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# Role of Glutamate and Dopamine Receptors in the Psychopharmacological Profile of the Indole Alkaloid Psychollatine[⊥]

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Psychollatine (**1**), a new glycoside indole monoterpene alkaloid isolated from *Psychotria umbellata*, has shown an interesting psychopharmacological profile. This study aimed to investigate the role of NMDA glutamate and dopamine receptors in mediating the properties of **1**. Psychollatine (**1**) was assessed for NMDA-induced seizures, MK-801-induced hyperlocomotion, amphetamine-induced lethality, and apomorphine-induced climbing behavior in mice. Psychollatine (**1**) (100 mg/kg) and MK-801 (0.3 mg/kg) prevented NMDA-induced seizures ($P < 0.01$), while **1** (100 mg/kg) attenuated the MK-801-induced hyperlocomotion ($P < 0.05$). Compound **1** (3 and 10 mg/kg), as well as chlorpromazine (4 mg/kg), prevented amphetamine-induced lethality ($P < 0.05$). Finally, **1** (10 mg/kg) ($P < 0.05$), MK-801 (0.2 mg/kg) ($P < 0.01$), and chlorpromazine (4 mg/kg) ($P < 0.01$) attenuated apomorphine-induced climbing behavior. The present results strongly support the involvement of NMDA glutamate receptors in the mode of action of psychollatine (**1**).

There are a number of reasons to investigate drugs that modulate NMDA glutamate receptors. The role of *N*-methyl-D-aspartate (NMDA) glutamate receptors is recognized as being crucial in synaptic plasticity and long-term potentiation, neurophysiological processes thought to underlie learning and memory.[1,2] Additionally, a growing body of evidence suggests the antagonism of the NMDA receptor as a potential mechanism of action for anxiolytic[3,4] and antidepressant drugs.[5−7] Moreover, dizocilpine (MK-801) (a potent and selective noncompetitive antagonist of NMDA receptors)[8] has been shown to interfere with the development of tolerance and behavioral responses induced by a variety of drugs of abuse including cocaine,[9] morphine,[10] nicotine,[11] diazepam,[12] and ethanol.[13] NMDA receptors have also been implicated in a variety of neuropathological conditions including ischemia, epilepsy, various neurodegenerative diseases, and psychiatric illness, including schizophrenia.[2,13]

Along with the older and revised dopamine (DA) hypothesis of schizophrenia, a hypoglutamatergic state is one of the major current explanatory hypotheses for the pathophysiology of this psychiatric condition.[14,15] The hypoglutamatergic hypothesis originated from the observation that noncompetitive NMDA antagonists such as phencyclidine (PCP), ketamine, and MK-801, in elevated doses, mimic schizophrenia in volunteers and exacerbate symptoms in schizophrenic patients.[16] The DA hypothesis suggests that patients with schizophrenia have elevated levels of dopaminergic neurotransmission, congruent with the observation that all drugs effective in treating schizophrenia share the common feature of blocking dopamine $D_2$ receptors to some extent.[17] However, the dysfunction of dopamine may occur only in a subpopulation of patients suffering from this heterogeneous disorder.

The current understanding of schizophrenia allows for the fact that dopamine is not the only malfunctioning neurotransmitter and that other neurotransmitters (e.g., noradrenaline, serotonin, acetylcholine, glutamate, and GABA) may likewise present aberrant behavior.[18]

DA neurons seem to be physiologically regulated by glutamatergic neurons.[15,19] Systemic or local administration of PCP or MK-801 severely disrupts the afferent regulation of midbrain DA neuronal activity and largely alters the functioning of, for instance, the mesocortical and mesolimbic DA neurons.[14,18] Several other studies have shown that MK-801 indirectly stimulates DA release and turnover in the brain, and such increased DA states are thought to mediate the conditioned place preference effects of MK-801;[20] the same reasoning would apply to the complex behavioral syndrome characterized by increased locomotion, stereotypy, and impaired motor coordination that follows MK-801 administration to rodents.[21] All these effects are attenuated by $D_1$ and $D_{2/3}$ agonists or antagonists that inhibit DAergic activity either through presynaptic or postsynaptic mechanisms.[20,22]

However, some studies provide data that non-dopaminergic systems mediate the actions of NMDA antagonists, [23−25] pointing to the involvement of neurotransmitter systems other than dopamine in the central properties of NMDA antagonists. In fact, in various brain regions, including the prefrontal cortex, the hippocampus, and the raphe, NMDA antagonism stimulates serotonin (5-HT) turnover and release more consistently than the modulation of dopaminergic activity, demonstrating a close relationship of NMDA with serotonergic activity.[15,18,26,27] The psychotomimetic effects of NMDA antagonists can also be attenuated or blocked by partial 5-$HT_{2A}$ agonists and selective 5-$HT_{2A}$ antagonists.[8] It has been proposed that NMDA antagonists induce serotonin release, which in turn activates 5-$HT_{2A}$ receptors on glutamatergic neurons in the cortex, resulting in glutamate release.[25,27] This direct link between the serotonergic and glutamatergic systems is thought to be the basis for the observed decreased sensitization to NMDA antagonists for a persistent period after cessation of chronic exposure to antipsychotics.[15]

The genus *Psychotria* L. (Rubiaceae) has been subjected to considerable prior chemical and pharmacological investigation, revealing the presence of bioactive alkaloids.[28−31] Psychollatine (formerly known as umbellatine, **1**) is an indole-monoterpene alkaloid, isolated from *Psychotria umbellata* Vell. (Rubiaceae).[32] Psychollatine exhibits psychopharmacological activities, including mild analgesic effects against a number of algogenic stimuli,[33] and anxiolytic, antidepressive, and amnesic effects[34] in mice models; these data indicate that this compound modulates different neurotransmitter systems, including NMDA, opioid, and 5-$HT_{2A/C}$ receptors.

[⊥] Dedicated to Dr. Norman R. Farnsworth of the University of Illinois at Chicago for his pioneering work on bioactive natural products.

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**Table 1.** Effect of Psychollatine (**1**) against NMDA-Induced Seizures

| treatment (mg/kg) + NMDA (150) | seizures incidence | seizure latency (s)[a] | fatality incidence |
|---|---|---|---|
| saline | 16/22 | 540 ± 84.14 | 15/22 |
| MK-801 (0.3) | 7/21## | 360 ± 32.07 | 0/21## |
| psychollatine (50) | 12/22 | 850 ± 115.32 | 9/22 |
| psychollatine (75) | 10/20 | 1020 ± 146.15* | 6/20## |
| psychollatine (100) | 7/19## | 857.14 ± 133.34 | 6/19## |

[a] Latencies are expressed as mean ± SE. $**P < 0.01$, $*P < 0.05$ vs the control group (ANOVA); $##P < 0.01$ vs the control group, Fischer's exact test.

The present study has further investigated the role of NMDA and dopamine receptors in the mode of action of psychollatine (**1**), through the analysis of its effects on NMDA-induced seizures, MK-801-induced hyperlocomotion, apomorphine-induced climbing, and amphetamine-induced lethality in grouped mice.

## Results and Discussion

Newer atypical antipsychotic agents, such as clozapine, olanzapine, and risperidone, have significant effects not only on dopamine receptor subtypes but also on serotonergic receptors (5-$HT_{2A/C}$, 5-$HT_6$, and 5-$HT_7$), $\alpha_1$-adrenergic, histaminergic, muscarinic, and NMDA glutamate receptors.[13−15] Accordingly, there is ample evidence that in addition to dopamine and serotonin receptors other neurotransmitter systems, such as adrenergic and cholinergic, are also involved in the behavioral psychotomimetic syndrome induced by NMDA antagonists.[26,35] Adding to previously observed effects,[34] this study shows that psychollatine (**1**) interferes with behaviors known to be mediated by glutamate NMDA and dopamine central receptors.

**NMDA-Induced Seizures.** Psychollatine (**1**, 100 mg/kg) and MK-801 (0.3 mg/kg) reduced the incidence of NMDA seizures. A significant delay in seizure onset was observed only in mice treated with the intermediate dose (75 mg/kg) of **1** ($P < 0.05$) (Table 1). Psychollatine at 75 and 100 mg/kg and MK-801 at 0.3 mg/kg significantly protected mice from NMDA-induced fatal seizures ($P < 0.01$). These results suggested a moderate but significant antagonist effect of **1** on NMDA receptors.

**MK-801-Induced Hyperactivity.** The stimulant properties of MK-801 on locomotion have been accepted as a glutamatergic hypofunction animal model of psychosis that seems to be of clinical relevance and may be of value in the search for new antipsychotic agents.[16] Typical and atypical antypsychotic agents inhibit MK-801-induced locomotion.[16,36,37] Our data demonstrate that psychollatine (**1**) at 7.5 mg/kg [$F_{(2,40)} = 3.9$, $P < 0.05$] and 10 mg/kg [$F_{(2,39)} = 8.7$, $P < 0.05$] significantly reduced MK-801-induced hyperlocomotion [$F_{(2,40)} = 19.3$, $P < 0.05$] at doses that per se had no effect on locomotion.[34] Compound **1** at 100 mg/kg [$F_{(2,38)} = 10.1$, $P < 0.05$] prevented MK-801-induced hyperactivity (Figure 1b) and significantly reduced locomotion on its own (Figure 1a).

The analgesic effects of psychollatine (**1**) and its synergistic action with MK-801 against capsaicin-induced pain suggested that **1** acts as a NMDA antagonist.[33] The present results may also be understood as a consequence of NMDA antagonism, since acute and chronic administration of NMDA antagonists facilitate glutamate release,[38−41] thus minimizing some NMDA antagonist related behaviors.[38] It has been suggested that glutamate is released as a compensatory response to NMDA blockade; the released glutamate, by acting at non-NMDA receptors, causes changes in behaviors elicited by NMDA antagonists.[15,38] Although GABA receptors have been previously shown to be irrelevant for psychollatine (**1**)[34] effects, the possibility that **1** reverses MK801-induced hyperlocomotion by acting in low doses as a partial NMDA agonist cannot be ruled out.

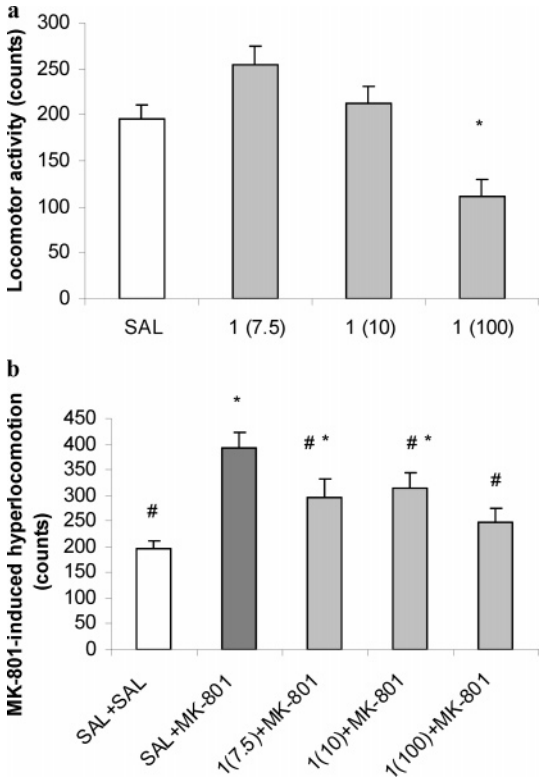


**Figure 1.** Effect of psychollatine (**1**) on spontaneous locomotion (a) and on MK-801-induced hyperlocomotion (b). SAL, saline 0.9%; dosages in mg/kg are indicated after the treatments. Each column represents the mean ± SEM ($n = 9-12$). * = $P < 0.05$ compared with SAL+SAL, and # = $P < 0.05$ compared with SAL+MK-801, ANOVA/SNK.

An alternative interpretation of these results is an indirect modulation of DA and 5-HT receptors via psychollatine (**1**) NMDA antagonism.[41] It has been demonstrated that the motor stimulatory effects of PCP or MK-801 may be understood as the result of an increased nigrostriatal dopaminergic tone.[17] It was also verified that the NMDA antagonist-induced hyperactivity is mediated via 5-$HT_{2A}$ receptor activation, and 5-$HT_2$ receptor antagonists (such as clozapine and ritanserin) are effective in preventing NMDA-induced hyperlocomotion.[14,42,43] It has been suggested that these serotonergic antagonists could specifically restore the impaired burst firing in mesocortical neurons caused by systemic administration of psychotomimetic NMDA antagonists (such as PCP and MK-801), attenuating the locomotor activity.[14,36,42] In fact, we have previously reported that **1** acts as a $5HT_{2A/C}$ modulator, with patterns compatible with mixed agonist or inverse agonist.[34] Therefore, a direct psychollatine (**1**) action as a serotonin modulator as the basis for reducing NMDA-induced hyperlocomotion should not be ruled out.

**Protection of Lethality Induced by Amphetamine in Grouped Mice.** The increased lethality induced by amphetamine in grouped mice is prevented by antipsychotics (older and atypical), but not tranquilizers (e.g., barbiturates and benzodiazepines).[44] The effectiveness of antipsychotics in this model is related to their ability to block $D_2$ receptors,[44−46] a common feature of all effective antipsychotic medication. As it can be seen in Figure 2, chlorpromazine was active, whereas diazepam was inactive. Psychollatine (**1**, 3 and 10 mg/kg) significantly protected grouped mice from amphetamine-induced lethality, whereas 30 and 100 mg/kg were ineffective (Figure 2), indicating that this alkaloid may interfere with dopamine receptors in lower doses. The lack of effect of higher doses of **1** needs further clarification, but bell-shaped dose−response curves have been previously observed with dopamine- and amphetamine-related behaviors.[47−49]

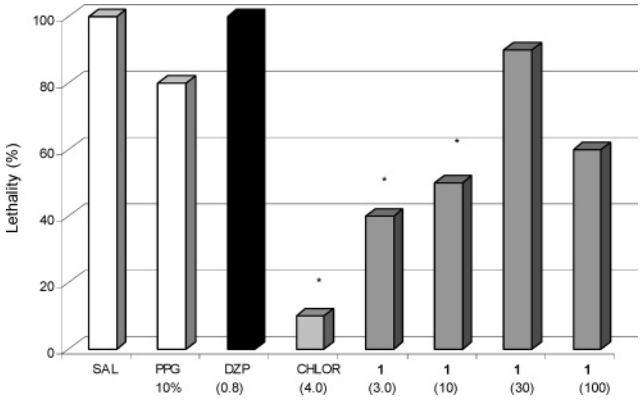


**Figure 2.** Effect of psychollatine (**1**) and chlorpromazine on amphetamine-induced lethality in grouped mice. PPG10%, propylene glycol; DZP, diazepam; CHLORP, chlorpromazine; dosages in mg/kg are indicated after the treatments. $n = 10$. * = $P < 0.05$ compared with controls, Fischer.

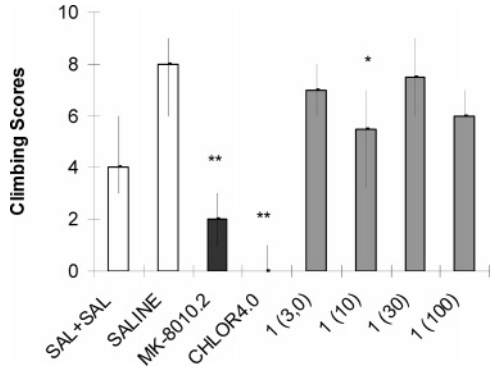


**Figure 3.** Effect of psychollatine (**1**), chlorpromazine, and MK-801 on apomorphine-induced climbing behavior in mice. SAL+SAL = saline+saline; SAL, saline+apomorphine; CHLORP, chlorpromazine+apomorphine; dosages in mg/kg are indicated after the treatments. $n = 11-14$. ** = $P < 0.05$ and * = $P < 0.01$ compared with saline+apomorphine, Mann−Whitney/Kruskal−Wallis.

**Apomorphine-Induced Climbing.** Antagonism of apomorphine-induced climbing is one of the most widely used tests to predict dopamine antagonist properties in vivo.[21,50,51] Mice treated with apomorphine, a mixed $D_1/D_2$ agonist that stimulates postsynaptic dopamine receptors in the striatum, tend to adopt a vertical position along the walls of the cage;[52] the behavior is thought to be mediated by $D_1$ and $D_2$ activation.[53] As expected, chlorpromazine (4 mg/kg) inhibited apomorphine-induced climbing behavior (0[0−1], $P < 0.01$) when compared to a control group (8[6−9], $P < 0.01$) (Figure 3). Psychollatine (**1**, 10 mg/kg) and MK-801 (0.2 mg/kg) inhibited apomorphine-induced climbing behavior (5.5[3.25−7] $P < 0.05$, 2[1−3] $P < 0.01$, respectively), although to a lesser extent in comparison with chlorpromazine. Psychollatine inhibition of apomorphine-induced climbing could result from $D_1/D_2$ dopaminergic antagonism, but also by a dopaminergic modulation via glutamate NMDA receptors.[21] The effect of compound **1** was not dose-dependent, conceivably related to an optimal level of NMDA antagonism relevant for postsynaptic dopamine receptor antagonism.

In recent years, cross talk among glutamate, 5-HT, and DA systems has been well documented.[20,27,54−56] Considering the current and previously reported results,[33,34] the overall data suggest that the behavioral effects of psychollatine (**1**) are related to its interference with the NMDA, 5-HT, and DA receptor cross talk. Undoubtedly, binding studies would be useful to further clarify the molecular mechanism of psychollatine (**1**) and its complex dose−effect pattern. Given that interactions at multiple receptors ($D_2$, 5-$HT_2$, α1-adrenoceptor, NMDA) seem to be the key factors that vary the effectiveness of novel atypical agents in negative symptoms of schizophrenia as well as minimum extra pyramidal adverse effects,[13] it can be argued that psychollatine (**1**) is a potential antipsychotic. Nevertheless, its general profile indicates few advantages compared to known drugs (e.g., an amnesic effect). However, this study supports the further investigation of the indole monoterpene alkaloid psychollatine (**1**) as an interesting template for the development of new psychoactive drugs.

## Experimental Section

**General Experimental Procedures.** Diazepam (DZP), *N*-methyl-D-aspartate (NMDA), and propylene glycol (PPG) were acquired from Sigma; MK-801 was acquired from RBI (USA). Drugs and vehicles were administered intraperitoneally (ip), except for apomorphine, given subcutaneously (sc), as 0.1 mL/10 g of body weight. Diazepam (0.8 mg/kg) was suspended in propylene glycol 10% (v/v). Psychollatine (**1**, 3−100 mg/kg) was solubilized in one or a few drops (20−60 μL) of HCl (1 N); the final volume was adjusted with saline, and the pH adjusted (7.0) with a few drops of NaOH (1 N). NMDA (150 mg/kg), MK-801 (0.2−0.3 mg/kg), amphetamine (12.5 mg/kg), chlorpromazine (4.0 mg/kg), and apomorphine (2 mg/kg) were diluted in saline. Control groups received saline (NaCl 0.9%) or PPG (10%) as appropriate.

**Plant Material.** *Psychotria umbellata* Vell. (Rubiaceae) leaves were collected at Torres (Rio Grande do Sul, Brazil) in February 2003; voucher material (MBM 48571) has been deposited at the herbarium of the Museu Botânico Municipal de Curitiba (PR, Brazil).

**Extraction and Isolation.** The procedures used for isolating psychollatine (**1**) were detailed elsewhere;[34] **1** exhibited physical and spectroscopic data consistent with literature values.[32,34]

**Animals.** Experiments were performed with male adult mice (CF1), acquired from Fundação Estadual de Produção e Pesquisa em Saúde (FEPPS) at 2 months of age. Animals were maintained in our own facilities [22 ± 1 °C, 12 h light/dark cycle, free access to food (Nuvilab CR1) and water] for at least two weeks before the experiments. All procedures were carried out according to institutional policies on experimental animal handling.

**NMDA-Induced Seizures.** NMDA was administered at 150 mg/kg (ip). MK-801 (0.3 mg/kg), saline, and psychollatine (**1**, 50, 75, and 100 mg/kg) were given ip 30 min before the administration of NMDA. Immediately after administration of the NMDA, animals were individually placed in acrylic cages, and the occurrence of seizure was observed for 30 min. A full seizure was recorded when clonic movements of the limbs were observed, accompanied by loss of righting reflex. The presence of convulsions, latency to the first convulsive episode, and lethality were noted.[57] Each experimental group consisted of at least 10 animals. Fisher's exact test was used for statistical analysis.

**MK-801-Induced Hyperactivity.** The method was adapted from Ninan and Kulkarni.[58] Locomotion activity was measured by using activity cages. Mice ($n = 10-25$) were treated with saline or psychollatine (**1**, 7.5, 10, and 100 mg/kg) and 30 min later received MK-801 (0.25 mg/kg). Thirty minutes after MK-801 administration, mice were placed individually in the activity cages, and the motor activity was recorded for 5 min, starting 2 min after the mice were placed in the cage. Statistical analysis involved an initial one-way analysis of variance (ANOVA), followed by Student Newman Keuls (SNK).

**Protection of Lethality by Amphetamine in Grouped Mice.** Mice were divided in groups of 10 and received amphetamine (12.5 mg/kg, ip) before being placed in small boxes (19.0 × 9.0 × 9.5 cm). Chlorpromazine (4 mg/kg) and psychollatine (**1**, 3−100 mg/kg) were given ip 30 min before amphetamine. Lethality was noted 24 h after amphetamine administration.[44] Fisher's exact test was used for statistical analysis.

**Apomorphine-Induced Climbing Behavior.** The method was adapted from Pinsky et al.[59] Saline (0.9%), MK-801 (0.2 mg/kg), chlorpromazine (4.0 mg/kg), and psychollatine (**1**, 3−100 mg/kg) were administered (ip) to mice ($n = 11-14$) 30 min before the injection of apomorphine, 2 mg/kg (sc). Immediately after being injected with apomorphine, the mice were placed individually into cylindrical cages (diameter, 12 cm; height, 14 cm) with the floor and wall consisting of metal bars (0.2 cm diameter; separated by 1 cm gaps). Climbing behavior was measured by an observer at 5, 10, 15, 20, 25, and 30 min after apomorphine administration. Climbing behavior was scored

for 1 min during the observation periods, and the highest rating observed during this 1 min was used in the calculations. Scores were as follows: four paws on the floor (0 point), forefeet holding the wall at 45° (1 point), forefeet holding the wall at 90° (2 points), and all four paws holding the wall (3 points), with a maximum of 18 points. The scores are expressed as median (interquartile ranges) and analyzed by Kruskal−Wallis followed by Mann−Whitney U-test (two-tailed).

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