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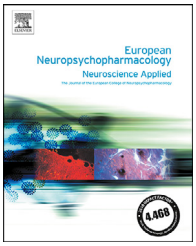

SHORT COMMUNICATION

Enhancement of the antipsychotic effect of risperidone by sodium nitroprusside in rats

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Abstract
Recently, a single injection of the nitric oxide donor sodium nitroprusside (SNP) was found to induce a rapid and sustained antipsychotic effect in treatment-resistant schizophrenia (TRS). Moreover, a single i.p. injection of SNP in rats was found to generate both rapid and persisting changes in brain synaptic plasticity, including enhanced excitatory postsynaptic current responses and spine morphology in layer V pyramidal cells in the medial prefrontal cortex (mPFC) brain slices. Here we used the conditioned avoidance response (CAR) test in rats to investigate the antipsychotic-like efficacy of SNP in combination with low-dose risperidone. In addition, we performed microdialysis experiments in freely moving rats to measure neurotransmitter efflux in the mPFC and the nucleus accumbens (NAc). Risperidone caused only 20% suppression of CAR, which is far below the degree of CAR suppression required to predict a significant clinical antipsychotic effect. Addition of a low dose of SNP to risperidone dramatically enhanced the antipsychotic-like effect to a clinically relevant level. SNP significantly enhanced the risperidone-induced dopamine output in the mPFC but not in the NAc. The increased prefrontal dopamine release induced by the drug combination may also improve cognition as indicated by previous preclinical and clinical studies and, furthermore, via enhanced synaptic spine function and morphology in mPFC generate a both rapid and prolonged antipsychotic and pro-cognitive effect. Our results delineate SNP as a promising new treatment option

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for schizophrenia, including TRS, when added to currently available antipsychotic medication in order to improve efficacy at maintained or even reduced dosage.

1. Introduction

Schizophrenia is a serious mental disorder that affects approximately 1% of the global population and has a huge impact on the quality of life of patients as well as their families. For 25% of the patients there is currently no effective medication available (Harvey and Rosenthal, 2015). This emphasizes the high need for novel, more efficacious drugs for the treatment of schizophrenia, in particular treatment-resistant schizophrenia (TRS).

Recently, the glutamate-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway, has received increased interest as a target for novel antipsychotic drugs (APDs), since the pathway has been implicated in the pathogenesis of schizophrenia (Bernstein et al., 2011). Moreover, in schizophrenic patients reduced brain NO levels compared to healthy individuals have been found in cerebrospinal fluid (Ramirez et al., 2004). Furthermore, postmortem studies demonstrated that schizophrenic patients have significantly fewer NO synthase (NOS)-containing striatal interneurons (Akbarian et al., 1993; Fritzen et al., 2007). NO is synthesized after N-methyl-D-aspartate receptor (NMDAR) activation and will diffuse and activate soluble guanylyl cyclase, which will subsequently produce cGMP (Shim et al., 2016). As brain NMDAR dysfunction has been solidly demonstrated in schizophrenia (c.f. Howes et al., 2015), this may clearly contribute to the reduced brain NO levels in the patients. Moreover, it has been shown that polymorphisms in the NOS1 gene are associated with schizophrenia, thus decreased NOS1 expression might increase the susceptibility to develop schizophrenia by contributing to the hippocampal hypoglutamatergic state (c.f. Reif et al., 2006).

A single injection of the antihypertensive NO donor sodium nitroprusside (SNP) may induce a rapid (within 4 h) and sustained (several weeks) antipsychotic effect in young treatment-resistant schizophrenic patients on a stable antipsychotic medication (Hallak et al., 2013). In an additional case study, also clozapine-refractory schizophrenic patients showed the same effect (Maia-de-Oliveira et al., 2014). Since clozapine is the only FDA approved APD for TRS, these findings underline the clinical potential of SNP. An analogous study also revealed improved cognition (Maia-de-Oliveira, et al., 2015a, 2015b). Moreover, a double blind study in healthy individuals showed that SNP reduced psychotomimetic symptoms induced by ketamine (Rezende et al., 2017).

Previous preclinical behavioral studies suggest that SNP may possess antipsychotic potential. Thus, SNP administration in rats completely abolished phencyclidine (PCP) induced hyperactivity (Bujas-Bobanovic et al., 2000). Moreover, a single dose of SNP was found to prevent ketamine induced hyperactivity up to a week after the SNP injection (Maia-de-Oliveira et al., 2015a) and also restored memory deficits caused by ketamine in the novel object recognition test (Trevlopoulou et al., 2016).

Using whole cell patch clamp recording Liu et al. showed that a single intraperitoneal (i.p.) injection of SNP (3 mg/kg) causes both rapid and persisting changes in brain synaptic plasticity, including enhanced excitatory postsynaptic current responses and spine morphology in layer V pyramidal cells in rat medial prefrontal cortex (mPFC) brain slices (Liu et al., 2015).

In the present study the antipsychotic effect of a low dose of SNP in combination with a sub-effective dose of risperidone was investigated both behaviorally and biochemically in rats in order to further elucidate the underlying mechanisms in the brain.

2. Experimental procedures

2.1. Animals

Young adult male Wistar rats were obtained from Charles River (Germany) and Janvier (France) for behavioral and microdialysis studies respectively and weighed approximately 200 g at arrival. The rats were housed in groups of 4 in standard laboratory conditions, at a room temperature of ~21 °C, relative humidity of 55-65% and food and water available *ad libitum*. Animals had a plastic tube, wooden block and sizzle-nest in their home cage as cage enrichment. The CAR animals were kept at a reversed 12 h day night cycle (lights off at 6:00 a.m.). The animals in the microdialysis experiments were kept at a normal 12 h day night cycle (lights on at 6:00 a.m.). All animals were allowed to acclimatize for 1 week before the experiment started. Experiments were approved by the local animal ethics committee, Stockholm North, and the Karolinska Institutet, Sweden.

2.2. Drugs

Risperidone was provided by Johnson & Johnson, SNP was obtained from Sigma-Aldrich. Risperidone was dissolved in a minimal amount of acetic acid (10 μl/mg risperidone) and afterwards dissolved in 5.5% glucose. Vehicle consisted of 10 μl/ml acetic acid in 5.5% glucose. SNP was dissolved in saline (0.9% NaCl) and kept in the dark until injection, since it is photosensitive. All treatments were administered intraperitoneally (i.p.) at a volume of 2 ml/kg in the CAR experiments and at a volume of 1 ml/kg for the microdialysis experiment. The used doses of SNP (1 and 1.5 mg/kg) were chosen based on previous preclinical behavioral studies (c.f. Bujas-Bobanovic et al., 2000).

2.3. Conditioned avoidance response (CAR)

Rats were trained and tested in conventional shuttle boxes (530 × 250 × 225 mm), which were divided into 2 compartments of equal size by a plastic divider with an opening in the middle. Before testing, the rats were habituated to the shuttle box for 5 min. When an 80 dB white noise was presented to the rats, they had 10 s to move from one compartment to the other, if they did this within 10 s this was defined as an avoidance. When they failed to do so, an intermittent foot shock of ~0.4 mA

was delivered to the grid floor, the shock duration was 0.5 s and the inter shock interval was 2.5 s. When the rats moved to the other compartment, the shocks and the noise stopped, this was defined as an escape. If a rat failed to move to the other compartment within 60 s after the noise had started, the shocks and the noise would stop and this was termed an escape failure. If 3 escape failures in a row occurred, the session automatically stopped. Animals were trained daily for 5 days, each session consisted of approximately 20 trials randomly divided over 15 min. The rats had to reach a criterion of at least 85% avoidance to be included in the experiment. Experimental sessions lasted 10 min and were performed before drugs were administered (pretest), 20, 90 and 240 min after injection of the drugs. Experimental days were separated by at least 2 non-experimental days. 10 animals were tested in a counterbalanced change-over design, in which they served as their own controls.

2.4. *In vivo* microdialysis

Rats were anaesthetized with a cocktail of Hypnorm® (0.315 mg/ml fentanyl citrate and 10 mg/ml fluanisone; Jansen-Cilag Ltd, UK) and Dormicum® (5 mg/ml midazolam; Roche AB, Sweden) diluted with distilled water (1:1:2), 5 ml/kg of this cocktail was injected i.p. before surgery. The rats were mounted into a strereotaxic frame and kept on a heating pad to prevent hypothermia. Dialysis probes were then implanted into the medial prefrontal cortex (mPFC; with an angle of 12°) or nucleus accumbens (NAc), the coordinates (in mm) were anteroposterior +2.5, +1.6; mediolateral −1.4, −1.4; dorsoventral −6.0, −8.2, respectively and relative to bregma or dural surface (Paxinos and Watson, 2006). A semipermeable membrane (Filtral AN69, Hospal Industries, France) with an active surface length of 4 mm (mPFC) or 2 mm (NAc) was used for dialysis. Microdialysis experiments were performed 2 days after surgery in freely moving animals. The probe was perfused with perfusion solution (in mM 147 NaCl, 3.0 KCl, 1.3 $CaCl_2$, 1.0 $MgCl_2$, 1.0 Na HPO_4, pH 7.4) at a flow rate of 2.5 μl per minute set by a microinfusion pump (Harvard Apparatus, USA). Dialysate samples were collected for 30 (mPFC) or 15 (NAc) minutes and then analyzed by reversed phase high-performance liquid chromatography (HPLC) coupled to electrochemical detection with a detection limit of ∼0.08 nM (ESA, Bioscience, USA) in order to monitor dopamine. The injector (Valco Instruments, USA) was directed by a computerized system (Clarity 7.0, DataApex, Czech Republic). The mobile phase of the HPLC consisted of 10% methanol, ∼120 mg/L octanesulfonic acid, 10 μM EDTA, 55 mM sodium acetate and acetic acid was added till pH 4.0.

Injection of drugs was performed when rats showed a stable dopamine outflow over an hour. First, SNP or saline was injected, 30 min later, risperidone or vehicle was administered. Baseline was calculated as the average dopamine outflow of the last 2 (mPFC) or 4 (NAc) samples before injection. The dopamine levels were expressed as a percentage of these baseline levels. After the experiment the placement of the probe was histologically verified.

2.5. Statistics

The data from the CAR experiments were analyzed with Friedman's analysis of variance (ANOVA). When this showed significant differences between groups, Wilcoxon matched-pairs signed-ranks tests were performed as follow up test. The area under the curve (AUC) was used for the analysis of the microdialysis data (mPFC: minute 60-150, NAc: minute 45-135). The AUC was calculated and compared between treatments using a one-way ANOVA followed by planned comparisons, to see whether there were differences between treatments in dopamine outflow in the mPFC or NAc. In order to find out whether there were differences between baseline values among the animals a one-way ANOVA was performed. Finally, to detect possible outliers, the Grubbs test was performed.

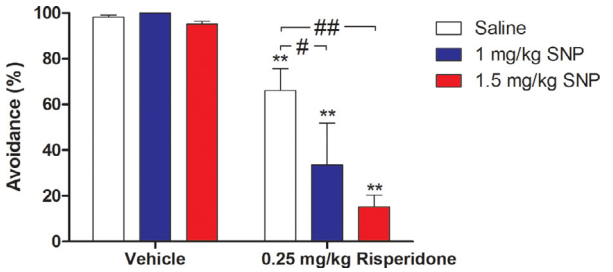

Fig. 1 The effect of sodium nitroprusside (SNP) (1 and 1.5 mg/kg) alone and in combination with risperidone (0.25 mg/kg) on CAR behavior 20 min after drug administration. The results are presented as median ± semi-interquartile range. $^{**}p<0.01$ compared to vehicle + saline, $^{\#}p<0.05$, $^{\#\#}p<0.01$ compared to risperidone (0.25 mg/kg) + saline, $n=10$.

3. Results

3.1. Conditioned avoidance response

A significant effect of treatment was found in the CAR test 20 min after drug administration ($\chi^2(5)= 45.836$, $p< 0.001$). Post-hoc tests showed that risperidone (0.25 mg/kg) + saline caused significantly lower avoidance levels than vehicle + saline ($Z= -2.807$, $p=0.005$) (Fig. 1). Furthermore, both risperidone (0.25 mg/kg) + SNP (1 mg/kg) and risperidone (0.25 mg/kg) + SNP (1.5 mg/kg) caused a significant decrease in avoidance behavior compared to vehicle + saline ($Z= -2.812$, $p=0.005$; $Z= -2.807$, $p=0.005$) and risperidone (0.25 mg/kg) + saline ($Z= -2.312$, $p=0.021$) ($Z= -2.805$, $p=0.005$) (Fig. 1). 2 rats treated with risperidone (0.25 mg/kg) + SNP (1.5 mg/kg) had 1 escape failure, indicating that there is a low risk of unspecific side effects. Moreover, at 90 and 240 min after drug administration all the rats had returned to baseline levels of CAR suppression (≤15% suppression of CAR).

3.2. *In vivo* microdialysis

There were no significant differences between the groups in the baseline values of dopamine. To compare dopamine outflow between the different treatments the AUC was used. A significant effect of treatment was found when the different AUCs of dopamine outflow in the mPFC and NAc were compared ($F_{(5,42)}= 15.659$, $p<0.001$ and $F_{(5,35)}= 6.987$, $p<0.001$). Post-hoc analysis with planned comparisons revealed that rats treated with risperidone (0.25 mg/kg) + saline ($t=2.451$, $p=0.019$), risperidone (0.25 mg/kg) + SNP (1 mg/kg) ($t=4.483$, $p<0.001$) or risperidone (0.25 mg/kg) + SNP (1.5 mg/kg) ($t=7.341$, $p<0.001$) significantly increased their dopamine outflow in the mPFC compared to vehicle + saline treated rats. Moreover, risperidone (0.25 mg/kg) + SNP (1.5 mg/kg) showed

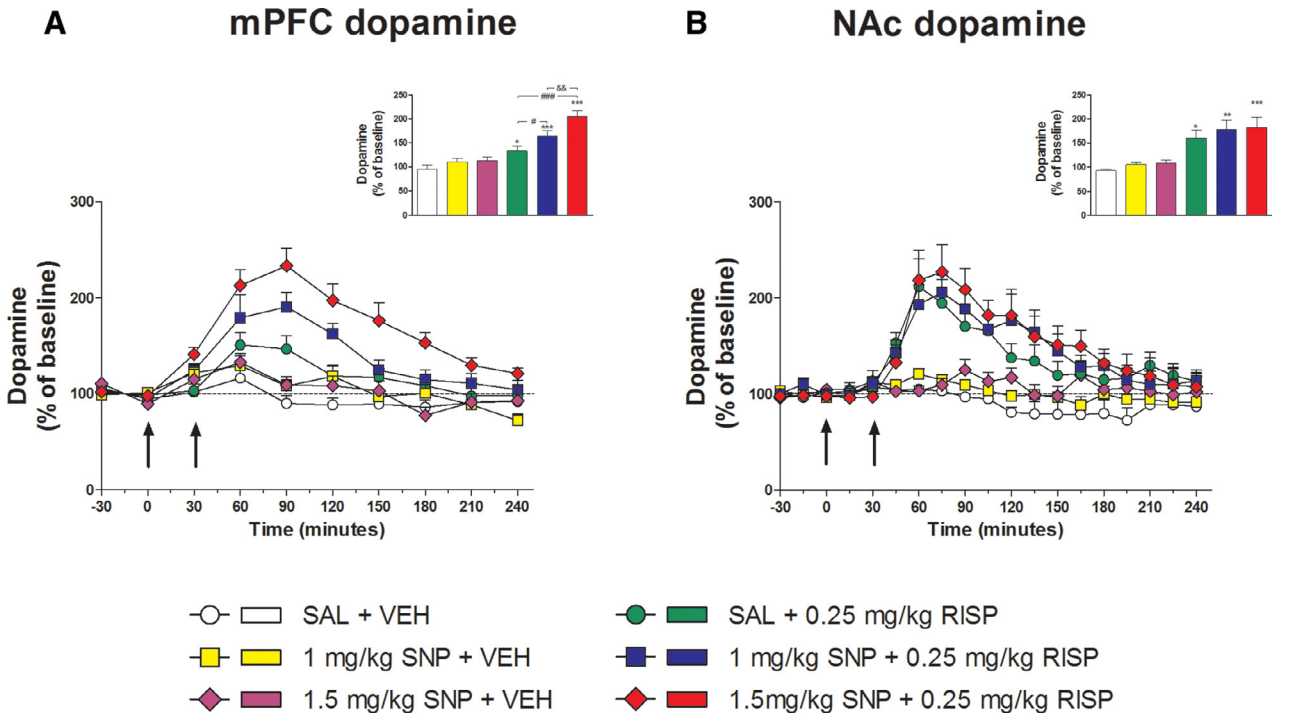

Fig. 2 The effect of SNP (1 and 1.5 mg/kg) alone and in combination with 0.25 mg/kg risperidone on dopamine outflow in the medial prefrontal cortex (A) and nucleus accumbens (B). The results are presented as mean + SEM, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ compared to vehicle (VEH) + saline, $^{\#}p<0.05$, $^{\#\#\#}p<0.001$ compared to risperidone (RISP) (0.25 mg/kg) + saline, $^{\&\&}p<0.01$ compared to SNP (1 mg/kg) + risperidone (0.25 mg/kg). $n = 5$-9.

significantly higher dopamine outflow compared to risperidone (0.25 mg/kg) + saline ($t = 5.185$, $p < 0.001$) and risperidone (0.25 mg/kg) + SNP (1 mg/kg) ($t = 2.956$, $p = 0.005$).

Furthermore, post-hoc analysis showed that rats treated with risperidone (0.25 mg/kg) + saline ($t = 3.290$, $p = 0.002$), risperidone (0.25 mg/kg) + SNP (1 mg/kg) ($t = 3.518$, $p = 0.001$) or risperidone (0.25 mg/kg) + SNP (1.5 mg/kg)($t = 4.340$, $p < 0.001$) showed significantly higher dopamine levels in the NAc compared to rats treated with vehicle + saline. The dopamine outflow in the mPFC and NAc over time and the differences in the AUCs are shown in Fig. 2(A) and (B) respectively.

4. Discussion

The present study shows that a single injection of a low dose SNP may significantly enhance the antipsychotic-like effect of a sub-effective dose of risperidone in the CAR test, although SNP on its own had no antipsychotic-like effect. The CAR test has shown excellent predictive validity in determining the clinical antipsychotic potential of drugs (Wadenberg, 2010). Therefore, our behavioral data provide both novel and strong support for the preceding clinical study by Hallak et al. (2013), but not for three subsequent clinical trials (Stone et al., 2016; Wang et al., 2018; Brown et al., 2019), probably, related to the high age and long disease duration in the these patients. This seems highly significant, since there is a progressive disruption of neural circuits in schizophrenia which underpins the need to intervene as early as possible in the course of the disease (Millan et al., 2016). Indeed, the patients in the Hallak study had an average age of 25.6 years, whereas in the 3 subsequent studies the average ranged from 29 to 47.1 years. Consequently, adjunctive SNP should be more effective in younger patients with short disease duration.

Biochemically, we demonstrate that SNP may significantly enhance the risperidone-induced dopamine release in the mPFC, but not in the NAc, although SNP alone had no effect on dopamine release in the mPFC or NAc. Recent PET-fMRI data solidly confirm a reduced prefrontal dopamine release in schizophrenia, which relates to cognitive deficits and negative symptoms (Slifstein et al., 2015). Thus, the SNP-induced increase in risperidone-induced prefrontal dopamine release may substantially contribute to the improvement of cognitive impairment as well as negative and depressive symptoms in schizophrenic patients (Hallak et al., 2013; Maia-de-Oliveira et al., 2014; 2015a, 2015b). This is very important, since the degree of cognitive impairment is a critical determinant of treatment outcome (c.f. Goldman-Rakic et al. 2004).

The antipsychotic augmentation by a single injection of SNP considerably outlasts its presence in the body (Hallak et al., 2013), which is also supported by previous preclinical data (Maia-de-Oliveira et al. 2015a, 2015b; Liu et al. 2015). Furthermore, our preliminary data on NO levels in the mPFC and NAc, as measured by highly sensitive NO amperometric microsensors, show that SNP administration (1.5 mg/kg i.p.) causes a rapid, short-lasting and major increase in NO levels, which is in accordance with previous results (Selvakumar et al., 2014), where a systemic injec-

tion of SNP induced a rapid increase of NO levels in the NAc. This may thus be the critical mechanism required to generate the long lasting clinically observed effects as well as the enhanced synaptic plasticity observed by Liu et al. (2015).

In conclusion, our study provides novel behavioral and biochemical support for the unique utility of low doses SNP to improve the efficacy of antipsychotic medication in schizophrenia. Moreover, our results propose that adjunct SNP treatment should allow for the use of lower doses of APDs with reduced risk of side effects.

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Declaration of Competing Interest

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CRediT authorship contribution statement

Joep Titulaer: Formal analysis, Data curation, Project administration, Writing - original draft, Writing - review & editing. **Anna Malmerfelt:** Formal analysis. **Monica M. Marcus:** Formal analysis, Supervision. **Torgny H. Svensson:** Funding acquisition, Supervision, Resources, Writing - review & editing.

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