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Research report

mGlu5 receptor antagonist blocks bromocriptine-induced conditioned place preference in bilateral mesolimbic-lesioned rat

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HIGHLIGHTS

- Dopamine replacement therapy induces dopamine dysregulation syndrome in PD patients by sensitizing the pVTA-NAc pathway.
- Dopamine receptor agonist bromocriptine induces a positive reinforcement in bilateral pVTA-lesioned rats.
- This reinforcement is due to the activation of mGluR5. This receptor and glutamate are over expressed in the NAc shell of pVTA-lesioned rats.
- Antagonizing mGluR5 blocked the conditioned place preference expression and acquisition in pVTA-lesioned rats.
- Bromocriptine-induced reinforcement is due to the activation of the mGluR5 pathway in the NAc of pVTA-lesioned rats.

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ABSTRACT

Dopamine dysregulation syndrome (DDS) has been attributed to both dopamine replacement therapies (DRT) and the mesencephalic dopaminergic lesion. The DRT reinforcement effect is due to its action on the reward system, particularly on the nucleus accumbens (NAc). This nucleus receives two major projections, a glutamatergic from the prefrontal cortex and a dopaminergic from the posterior ventral tegmental area (pVTA). The latter modulate the former within the NAc. pVTA has been demonstrated to be implicated in the motivational effect of bromocriptine (dopamine 2 receptor (D2R) agonist) in bilateral pVTA-lesioned animals. Therefore the potential implication of the metabotropic glutamate receptor 5 (mGluR5) antagonist (MTEP: 3-((2-Methyl-1,3-thiazol-4-yl)ethynyl)pyridine) on bromocriptine-induced conditioned place preference (CPP) was explored. Results showed that the administration of the MTEP blocked completely the bromocriptine-induced CPP in bilateral pVTA-lesioned rats. Both the CPP acquisition and expression were abolished. These effects are due, at least to an increase of the glutamate concentration and that of mGlu5 receptor expression in the NAc shell of the pVTA-lesioned animals. Altogether these data demonstrated the importance of the mGlu5 receptor in the bromocriptine induced-reinforcement and that DDS is probably due to DRT effect on this glutamate receptor.

1. Introduction

Parkinson's disease (PD) is characterized by a progressive loss of dopamine (DA) producing neurons which leads to motor disabilities (rigidity, akinesia, rest tremor and postural abnormalities), cognitive and vegetative disturbances [3,42]. Pharmacological therapies [26] rely mainly on dopamine replacement therapy (DRT), which consists of restoring the central DA transmission by providing the DA precursor L-3,4-dihydroxyphenylalanine (L-dopa), and/or by using dopamine receptor agonists. DRT acts positively by partially restoring the motor function by activating the motor dorso-striatal pathway. However, DRT has negative side effects like its potential capacity to induce impulse control disorders such as pathological gambling, hypersexuality, compulsive shopping, punding, compulsive eating behaviors, and dopamine dysregulation syndrome (DDS) [12,13,49], with a prevalence ranging from 14% to 43% [46,49,50]. These DRT side effects are mostly due to the activation of the dopaminergic mesolimbic pathway originating from the posterior ventral tegmental area (pVTA). This nucleus is also affected by the dopaminergic degenerative

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process in Parkinson's disease [16]. Animal studies have indicated that pVTA dopaminergic projections to the nucleus accumbens (NAc) are crucial in drugs tolerance/dependence [24,30]. The NAc or the meso-accumbens pathway (pVTA to NAc) is particularly important for the development of the behavioral sensitization induced by stimulants and drugs of abuse [25]. The implication of the pVTA in DA receptor agonist's motivational process has been demonstrated previously [39,40]. The NAc dopaminergic denervation constitutes a preliminary condition for DA receptor agonists to induce a hedonistic effect in rats [39,40]. D2R agonists were able to induce a conditioned place preference (CPP) in pVTA-lesioned rat [39] and this effect was attributed to an overexpression of D2R in the NAc shell [39]. Besides dopamine, the NAc also receives important glutamatergic projections from different cerebral structures such as the prefrontal cortex (PFC), the amygdala, the hippocampus and the thalamus [24]. DA modulates excitatory glutamatergic transmission within the NAc [18]. Both ionotropic and metabotropic glutamate receptors are involved in addictive behaviors [18]. More recently, different reports have highlighted the importance of the metabotropic glutamate receptor 5 in addiction [41]. mGlu5 receptor antagonists also ameliorate the motor alterations in parkinsonian animal models [3,42].

Although VTA-NAc projection is involved in psychomotor and incentive sensitization, alterations in glutamatergic transmission within the NAc play important roles [18]. Drug exposure increases glutamatergic inputs to NAc contributing to cue-triggered drug-seeking behavior [18]. The aim of our study was to investigate the role of mGlu5 receptor in the reinforcement, using the CPP paradigm, in bilateral pVTA-lesioned rats that have been previously sensitized with bromocriptine [39]. To this goal, a high specific mGlu5 receptor negative allosteric modulator 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) which crosses the blood brain barrier [2] was used. In addition, both the expression of mGlu5 receptor and that of glutamate concentration were explored in the NAc.

2. Materials and methods

2.1. Animals

A total of 60 adult male Sprague-Dawley rats (180–210 g) were obtained from Charles River (L'Arbresle, France) and maintained in a controlled environment (lights on 07:00–19:00, 22 °C) with food and water freely available. They were housed 4 per cage. The experiments followed the ethical guidelines of the International Association for the Study of Pain and the European Community Council directive and that of the animal ethical committee of the Clermont-University. All efforts were made to minimize the number of animals used.

2.2. Experimental protocol

Surgery was performed one week after animal arrival. Two weeks after surgery and before the CPP test, the locomotor tests and the mGlu5 receptor immunohistochemistry were performed. After the CPP test the rats were sacrificed and TH immunohistochemistry was performed to analyze the impact of the 6-OHDA on neuronal degeneration in the VTA.

2.3. Drugs

Drug	Company	Concentration/dose	administration	Time to CPP
Bromocriptine	Sigma-aldrich (France)	1 mg/Kg	Intra-peritoneal	60 min
MTEP	Tocris (France)	3 mg/Kg	Intra-peritoneal	30 min
6-OHDA	Tocris (France)	6 μg/μl	Intracranial	

All drugs were received as powder from manufacturers. They were dissolved in 0.9% saline and/or DMSO at corresponding dose before use.

2.4. Surgery

Surgery was performed one week after animal arrival. Rats were divided to two groups:

1. pVTA-lesioned animals received bilateral injection of 1 μL 6-OHDA solution (6 μg/μL, dissolved in its vehicle 0.02% ascorbic acid in 0.9% saline) into the posterior VTA.
2. Sham group received bilateral injection of the vehicle.

In order to preserve noradrenergic neurons from 6-OHDA toxicity, animals received desipramine (25 mg/kg, i.p., Sigma-Aldrich, France) 30 min prior to the toxin injection [39,40]. After being anesthetized with i.p injection of ketamine (75 mg/kg) and xylazine (50 mg/kg) each rat was placed in a stereotaxic apparatus and the neurotoxin or the vehicle was injected bilaterally into the pVTA. The injection velocity was 0.1 μL/min using a 5 μL Hamilton syringe. At the end of each injection the tip of the micropipette was rested in place for additional 5 min. The coordinates of the bilateral injection sites were as follows: −5.8 mm caudal to bregma, ±0.6 mm from the midline and −8.2 mm below the brain surface according to Paxinos and Watson's brain map.

The duration of the post-surgery recovery period was the same in all rats.

2.5. Locomotors impairment

2.5.1. Y-maze task

We used The Y-maze paradigm to assess short-term spatial memory which is based on the innate preference of animals to explore areas that have not been previously explored. The Y-maze apparatus consisted of three arms (45 cm long, 10 cm wide and 20 cm high). After acclimatization, rats were placed individually at the end of an arm and allowed to enter the maze freely for a 5-min test session. Rats were tested once only. An arm entry was defined as the entry of all four paws one arm. The sequence of arm entries was recorded. Positive alternations are the number of three consecutive entries into three different arms (A, B, C) such as ABC, BCA, and CAB. Then we calculate the score of alternation Z = X/Y, when X is the number of positive alternations and Y the number of total alternation. The results are presented as the means ± SEM.

2.5.2. Cylinder-test

To assess spontaneous vertical activity "rearing", rats were placed in a standard glass beaker (transparent cylinder: 20 cm diameter and 30 cm height, Bioseb) with video monitoring from the side for a total of 5 min. The number of full extension rears was manually scored post hoc by observer blind to treatment. The beaker was cleaned after each animal.

2.6. Measurement of conditioned place preference

2.6.1. Place conditioning apparatus

CPP experiments [23] were performed in three identical boxes (Imetronic, Pessac, France) formed by two lateral chambers (15 × 15 × 20 cm) connected by a central alley (5 × 15 × 20 cm) (middle neutral compartment). Two sliding doors separated the alley from the chambers. In each chamber two Plexiglas prisms with triangular bases (5 × 7 × 19 cm) were arranged to form different patterns (always covering the same surface of the chamber) and were used as conditioned stimuli. Two different metallic grids,