory effect on dopamine transporters, which could correct a reduced activity of dopamine in the prefrontal cortex and, through feedback loops, fix dopaminergic hyperactivity in both accumbens and striatum (Pycock et al., 1980). Interestingly, Issy et al. (2014) have recently shown in rats that pretreatment with SNP attenuated schizophrenia-like changes in PPI (prepulse inhibition) induced by amphetamine, a dopaminergic agonist (Issy et al., 2014). The precise antipsychotic mechanism of action of SNP is still unclear. Perhaps its antipsychotic effects could start faster than the usual antipsychotic medications because of SNP’s capacity to modulate the NMDA–NO–cGMP pathway (Hallak et al., 2013). If the effects of SNP on dopamine are confirmed by future and better designed studies, this may represent an exciting link between glutamate and dopamine, the two transmitters most widely investigated in schizophrenia (Coyle, 2012; Seeman, 2013), and yield important clues for the development of more effective antipsychotic drugs.

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JPM — literature search, figures, data collection, data analysis and writing; BLS — literature search, figures, data collection, data analysis and writing; GBB — literature search and writing; SMD — literature search and writing; and JECH — literature search and writing.

**Conflict of interest**

None of the authors have a conflict of interest in this project.

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Fig. 1. Treatment with SNP breaks the pattern of the sleep–wake cycle state map. Mice were treated with an intraperitoneal injection of one of the experimental drugs and then subjected to a 4 hour period of local field potential recordings from the hippocampus. A — State map from a mouse treated with a single saline injection. B — State map from a mouse treated with a single injection of ketamine at 30 mg/kg. C — State map from a mouse treated with a single injection of SNP at 8 mg/kg followed by a 30 mg/kg ketamine single injection. Two-dimensional state maps were generated by plotting the following spectral ratios: x-axis, 0.5–4.5 Hz/0.5–9.5 Hz; y-axis, 2–20 Hz/20–55 Hz. The black spots represent the wake cluster, the green spots represent the REM (rapid eye movement) sleep cluster and the red spots represent the SWS (slow wave sleep) cluster. All unassigned time points are coded gray and correspond to interstate transitions.