Cannabidiol and Sodium Nitroprusside: Two Novel Neuromodulatory Pharmacological Interventions to Treat and Prevent Psychosis

José Alexandre Crippa*,1, Jaime Eduardo Cecílio Hallak1, Vanessa Costhek Abílio2, Acioly Luiz Tavares de Lacerda3 and Antonio Waldo Zuardi1

1Department of Neuroscience and Behavior, University of São Paulo, Ribeirão Preto, São Paulo, Brazil
2Department of Pharmacology, Universidade Federal de São Paulo, São Paulo, Brazil
3Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil

Abstract: Since most patients with schizophrenia do not respond properly to treatment, scientific effort has been driven to the development of new compounds acting on pharmacological targets beyond the dopaminergic system. Therefore, the aim is to review basic and clinical research findings from studies evaluating the effects of cannabidiol (CBD), an inhibitor of the reuptake and metabolism of anandamide and several other effects on nervous system, and sodium nitroprusside, a nitric oxide donor, on the prevention and treatment of psychosis. Animal and human research supports that CBD and sodium nitroprusside might be effective in the prevention and treatment of psychosis in general and especially in schizophrenia. The evidence available to date shows that CBD and sodium nitroprusside act in pathways associated with psychotic symptoms and that they may be important agents in the management of prodromal psychotic states and psychosis. This underscores the relevance of further research on the effects of these agents and others that mediate the activity of the cannabinoid system and of nitric oxide, as well as comparative studies of their antipsychotic effects and those of other antipsychotic drugs currently used to treat schizophrenia.

Keywords: Antipsychotic, cannabidiol, psychosis, schizophrenia, sodium nitroprusside.

1. INTRODUCTION

Different sources of evidence suggest that early intervention in psychosis is associated with better outcomes. In addition, data from prevention programs have demonstrated that attenuated psychotic manifestations can be reliable predictors to transition in a significant proportion of subjects in ultra high risk for psychosis (UHR). Research has shown that even UHR subjects who do not develop psychosis usually have impaired social functioning, high distress levels and various comorbid conditions, carrying a poor prognosis for a range of adverse sequela. Keeping this in mind, preventive interventions have been designed to address a number of psychopathological manifestations and functional impairments associated with them [1].

Although still limited, pharmacological trials involving UHR subjects have provided insights on the potential role of some drugs as strategies to prevent psychosis. Antipsychotic drugs were shown to prevent transition to psychosis in UHR subjects, with decreases in transition rates ranging from 37 to 45% [2]. However, major concerns have been raised in respect to preventive interventions based on antipsychotics because of tolerability issues. In fact, significant side effects occur in most individuals exposed to this class of medicat-

*Address correspondence to this author at the Hospital das Clínicas - Terceiro Andar; Av. Bandeirantes, 3900; Ribeirão Preto - São Paulo, CEP - 14049-900, Brazil. Email: jcrippa@fmrp.usp.br

© 2015 Bentham Science Publishers
2. SEARCHING STRATEGY AND SELECTION CRITERIA

The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, Scielo, PubMed, and PsycINFO, combining the search terms "cannabidiol and psychosis", "cannabidiol and schizophrenia", "sodium nitroprusside and psychosis" and "sodium nitroprusside and schizophrenia". The reference lists of the publications included, review articles, and book chapters were handsearched for additional references. Experimental animal and human studies were included, with no time restraints.

2.1. Cannabidiol

Recent evidence suggests that a new drug to alleviate psychotic symptoms could be obtained from one of the oldest plants used by humans as a medicine: Cannabis sativa. This may sound paradoxical, as the earliest references to the use of Cannabis confirmed over time and by recent research - show that high concentrations of its main psychoactive component, ∆9-tetrahydrocannabinol (∆9-THC) in fact induce psychotic symptoms [3]. However, we know today that cannabis contains more than 80 cannabinoids, many of which have pharmacological properties.

The first evidence that one of such compounds could antagonize the effects of ∆9-THC emerged from a study on the interaction between cannabidiol (CBD) and ∆9-THC in healthy volunteers [4]. The co-administration of the two cannabinoids induced less anxiety and psychotomimetic symptoms than ∆9-THC alone. This observation triggered a series of studies, in both animals and humans, which have established a link between CBD and antipsychotic effects (Table 1).

In animals, evidence of the antipsychotic effects of CBD was obtained from different models used to assess antipsychotic activity, including apomorphine-induced stereotypy, prolactin levels, amphetamine- and ketamine-induced hyperlocomotion, MK-801 induced pre-pulse inhibition (PPI) disruption, social withdrawal provoked by ∆9-THC and MK-801, and MK-801-induced hyperactivity [3]. Recently, we have demonstrated that CBD also antagonizes the effects of ∆9-THC emerged from a study on the interaction between cannabidiol and ∆9-THC in healthy volunteers [4]. The co-administration of the two cannabinoids induced less anxiety and psychotomimetic symptoms than ∆9-THC alone. This observation triggered a series of studies, in both animals and humans, which have established a link between CBD and antipsychotic effects (Table 1).

In animals, evidence of the antipsychotic effects of CBD was obtained from different models used to assess antipsychotic activity, including apomorphine-induced stereotypy, prolactin levels, amphetamine- and ketamine-induced hyperlocomotion, MK-801 induced pre-pulse inhibition (PPI) disruption, social withdrawal provoked by ∆9-THC and MK-801, and MK-801-induced hyperactivity [3]. Recently, we have demonstrated that CBD also antagonizes the effects of ∆9-THC emerged from a study on the interaction between cannabidiol and ∆9-THC in healthy volunteers [4]. The co-administration of the two cannabinoids induced less anxiety and psychotomimetic symptoms than ∆9-THC alone. This observation triggered a series of studies, in both animals and humans, which have established a link between CBD and antipsychotic effects (Table 1).

The first case report of a schizophrenic patient treated with CBD involved a female patient with severe side effects from conventional antipsychotics [24]. The patient was treated with CBD for four weeks and had a significant reduction in the Brief Psychiatric Rating Scale (BPRS) scores. In a similar study, three male patients with treatment-resistant schizophrenia were treated with CBD for 30 days and only one had a partial improvement [25]. However, of the two patients who did not respond, one responded only to clozapine and the other did not respond even to this drug.

An open clinical trial with six outpatients with Parkinson’s disease (PD) who had psychotic symptoms showed a significant reduction in the scores of the BPRS and the Parkinson Psychosis Questionnaire under CBD treatment added to treatment as usual [26].

To date, two double-blind controlled clinical trials investigated the efficacy and tolerability of CBD in schizophrenia patients. One study compared the effects of CBD and amisulpride, an atypical antipsychotic, in 42 schizophrenia patients. Researchers measured ∆9-THC/CBD ratios in hair samples of cannabis users and observed that subjects who had only ∆9-THC in their hair had more positive psychotic symptoms than those with a mixture of ∆9-THC and CBD [18, 20]. Studying users in episodes of acute intoxication by cannabis samples with high and low concentrations of CBD, those same researchers failed to find any protective effects of CBD against psychotomimetic symptoms [20]. However, this lack of protective effects could be attributed to a lower CBD/THC ratio in the cannabis samples smoked by users compared with studies in which such effects were observed.

The view that CBD could have antipsychotic effects is further supported by studies in healthy human subjects with artificially induced psychosis. CBD was shown to attenuate psychotic symptoms caused by acute administration of ∆9-THC, the perceptual impairment of the illusory image (Binocular Depth Inversion test) induced by nabilone, and depersonalization symptoms induced by ketamine [3].

Naturalistic studies with marijuana users suggest a protective effect of high CBD concentrations in samples of the plant against psychotic symptoms. Researchers measured ∆9-THC/CBD ratios in hair samples of cannabis users and observed that subjects who had only ∆9-THC in their hair had more positive psychotic symptoms than those with a mixture of ∆9-THC and CBD [18, 20]. Studying users in episodes of acute intoxication by cannabis samples with high and low concentrations of CBD, those same researchers failed to find any protective effects of CBD against psychotomimetic symptoms [20]. However, this lack of protective effects could be attributed to a lower CBD/THC ratio in the cannabis samples smoked by users compared with studies in which such effects were observed.

The view that CBD could have antipsychotic effects is further supported by studies in healthy human subjects with artificially induced psychosis. CBD was shown to attenuate psychotic symptoms caused by acute administration of ∆9-THC, the perceptual impairment of the illusory image (Binocular Depth Inversion test) induced by nabilone, and depersonalization symptoms induced by ketamine [3].

Despite the existence of negative results, the studies mentioned above suggested an antipsychotic action of CBD. The mechanism through which CBD exerts its antipsychotic effect is not yet clear; however, some experimental results allow the formulation of initial hypotheses.
Table 1. Antipsychotic effects of cannabidiol (CBD).

<table>
<thead>
<tr>
<th>Mode</th>
<th>Subjects</th>
<th>Results (Symbol*)</th>
<th>Dose with Significant Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal Models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apomorphine stereotypy</td>
<td>Rats</td>
<td>Reduction</td>
<td>(+) 60 mg/kg</td>
<td>Zuardi et al., 1991 [5]</td>
</tr>
<tr>
<td>Prolactin levels</td>
<td>Rats</td>
<td>Increase</td>
<td>(+) 240 mg/kg</td>
<td>Zuardi et al. 1991 [5]</td>
</tr>
<tr>
<td>Amphetamine hyperlocomotion</td>
<td>Mice</td>
<td>Reduction</td>
<td>(+) 30, 60 mg/kg</td>
<td>Moreira &amp; Guimarães, 2005 [6]</td>
</tr>
<tr>
<td>Ketamine hyperlocomotion</td>
<td>Mice</td>
<td>Reduction</td>
<td>(+) 30 mg/kg</td>
<td>Moreira &amp; Guimarães, 2005 [6]</td>
</tr>
<tr>
<td>MK-801 - PPI disruption</td>
<td>Mice</td>
<td>Reduction</td>
<td>(+) 5 mg/kg</td>
<td>Long et al., 2006 [7]</td>
</tr>
<tr>
<td>Δ9-THC - social withdrawal</td>
<td>Rats</td>
<td>Reduction</td>
<td>(+) 20 mg/kg</td>
<td>Malone et al., 2009 [8]</td>
</tr>
<tr>
<td>D-amphetamine hyperlocomotion</td>
<td>Mice</td>
<td>Negative acute effect</td>
<td>(-) - 50 mg/kg</td>
<td>Long et al., 2010 [9]</td>
</tr>
<tr>
<td>PPI - increase</td>
<td>Mice</td>
<td>Increase (acute and chronic)</td>
<td>(+) 1, 5, 50 mg/kg</td>
<td>Long et al., 2010 [9]</td>
</tr>
<tr>
<td>MK-801 - PPI disruption</td>
<td>Rats</td>
<td>No change</td>
<td>(-) -</td>
<td>Gururajan et al., 2011 [10]</td>
</tr>
<tr>
<td>MK-801 - hyperlocomotion</td>
<td>Rats</td>
<td>No effect</td>
<td>(-) -</td>
<td>Gururajan et al., 2011 [10]</td>
</tr>
<tr>
<td>MK-801 - social withdrawal</td>
<td>Rats</td>
<td>Reduction (partially)</td>
<td>(+) 3, 10 mg/kg</td>
<td>Gururajan et al., 2011 [10]</td>
</tr>
<tr>
<td>Δ9-THC (chronic) - social withdrawal</td>
<td>Rats</td>
<td>Potentiated</td>
<td>(-) 3 mg/kg</td>
<td>Klein et al., 2011 [11]</td>
</tr>
<tr>
<td>SHR1 decreased freezing response to CFC2</td>
<td>Rats</td>
<td>Reduction</td>
<td>(+) 1 mg/kg</td>
<td>Levin et al., 2012 [12]</td>
</tr>
<tr>
<td>SHR1 strain -hyperlocomotion</td>
<td>Rats</td>
<td>No change</td>
<td>(-) -</td>
<td>Almeida et al., 2013 [13]</td>
</tr>
<tr>
<td>SHR1 strain - deficit in social interaction</td>
<td>Rats</td>
<td>No change</td>
<td>(-) -</td>
<td>Almeida et al., 2013 [13]</td>
</tr>
<tr>
<td>SHR1 strain - PPI disruption</td>
<td>Rats</td>
<td>Reduction</td>
<td>(+) 30 mg/kg</td>
<td>Levin et al., 2014 [14]</td>
</tr>
<tr>
<td><strong>Psychotic Models in Humans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ9-THC induced psychotic symptoms</td>
<td>Healthy humans</td>
<td>Reduction</td>
<td>(+) 1 mg/kg</td>
<td>Zuardi et al., 1982 [15]</td>
</tr>
<tr>
<td>Nabilone induce impaired perception of BD1</td>
<td>Healthy humans</td>
<td>Reduction</td>
<td>(+) 200 mg</td>
<td>Leweke et al., 2000 [16]</td>
</tr>
<tr>
<td>Auditory evoked mismatch negativity</td>
<td>Healthy humans</td>
<td>CBD + THC &gt; THC alone</td>
<td>(+) 5, 4 mg</td>
<td>Juckel et al., 2007 [17]</td>
</tr>
<tr>
<td>Δ9-THC/CBD ratio in hair samples</td>
<td>Cannabis users</td>
<td>Protective effect on psychotic symptoms</td>
<td>(+) -</td>
<td>Morgan and Curran, 2008 [18]</td>
</tr>
<tr>
<td>Δ9-THC (IV) induced psychotic symptoms</td>
<td>Healthy humans</td>
<td>Reduction</td>
<td>(+) 5 mg (IV)</td>
<td>Bhattacharyya et al., 2010 [19]</td>
</tr>
<tr>
<td>Acute cannabis intoxication</td>
<td>Cannabis users</td>
<td>No difference between low (0.02) and high (0.64) CBD/THC ratio</td>
<td>(-) -</td>
<td>Morgan et al., 2010 [20]</td>
</tr>
<tr>
<td>Ketamine induced dissociative symptoms</td>
<td>Healthy humans</td>
<td>Reduction</td>
<td>(+) 600 mg</td>
<td>Hallak et al., 2011 [21]</td>
</tr>
<tr>
<td>Δ9-THC/CBD ratio in hair samples</td>
<td>Cannabis users</td>
<td>Protective effect on psychotic symptoms</td>
<td>(+) -</td>
<td>Morgan et al., 2012 [22]</td>
</tr>
<tr>
<td>Δ9-THC (IV) induced psychotic symptoms</td>
<td>Healthy humans</td>
<td>Reduction</td>
<td>(+) 600 mg</td>
<td>Englund et al., 2013 [23]</td>
</tr>
</tbody>
</table>
Cannabidiol and Sodium Nitroprusside

**Clinical Studies**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Subjects</th>
<th>Results (Symbol*)</th>
<th>Dose with Significant Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report</td>
<td>One schizophrenia patients</td>
<td>Reduction psychotic symptoms (+)</td>
<td>Up to 1500 mg/day (four weeks)</td>
<td>Zuardi et al., 1995</td>
</tr>
<tr>
<td>Case report</td>
<td>Three treatment-resistant schizophrenia patients</td>
<td>One patient had partial improvement (+/−)</td>
<td>Up to 1280 mg/day (30 days)</td>
<td>Zuardi et al., 2006</td>
</tr>
<tr>
<td>Open clinical trial</td>
<td>Six Parkinson’s Disease with psychotic symptoms</td>
<td>Reduction psychotic symptoms (+)</td>
<td>150 to 400mg/day (four weeks)</td>
<td>Zuardi et al., 2009</td>
</tr>
<tr>
<td>Double-blind, cross-over clinical trial compared with placebo</td>
<td>Eighteen first-episode schizophrenia patients</td>
<td>Reduction psychotic symptoms (+/−)</td>
<td>800 mg/day (14 days)</td>
<td>Leweke et al., 2011</td>
</tr>
<tr>
<td>Double-blind, randomized clinical trial compared with amisulpride</td>
<td>Forty-two schizophrenia patients</td>
<td>Significant clinical improvement equivalent to amisulpride (+)</td>
<td>800 mg/day (four weeks)</td>
<td>Leweke et al., 2012</td>
</tr>
</tbody>
</table>

* Positive (+) or Negative (−) antipsychotic effect; 1 - SHR = Spontaneously Hypertensive Rats; 2 - CFC = Contextual Fear Conditioning; 3 - BDI = Binocular Depth Inversion.

Experimental evidence provides clues concerning brain areas that seem to underlie the antipsychotic action of CBD. In animals, CBD increased neuronal activation as assessed through c-Fos expression in the prefrontal cortex and nucleus accumbens, but not in the dorsal striatum, a profile similar to that seen for clozapine and different from that of haloperidol. This atypical antipsychotic profile is consistent with the non-catatonic effect of CBD in rodents. In healthy humans, functional magnetic resonance imaging (fMRI) studies showed opposite brain activation patterns following the administration of CBD and Δ⁹-THC in a dose able to induce psychotic symptoms [3, 30]. Compared to placebo, the psychotic-like effects of Δ⁹-THC were correlated with decreased activation in the ventral striatum and anterior cingulate gyrus during word recall, in the dorsal striatum during “oddball” stimuli processing, and in the right temporal cortex during auditory processing. In all these areas, the effects of CBD on brain activation compared to placebo were opposite to those of THC, suggesting that they may be involved in CBD’s antipsychotic properties (Fig. 1).

The pharmacological mechanisms underlying the antipsychotic action of CBD must be complex as this cannabinoid interferes with neurotransmitter systems in a number of ways [3]. Specifically, the inhibition of the reuptake and metabolism of anandamide may be implicated in the antipsychotic effect of CBD. Anandamide concentrations in the cerebrospinal fluid (CSF) of schizophrenia patients are higher than those of healthy volunteers and patients with affective disorders and dementia, and are negatively correlated with psychotic symptoms [33]. This inverse correlation suggests the existence of a feedback mechanism in which the anandamide increase counterbalances the occurrence of psychotic symptoms. Two additional observations lend support to this view: (1) patients in prodromal states of psychosis have higher levels of anandamide in the CSF than controls and higher anandamide concentrations are associated with delayed onset of full-blown psychosis [34]; and (2) the clinical improvement of schizophrenia patients under CBD has been associated with increased CSF anandamide levels [28]. The influence of CBD on anandamide regulation in brain areas related to the pathophysiology of schizophrenia could explain its antipsychotic action, as hypothesized recently [3]. Additional mechanisms that could explain the antipsychotic action of CBD include the CBD-induced increase in hippocampal neurogenesis, its interaction with 5HT1A and TRPV1 receptors, and its antioxidant and neuroprotective effects [35-38]. It is also important to highlight that certain second-generation (“atypical”) antipsychotics, such as aripiprazole and ziprasidone also activate 5-HT1A receptors. This mechanism may, at least in part, help to explain the favorable safety extrapyramidal side effects profile of CBD.

### 2.2. Sodium Nitroprusside

A new paradigm for the treatment of schizophrenia seems to arise from the modulation of the nitric oxide (NO) pathway. Our group has recently published the results of a double-blind placebo controlled trial showing that an infusion of sodium nitroprusside (SNP) improved acute psychotic symptoms of schizophrenia patients within few hours. After the infusion, SNP leads to an increase in the levels of NO. To our knowledge, this was the first time that the antipsychotic properties of SNP in humans were shown [39].

The rationale for this experiment was based on the glutamatergic hypothesis of schizophrenia. There is robust evidence suggesting that this hypothesis offers a better explanation for the main symptoms presented by schizophrenia patients than the dopamine hypothesis alone, since drugs such as ketamine and phencyclidine (PCP), which cause the blockade of N-methyl-D-aspartate (NMDA) glutamate receptors, induce positive, negative, thought disorder, and cognitive symptoms that closely resemble those of schizophrenia [40].
The NMDA receptor (Fig. 2) is activated by a complex interaction between the neurotransmitter glutamate, the co-agonists d-serine and glycine, and the depolarization of postsynaptic membrane potential resulting in calcium influx into the cell. Calcium binds to calmodulin and stimulates the neuronal nitric oxide synthase (nNOS) enzyme, which produces NO in the central nervous system (CNS). Then, 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 in target cells. In other words, the blockade of NMDA reduces the production of NO [40].

After a preclinical study showing that the infusion of SNP attenuated the psychosis-like behavior and c-Fos expression in the brain of rats induced by PCP, our group designed this translational trial to evaluate the effects of the NO donor in acute schizophrenia exacerbation in humans. We found a marked improvement of positive, negative, anxious and depressive symptoms in patients with schizophrenia after a single four-hour infusion of SNP compared to placebo [39]. Although the trial involved a small sample and replication is required in larger samples, the results are promising and strongly encourage further investigation.

Despite the above, there is no consensus concerning the role of nitric oxide in schizophrenia, and there are several studies showing contradictory results in this area (see Table 2). Some of them support our hypotheses and suggest a deficit in NO-mediated neurotransmission in schizophrenia, whereas others support the opposite, that is, an enhancement of activity in NO-mediated neurotransmission. In an attempt to understand these contradictory findings [41], we made a separate analysis including only those studies that involved schizophrenia patients under antipsychotic treatment and found a significant difference between patients and controls...
showing that patients taking antipsychotic medications have higher levels of plasma/serum NO than healthy volunteers [42]. In one interesting example, Lee and colleagues [43] reported decreased serum levels of NO in schizophrenia patients compared to control subjects at baseline, and that a six-week antipsychotic treatment with risperidone increased NO levels, which, in turn, were associated with psychotic symptoms improvement. The authors described that, among the patients with clinical improvement (≥ 30% in PANSS total score), NO levels increased significantly after risperidone treatment, and argued that this better outcome could be due to a normalization of reduced NO levels after treatment [43].

---

**Fig. (2).** Regular function of the N-methyl-D-aspartate (NMDA) and psychosis as a result of disrupted (nitric oxide) NO production. (A) The activation of NMDA receptors by glutamate results in calcium influx into the cell, which binds to calmodulin (CaM) and stimulates the neuronal nitric oxide synthase (nNOS) enzyme to produce NO. NO activates guanylate cyclase, which increases the levels of the second messenger cyclic GMP which in turn influences the activity of kinase cascades, transcription factors and primary gene products. (B) Phencyclidine (PCP) blocks the calcium influx into NMDA receptors and affects the conversion of L-arginine into NO and L-citrulline by nNOS disrupting regular kinase cascades and causing psychosis. (C) The reestablishment of NO availability by the administration of an NO-donor reverses PCP-induced psychosis.
Additionally, in support to the view that SNP could be effective in schizophrenia, we found three interesting studies that showed increased cGMP levels in the cerebrospinal fluid of schizophrenia patients after treatment with antipsychotic drugs [52-54]. As seen before, NO induces increases in cGMP concentrations through the activation of soluble guanylate cyclase. In the same direction, there are two studies that investigated the effects of increasing cGMP levels in patients with schizophrenia through the use of sildenafil, an inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cGMP: Akhondzadeh and colleagues [55] reported the use of sildenafil as an effective strategy for the management of negative symptoms in schizophrenia, although it failed to counteract cognitive symptoms in another study.

Recently, Brennand and colleagues [56] reprogrammed fibroblasts from schizophrenia patients into human induced pluripotent stem cells (hiPSCs) and subsequently differentiated them into neurons. These neurons showed diminished neuronal connectivity in conjunction with decreased neurite numbers, PSD-95 (postsynaptic density protein 95) levels, and glutamate receptor expression. PSD-95, also known as SAP-90 (synapse-associated protein 90), is a protein that directly links the NR2 subunit of the NMDA receptor to nNOS. Since this link is critical for the production of NO in the CNS as is glutamate receptor expression, these findings indicate that some neuronal components necessary to produce adequate levels of NO in the brain are diminished in the neurons of schizophrenia patients, corroborating the hypothesis of impaired NO neurotransmission in schizophrenia.

Several pre-clinical studies support the modulatory role of NO signaling in schizophrenia, pointing to potential benefits of both increases and decreases in NO production [41, 42]. On one side, nitric oxide synthase (NOS) inhibitors can improve schizophrenia-related behavioral abnormalities induced by dopamine agonists and NMDA antagonists and an increase in brain NO levels are induced by neonatal ventral hippocampus, lesion, a neurodevelopmental animal model of schizophrenia. Conversely, the antipsychotic property of SNP described by us [39] is supported by data describing its beneficial effects against schizophrenia-related behaviors induced by dopamine agonists and NMDA antagonists. Along the same line, nitric oxide synthase inhibitors have also been shown to potentiate PCP-induced behavioral abnormalities and nNOS knockout mice exhibit schizophrenia-like behaviors. Importantly, neonatal NOS inhibition induces schizophrenia-like behaviors in adulthood, indicating the role of NO signaling in the neurodevelopmental pathophysiological processes underlying schizophrenia and suggesting that this might be a potential target for preventive treatments.

An important challenge for the clinical use of SNP by infusion is dealing with its side-effects. These include headache, apprehension, dizziness and restlessness associated with excessively rapid decreases in blood pressure; and ataxia, seizures, confusion and drowsiness usually due to cyanide toxicity. Therefore, the search for newer and safer ways of SNP administration is clearly needed.

**CONCLUSION**

The effects of CBD and SNP on schizophrenia patients strengthen the hypotheses of the involvement of the endocannabinoid system in schizophrenia and of the activation of the NMDA-NO-cGMP cascade as a form of improving schizophrenia symptoms faster than currently used antipsychotics. This sets new treatment paradigms in the field, informed by research based on animal models of the disorder. We believe that the development of drugs that are able to inhibit the reuptake and metabolism of anandamide, such as CBD, or to increase NO levels in the brain, such as SNP, are promising targets to be pursued in the development of the next generation of antipsychotic drugs. Therefore, the investigation of the potential preventive action of these compounds in patients in prodromal states of schizophrenia will not only assist in the therapeutic management of the disease but also in the prevention of the disorder.
psychosis and in individuals at ultra high risk, as well as comparative studies of their antipsychotic effects and of those produced by other antipsychotics in schizophrenia patients, are clearly necessary and opportune.

CONFLICT OF INTEREST

JEH, AWZ and JAC are co-inventors of the patent “Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023”.

ACKNOWLEDGEMENTS

We kindly thank Prof Maia-de-Oliveira for his comments and suggestions in the manuscript.

Financial Support

J.A. C (1B), A.W.Z. (1C). V.C.A (1D). A.L.T.L (2) and J.E.C.H (1D) are recipients of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) Productivity fellowships. Research was supported in part by a grant from Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FAEPA, Brazil), Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, São Paulo, Brazil (NAPNA) and National Institute for Translational Medicine (INCT-TM; CNPq, Brazil).

REFERENCES


[38] Campos AC, Guimarães FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology 2008; 199: 223-30.


[43] Lee BH, Kim YK. Reduced plasma nitric oxide metabolites before and after antipsychotic treatment in patients with schizophrenia compared to controls. Schizophr Res 2008; 104: 36-43.


