Effects of sodium nitroprusside in the prevention of schizophrenia-like symptoms induced by ketamine – A translational double-blind study

Tatiana M. N. Rezende[1], João Paulo Maia-de-Oliveira[2,3], Ludmyla Kandratavicius[1], João Paulo Machado-de-Sousa[1,2], João Abrão[1], Daniel Almeida Prado[1], Rodrigo A. Bressan[4], Acioly L. T. Lacerda[4], Antonio W. Zuardi[1,2], Glen B. Baker[2,5], Serdar M. Dursun[2,5], Jaime E. C. Hallak[1,2]

[1] *Department of Neuroscience and Behavior, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil*
[2] *National Institute of Science and Technology – Translational Medicine (INCT-TM), Brazil.*
[3] *Department of Clinical Medicine, Federal University of Rio Grande do Norte, Natal, RN, Brazil.*
[4] *Department of Psychiatry, Federal University of São Paulo (Unifesp), São Paulo, SP, Brazil.*
[5] *Neurochemical Research Unit, Department of Psychiatry, University of Alberta, Edmonton, Canada.*

Institution where the study was conducted: Clinical Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.

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Abstract

Background: Recent evidence has shown improvements in schizophrenia symptoms after the infusion of sodium nitroprusside (SNP), a nitric oxide (NO) donor. In the rat model of schizophrenia using ketamine injection, pretreatment with SNP seems to prevent behavioral changes associated with positive symptoms for up to one week. **Objective:** We investigated whether SNP would have preventative effects on psychogenic symptoms induced by ketamine in healthy subjects. **Methods:** Healthy subjects (N = 38) were assigned to distinct groups that received SNP in different doses (0.15, 0.25, and 0.5 mcg/kg/min). First, participants received an infusion of SNP or placebo over 75 minutes. After 10 minutes, they were injected for 1 minute with a bolus of 0.26 mg/kg of ketamine and a maintenance dose was started 5 minutes later, with 0.25 mg/kg/h of ketamine for 50 minutes. **Results:** Ketamine-induced psychopathological alterations induced were reduced by SNP, as assessed with the *Brief Psychological Rating Scale*. Scores in the objective subscale of the *Clinician-Administered Dissociative States Scale* were also lower in SNP sessions compared to placebo. SNP had protective effects against deterioration in facial emotion and identity recognition tasks induced by ketamine. **Discussion:** Our findings support the view that SNP has preventative properties against psychotic manifestations.

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Keywords: Nitric oxide, sodium nitroprusside, ketamine, schizophrenia, psychosis.

Introduction

Schizophrenia treatment remains a major challenge for psychiatry[1,2], since currently available antipsychotics are mostly able to counteract positive symptoms such as hallucinations and delusions, but seem virtually useless against negative symptoms and cognitive decline. This has led researchers to search for alternatives and look into new neurotransmitter systems and psychopathological mechanisms that could be involved in the manifestations of schizophrenia.

One of these new targets of investigation is the glutamate system. Phencyclidine (PCP) and ketamine are widely used in animal models of schizophrenia, and both drugs act by blocking the action of glutamate on N-methyl-D-aspartate (NMDA) receptors[3,4]. These receptors mediate the production of neuronal nitric oxide (NO) and, therefore, the hypothesis was raised that schizophrenia could be related to decreased levels of NO in the brain.

To test this hypothesis, researchers pretreated rats with sodium nitroprusside (SNP), an NO donor, before injecting them with ketamine, which typically induces psychotic-like symptoms. They reported that pretreatment with SNP prevented behavioral changes in the animals that are commonly associated with positive symptoms in humans, such as hyperactivity and stereotypy, and that this effect lasted for up to one week[3,5].

Based on the results of animal studies and on the fact that SNP is a safe drug long used for the management of hypertension, clinical investigators decided to test the effects of the drug in schizophrenia patients. Hallak *et al.*[6] and Maia-de-Oliveira *et al.*[7,8] described rapid improvements in psychotic symptoms and cognitive measures after a single, acute infusion of SNP. Using the same design as Hallak *et al.*[6], Stone *et al.*[9] failed to find the same improvements, explaining that the divergent findings could result from differences in the clinical characteristics of the two samples, mainly length of illness and symptom exacerbation.

In order to further investigate the connection between glutamate, NO and schizophrenia, we conducted a double-blind, placebo-controlled trial to test whether the administration of SNP could prevent schizophrenia-like symptoms induced by ketamine in humans, and whether different doses of SNP would present differences in effectiveness and safety.

Methods

Subjects

The sample consisted of 38 healthy volunteers aged 18-45 years. The minimum education required was complete high school. Volunteers were recruited by advertisement in public areas. Exclusion criteria were the presence of clinical diseases or psychiatric disorders, history of hypersensitivity to ketamine or SNP, diagnosis of substance abuse or dependence, history of professional help-seeking for emotional difficulties, psychiatric disorders in first-degree relatives, clinically significant psychosocial stress and a positive pregnancy test.

Drugs

The experimental substances used were: (i) SNP (Nipride®, Biolab Sanus) in lyophilized powder, dissolved in physiological saline solution, and administered by intravenous infusion, in three different doses (0.125; 0.25 and 0.5 mcg/kg/min); (ii) ketamine ((S)-

Address for correspondence: Jaime E. C. Hallak. Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo. Av. Bandeirantes, 3900, 3º andar – 14048-900 – Ribeirão Preto, SP, Brazil. Telephone: +55 (16) 3602-2853. E-mail: jechallak@gmail.com

ketamine – Ketalar®), dissolved in saline solution, and administered by intravenous infusion (0.26 mg/kg in bolus followed by 0.25 mg/kg/h); and (iii) placebo, which consisted of saline solution infused according to the same procedures as SNP.

Assessments

General psychopathology was assessed using the Brazilian Portuguese version of the Brief Psychiatric Rating Scale (BPRS)[10] and dissociative symptoms were quantified using the Clinician-Administered Dissociative States Scale (CADSS)[11].

The basic cognitive domains investigated included attention, working memory, and verbal fluency, respectively assessed using the Stroop Color Word Test (SCWT)[12], N-Back, and FAS. Facial affect processing, a component of social cognition, was assessed using a computerized facial emotional expression and identity matching task.

Procedure

The study was approved by the Research Ethics Committee of the Ribeirão Preto Medical School University Hospital and volunteers were informed about the characteristics and implications of the study and provided their signed consent to participate.

The subjects were assessed with screening interviews in the first meeting and two experimental sessions were performed within the following month with an interval of at least one week between sessions. They were instructed to remain abstinent from psychoactive substances for at least four weeks prior to the sessions.

In each session, volunteers were injected with ketamine and SNP or placebo. The 38 volunteers were randomly assigned to the three groups that received different doses of SNP (SNP-0125: n = 16; SNP-0250: n = 11; SNP-0500: n = 11). As they arrived at the Laboratory of Psychopharmacology, the first sequence of rating scales was completed. After vital signs were checked, the intravenous infusion of placebo or SNP was initiated and maintained for 75 minutes.

The BPRS was applied immediately after the beginning of the infusion. Ten minutes after the continuous infusion of placebo or SNP had been initiated in one of the subject's arms, a bolus injection of ketamine (0.26 mg/kg) was infused in the other arm over one minute. Ketamine was allowed to distribute for five minutes and then a maintenance dose of 0.25 mg/kg/h was administered for 50 minutes through an infusion pump. During the infusion of the experimental drugs, blood pressure was checked every five minutes, and heart rate and arterial oxygen saturation were continuously monitored. Shortly after the bolus infusion of ketamine, the BPRS and CADSS were applied and 15 minutes after the continuous infusion of ketamine was initiated, all tests proposed for the study were completed. At the end of the procedure, the CADSS and BPRS were completed once again.

Statistical analysis

The results were analyzed using repeated measures analyses of variance (rmANOVA) with drug (SNP and placebo), phase, and treatment group (SNP-0125, SNP-0250, and SNP-0500) as factors, followed by paired *t*-tests when indicated. Demographic characteristics were analyzed using analysis of variance for continuous variables (age and weight) and the chi-square test (χ^2) for the nominal variables gender and education. The physiological measures (maximum and minimum blood pressure and heart rate) were analyzed considering four measurements performed for each item (baseline, five minutes after the infusion of SNP or placebo, five minutes after the ketamine bolus and at the end of the experiment), with rmANOVA followed by paired *t*-tests when drug effects or drug-phase interactions were observed. All statistical tests were performed with SPSS software version 17.0.

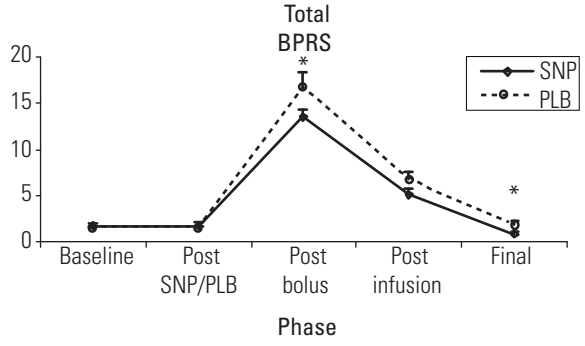
Results

There were no differences across the groups regarding age, sex, weight and education ($\chi^2 = 0.41$; df = 2; $p = 0.82$).

Overall, the tolerability, side effects, and effects on physiological parameters during the sessions were good. All subjects tolerated both experimental sessions well. The most common side effect reported was nausea, particularly at the end of the experiment, which was already expected since it is relatively common after the administration of ketamine[13].

Regarding the physiological measures (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate [HR]), the rmANOVA showed phase effects on SBP ($F_{3-96} = 121.18$; $p < 0.01$), DBP ($F_{3-96} = 157.23$; $p < 0.01$) and HR ($F_{3-96} = 34.99$; $p < 0.01$). Drug effects were found on SBP ($F_{1-32} = 4.14$; $p = 0.05$) and DBP ($F_{1-32} = 4.65$; $p = 0.04$), but not on HR ($F_{1-32} = 0.02$, $p = 0.96$) with the infusion of SNP, which resulted in lower values compared to the placebo session. There were no interactions between drug and phase in any of the physiological measures and no evidence of dose-related effects of SNP either.

The analysis of BPRS total scores showed effects of phase ($F_{4-128} = 273.24$, $p < 0.01$), drug ($F_{1-32} = 6.38$, $p = 0.02$), and interaction between drug and phase ($F_{4-128} = 4.33$, $p < 0.01$), with the group that received SNP showing lower psychopathology scores in the evaluation following the ketamine bolus (t = 2.27, df = 34, p = 0.03) and in the final assessment (t = 2.48, df = 34, p = 0.02), compared to the placebo session (Figure 1).

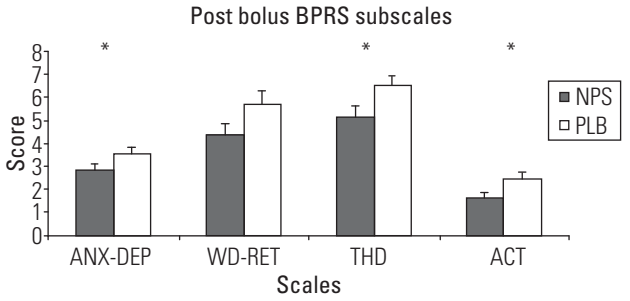


SNP: sodium nitroprusside; PLB: placebo; Post bolus: evaluation after bolus administration of ketamine; Post infusion: measure after 40 minutes of ketamine infusion. Final: measure after volunteer recovery phase. * p < 0.05.

Figure 1. Total BPRS scores in different time points.

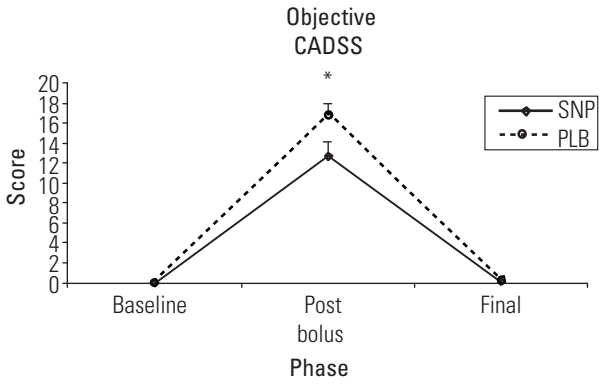
There were no detectable effects of specific doses of SNP doses ($F_{2-32} = 1.90$, $p = 0.17$). Regarding the BPRS subscales in the post bolus phase, scores in the SNP sessions were lower than those in the placebo session, showing statistically significant differences for the subscales anxiety-depression (t = 2.02, df = 34, $p = 0.05$), thought disorder (t = 2.46, df = 34, $p = 0.02$) and activation (t = 2.02, df = 34, $p = 0.05$), with a tendency to a significant difference between SNP and placebo in the emotional withdrawal subscale (t = 1.96, df = 34, $p = 0.06$) (Figure 2).

The CADSS is formed by two subscales, with subjective and objective items. With respect to the subjective items, rmANOVA showed an effect of phase ($F_{2-64} = 268.6$, $p < 0.01$), but no significant differences were observed for drug ($F_{1-32} = 2.69$, $p = 0.11$), interaction between drug and phase ($F_{2-64} = 1.76$, $p = 0.18$) or SNP dose ($F_{1-32} = 0.23$, $p = 0.79$). The analysis of the scores in the objective items showed effects of phase, drug, and interaction between drug and phase. The group taking SNP presented lower general scores and lesser score variations in the post bolus evaluation when compared to baseline (Figure 3). There was no evidence of effect of the dose of SNP.



SNP: sodium nitroprusside; PLB: placebo; ANX-DEP: anxiety-depression subscale; WD-RET: withdrawal-retardation subscale; THD: thought disorder subscale; ACT: activation subscale. * p < 0.05.

Figure 2. Scores in the subscales of the BPRS after injection of the ketamine bolus.



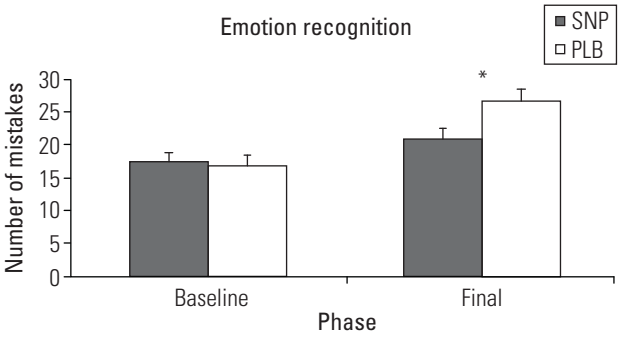
SNP: sodium nitroprusside; PLB: placebo; Post bolus: evaluation after bolus administration of ketamine; Final: measured after volunteer recovery phase. * p < 0.05.

Figure 3. Scores in the objective items of the CADSS at different time points.

The analysis of the performance in the Stroop Color Word Test showed only an effect of phase regarding the time spent for the execution of the task ($F_{1-32} = 3.78$, $p = 0.05$) and number of mistakes ($F_{1-32} = 26.84$, $p < 0.01$), in both charts 1 and 2 (time: $F_{1-32} = 17.93$, $p < 0.01$; number of mistakes: $F_{1-32} = 17.42$, $p < 0.01$). However, no effects of drug, SNP dose, or interaction between drug and phase were observed. Similarly, the analysis of the performance in the N-back also showed an effect of phase ($F_{1-32} = 31.51$, $p < 0.01$), but no significant effects of drug ($F_{1-32} = 0.46$; $p = 0.5$), SNP dose ($F_{2-32} = 0.210$, $p = 0.9$) or interaction between drug and phase ($F_{2-32} = 0.7$, $p = 0.51$). The results in the FAS showed no differences with respect to letters F and A. Effects of phase ($F_{1-32} = 6.37$, $p = 0.02$) and drug ($F_{1-32} = 10.6$, $p < 0.01$) were found in regard to letter S, with a better performance of the group that was treated with SNP. However, no dose ($F_{2-32} = 0.06$, $p = 0.95$) or interaction ($F_{1-32} = 1.16$, $p = 0.29$) effects were observed.

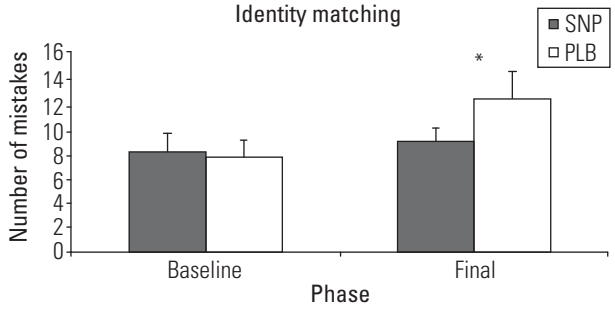
The analysis of emotion recognition data showed effects of phase ($F_{1-32} = 29.78$, $p < 0.01$), drug ($F_{1-32} = 4.92$, p = 0.03) and interaction between phase and drug ($F_{1-32} = 5.78$, $p = 0.02$), but no effect of SNP dose ($F_{2-32} = 0.92$, $p = 0.41$) regarding the number of mistakes. The *t*-test showed that the SNP group made fewer mistakes in these tasks (t = 3.32, df = 32, $p < 0.01$) (Figure 4).

Regarding the time for matching emotions, only effects of phase were observed ($F_{1-32} = 4.94$, $p = 0.03$). There were no effects of drug ($F_{1-32} = 0.01$, $p = 0.99$), interaction between drug and phase ($F_{1-32} = 0.96$, $p = 0.33$) or dose ($F_{2-32} = 1.83$, p = 0.19). As for the number of mistakes in the identity matching task, no effects were found for phase ($F_{1-32} = 2.40$, $p = 0.13$) or dose ($F_{2-32} = 0.95$, $p = 0.4$), but there were significant effects of drug ($F_{1-32} = 4.71$, $p = 0.04$) and interaction between phase and drug ($F_{1-32} = 4.18$, $p = 0.05$), with fewer mistakes in the SNP group (t = 2.36, df = 32, $p = 0.03$) (Figure 5). The analysis of the mean time for matching facial identities revealed no significant difference between groups. In shape matching, no differences between groups were found with regard to time or number of mistakes. In the color matching task, an effect of phase was observed in matching time ($F_{1-32} = 11.80$, $p < 0.01$), but no effects were observed for drug, dose or interaction between drug and phase. The control tasks showed differences only in the number of mistakes in color matching, with fewer mistakes in the SNP group (Figure 6).



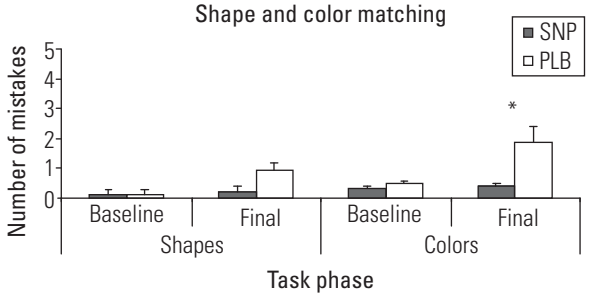
SNP: sodium nitroprusside; PLB: placebo; Final: final measure. * p < 0.05.

Figure 4. Number of mistakes in the emotion matching task.



SNP: sodium nitroprusside; PLB: placebo; Final: final measure. * p < 0.05.

Figure 5. Number of mistakes in the identity matching task.



SNP: sodium nitroprusside; PLB: placebo; Final: final measure. * p < 0.05.

Figure 6. Number of mistakes in the tasks of shape and color matching.

Discussion

To our knowledge, this was the first study to test the effects of SNP in healthy human volunteers injected with ketamine. As expected, blood pressure was increased immediately after the intravenous bolus infusion of ketamine during the placebo session, returning to normal levels near the end of the session, which indicates a transient increase that did not reach dangerous levels in any of the volunteers. The same was observed in respect to heart rate. These findings strengthen the cardiovascular safety of the administration of ketamine[14].

During the session with SNP, lower values of SBP and DBP were observed after the bolus of ketamine, as well as a faster recovery from the transient increase in blood pressure compared with the placebo session. These results were also expected since SNP has been used as a hypotensive agent in episodes of severe hypertension[15]. It is important to highlight that there were no significant changes in the physiological parameters for the different doses of SNP used. One possibility to explain this lack of difference among the SNP doses is that all three doses (0.125, 0.25, and 0.5 mcg/kg/min) were actually low compared to the dose required for SNP to achieve its hypotensive effect (the usual dose to treat hypertension is about 0.5-10 mcg/kg/min). Another possibility to explain this phenomenon is that individuals with no history of hypertension are more resistant to the hypotensive effects of SNP[16].

The psychotic-like manifestations induced by ketamine and evaluated with the BPRS were significantly lower during the administration of SNP when compared to placebo. This difference was observed both in the post bolus phase, indicating a lower induction of psychopathological symptoms in the acute phase, and in the final phase, suggesting a protective effect of SNP. When the scores of the BPRS subscales were analyzed separately, a reduction in the onset of symptoms induced by ketamine appeared in all four BPRS subscales in the SNP group, with significantly lower scores compared to placebo in the anxiety-depression, thought disorder and activation subscales, and with a tendency to significant reduction in the scores of the emotional withdrawal subscale.

The analysis of the objective items of the CADSS showed significantly decreased scores in the sessions with SNP compared with placebo. Although volunteers were unable to identify in which of the sessions they had received SNP, the clinical protection was significantly noticeable in these sessions. However, subjects did not recognize and did not identify this protection, which can be confirmed by the similar results on CADSS subjective scores between SNP and placebo sessions. This inability to identify clinical protection when under the effect of SNP may be attributed to the dissociative and amnestic effects induced by ketamine, which could have impaired the subjects' capacity for self-assessment.

In the Stroop test, a slightly faster reading pattern in sessions with SNP compared to placebo was found, but no statistical significance was reached. Neither the N-back nor the FAS scores presented significant differences between the SNP and placebo sessions. An interesting phenomenon was observed in the N-back test that suggests the possibility of a learning effect, since all the subjects showed an improvement in task performance in the second evaluation when compared to the first evaluation.

Although the Stroop, N-Back and FAS showed no evidence of enhanced cognitive performance in subjects treated with SNP, tests that evaluate social cognition (computerized tasks for matching emotional expression and facial identity) did provide evidence of a better performance compared to the placebo group. Subjects using placebo made more mistakes than those taking SNP, suggesting that SNP was able to attenuate the impairment in social cognition induced by ketamine. Interestingly, these tests were not presented in the same way from one session to another, as the Stroop, N-Back and FAS were. For each session, there was a new random sequence of the same stimuli, which made the possibility of a learning effect unlikely. Regarding the control tasks (matching shapes and colors), a change in scores among groups was not expected since these are tasks of low complexity. However, a significant difference in scores between the groups was found in color matching. Volunteers who received SNP performed better when compared with volunteers who received placebo.

The precise mechanisms through which SNP may produce its antipsychotic effects are not completely understood. The most likely hypothesis to explain these findings seems to be related to SNP's ability to activate the NO pathway in the NMDA receptor. If the symptoms induced by ketamine are due to NMDA receptor antagonism, and consequently to an inhibition of NO production by nNOS, SNP would probably correct this dysfunction through its capacity to increase NO levels. Perhaps the ability of NO to modulate cascades of protein kinases, transcription factors, and other gene products means that its cascading effects last even when SNP is no longer directly active. There is also evidence that NO acts directly on NMDA receptors[17], which may correct an NMDA receptor dysfunction, and that NO also leads to an inhibition of dopamine transporters, which may counteract dopamine hypoactivity in the prefrontal cortex and, through feedback loops, fix a hyperactivity of dopamine in the accumbens and striatum, both abnormalities often found in individuals with schizophrenia[18].

Interestingly, we have recently found that the administration of SNP produced a break in the pattern of the sleep-wake cycle in mice treated with ketamine that was similar to that found in animals depleted of dopamine[19]. Bujas-Bobanovic *et al*.[4] described that SNP was able to inhibit the schizophrenia-like behavior and brain c-fos expression in rats induced by PCP, an NMDA receptor antagonist. Also, Issy *et al*.[20] reported that SNP attenuated the schizophrenia-like changes in prepulse inhibition in rats induced by amphetamine, a dopaminergic agonist.

The small sample size is a limitation of this study. Further work with larger numbers of participants is necessary. Also, to avoid adverse effects resulting from the formation of cyanide or thiocyanate which may occur when doses higher than 5 mcg/kg/min of SNP are used, typically for a period greater than 24 hours[21], SNP was used in this study in minimal doses (0.125; 0.25 and 0.5 mcg/kg/min), for a short period (75 minutes), and in a single infusion. The three doses of SNP showed no significant differences in any of the parameters evaluated. Future experiments should examine the effects and safety of higher doses and multiple infusions of SNP.

Since the schizophrenia-like syndrome induced by NMDA receptor antagonists is now a frequently used pharmacological model for studying schizophrenia, these findings give support to the hypothesis that NO donors such as SNP may have beneficial effects for schizophrenia patients[22-25]. Several studies have shown that the prevention of psychotic relapse has major implications for the minimization of damage and of some disabilities that typically affect patients with schizophrenia[26,27], and the results described here suggest that SNP may represent a new approach for the management of the disorder.

Disclosure

The authors report no conflicts of interest.

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