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MODULATION OF HALOPERIDOL-INDUCED CATALEPSY IN RATS BY GABAERGIC NEURAL SUBSTRATE IN THE INFERIOR COLLICULUS

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Abstract—Not only is the inferior colliculus (IC) a highly important center of integration within the central auditory pathway, but it may also play a modulatory role in sensory-motor circuitry. Previous evidence from our laboratory relating the IC to motor behavior shows that glutamate-mediated mechanisms within the IC modulate haloperidol-induced catalepsy. The high density of GABAergic receptors in the IC led to this study of a possible link between these receptors, haloperidol-induced catalepsy, and a possible involvement of the blockade of dopaminergic receptors. Catalepsy was evaluated by positioning both forepaws of rats on an elevated horizontal wooden bar and recording the time that the animal maintained this position. The present study shows that haloperidol-induced catalepsy was enhanced by local microinjection into the IC of midazolam (20 nmol/0.5 μl), a benzodiazepine receptor agonist, whereas animals receiving a microinjection of bicuculline (40 or 80 ng/0.5 μl), a GABAergic antagonist, showed a reduction in the time of catalepsy. However, the microinjection of haloperidol (2.5 or 5.0 μg/0.5 μl) bilaterally into the IC did not induce catalepsy. Therefore, our results suggest the involvement of the IC in the modulation of catalepsy induced by haloperidol, even though the dopaminergic mechanisms of the IC are unable to induce catalepsy when blocked by the direct microinjection of haloperidol. It is thus possible that the IC plays a role in sensorimotor gating and that GABA-mediated mechanisms are involved. **© 2013 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: haloperidol, catalepsy, GABA, midazolam, bicuculline, inferior colliculus.

INTRODUCTION

The inferior colliculus (IC) is primarily involved in the processing of auditory information, but it may also play a role in the transmission of this auditory information to motor centers participating in behaviors such as prey catching, predator avoidance and attention to a novel auditory stimulus (Casseday and Covey, 1996). Interestingly, some evidence suggests that motor systems project to the IC, since projections from the substantia nigra pars reticulata (SNpr) (Olazábal and Moore, 1989) and from the globus pallidus to the IC have been reported in rats (Moriizumi and Hattori, 1991).

The IC contains a high density of $GABA_A$ receptors in the rat brain (Pirker et al., 2000). The tonic inhibitory GABAergic influence on the IC is subserved, in part, by local GABAergic inhibitory circuits within the IC and exogenous GABAergic inhibitory projections to the IC from other nuclei (Faingold et al., 1989, 1991, 1993; Gonzalez-Hernandez et al., 1996; Li and Kelly, 1992).

Parkinson's disease (PD) is a neurodegenerative disease which affects primarily dopaminergic neurons. It manifests itself in various clinical forms (i.e., akinetic-rigid and tremulous), and produces various symptoms, including the motor triad (tremor, rigidity, and bradykinesia). Rats treated with the potent antipsychotic haloperidol show symptoms similar to those observed in PD, which are attributed the drug's high potential to block D2-type receptors (Hornykiewicz, 1973; Sanberg, 1980; Wadenberg et al., 2001).

Catalepsy is observed when animals are placed in abnormal or unusual postures, which they maintain for a period of time. A normal animal will revert to a more normal position within seconds and proceed to explore its environment, whereas a cataleptic animal will maintain this externally imposed posture for a prolonged period of time (Sanberg et al., 1988; Miller et al., 1990; Ossowska et al., 1990).

We have demonstrated that intracollicular administration of glutamate receptor antagonists (AP7 and MK-801) and or the agonist *N*-methyl-D-aspartate (NMDA) influence haloperidol-induced catalepsy in rats, with the antagonists attenuating catalepsy and the agonist potentiating it (Melo et al., 2010). In this same line of work, we have more recently shown the involvement of IC neuronal glutamatergic circuits in the regulation of catalepsy induced by NG-nitro-L-arginine (L-NOARG), a nitric oxide synthase inhibitor (Iacopucci et al., 2012). These findings all point in the same direction, suggesting the participation of the IC in the modulation of motor function.

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Abbreviations: IC, inferior colliculus; MDZ, midazolam; MK-801, (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine maleate; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; SNpr, substantia nigra pars reticulata.

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Since one IC neurotransmitter (glutamate) has a proven role in catalepsy, it seems possible that another, the widely distributed GABAergic neurotransmitter, might also be involved. The objective of the present study was thus to investigate a possible role for the GABAergic neural substrate in the modulation of haloperidol-induced catalepsy. The possible development of catalepsy after microinjection of haloperidol into the IC was also investigated.

EXPERIMENTAL PROCEDURES

Animals

Male Wistar rats from the animal facility of the State University of Campinas (UNICAMP) weighing 220–250 g at the beginning of the experiments were used in the study. They were housed in Plexiglas-walled cages under a 12-h/12-h light/dark cycle (lights on at 07:00 h) at 23 ± 1 °C, with food and water available *ad libitum*. All experiments were conducted between 14:00 and 18:00 h, during the light phase of the light/dark cycle. They were performed in accordance with the recommendations of the Brazilian Society for Neuroscience and Behavior (SBNeC), based on the guidelines of the American National Institute of Health for the Care and Use of Laboratory Animals, with all efforts made to minimize the number of animals used and their suffering.

Surgery

Rats were anesthetized with ketamine (60 mg/kg) and xylazine hydrochloride (60 mg/kg) in a 1:1 ratio (i.p.) and fixed in a stereotaxic frame (Insight Ltda, Ribeirão Preto, São Paulo, Brazil). A 10 mm long stainless steel cannula (24 gauge) was implanted unilaterally into the IC. The upper incisor bar was set 2.5 mm below the interaural line, with the skull horizontal between bregma and lambda. A stainless steel wire was inserted into the cannula to prevent obstruction. It was introduced vertically and attached to the bones with stainless steel screws and acrylic cement. The coordinates for insertion (with bregma serving as the reference) were the following: anterior/posterior: −8.8 mm; medial/lateral: 1.5 mm; and dorsal/ventral: 3.5 mm (Paxinos and Watson, 2007). To examine the effect of intracollicular haloperidol, microinjections were made bilaterally according to the following coordinates anterior/posterior: −8.8 mm; medial/lateral: ±1.5 mm; and dorsal/ventral: 3.5 mm (Paxinos and Watson, 2007). After the surgery, each animal received an i.m. injection of a veterinary pentabiotic (120,000 UI, 0.2 ml) followed by the injection of the anti-inflammatory and analgesic drug Banamine (flumixin meglumine, 2.5 mg/kg).

Drugs and doses

Haloperidol (0.5 mg/kg; Janssen Pharmaceutica, Beerse, Belgium) was obtained in a commercial form for intravenous use, with the drug dissolved in 1 ml of a vehicle solution containing 6 mg of lactic acid diluted with physiological saline solution to obtain the required concentration of 1 mg/ml. For intracollicular microinjections haloperidol (Sigma–Aldrich, St. Louis, MO, USA) was dissolved with 40% glacial acetic acid and diluted with physiological saline solution to obtain the required concentrations of 2.5, 5.0, or 10 μg/0.5 μl. The agonist of the GABA–benzodiazepine complex, midazolam maleate (10 or 20 nmol/0.5 μl; Nortec Química, Duque de Caxias, Rio de Janeiro, Brazil), and the $GABA_A$ competitive antagonist, bicuculline (40 or 80 ng/0.5 μl; Sigma–Aldrich, St. Louis, MO, USA), were used dissolved in physiological saline solution. The doses of the drugs were selected based on previous studies (Melo et al., 1992; Borelli et al., 2005). All intracollicular microinjections consisted of a volume of 0.5 μl, whereas systemic injections involved a volume of 1 ml/kg. Controls received an equivalent volume of physiological saline solution. Drug solutions were freshly prepared before administration.

Microinjection procedure

After removal of the stylette, the drug solutions were microinjected using a thin dental needle made of stainless steel (30 gauge, outer diameter, 0.3 mm. Mizzy, São Paulo, Brazil) introduced through the guide cannula until the tip protruded 1 mm. This needle was connected to a 10 μl Hamilton syringe with a polyethylene tube, and an infusion pump (Model BI2000, Insight Instruments, Ribeirão Preto, Brazil) was used to control the injection of vehicle or drug solution directly into the IC over a period of 1 min. The needle was left in place for an additional minute after injection to allow for diffusion. Only naive rats were used in this study, and each received only one microinjection of a drug.

Induction and measurement of catalepsy

Catalepsy was evaluated by carefully positioning both forepaws of the animal on a horizontal wooden bar at a height 8 cm above the floor, while their hind paws remained on the floor (Morelli and Di Chiara, 1985). A cataleptic animal will maintain this position without stepping down. The time in seconds (s) for which the position was maintained (up to 600 s) was considered the time of catalepsy. This time measured for each animal was based on three separate 10 mm periods of observation made 10, 30, and 50 min after intraperitoneal administration of haloperidol or 10, 30, and 50 min after the microinjection of bicuculline into the IC. The experimental sessions were conducted in a quiet room recorded with a video-recording system.

Three separate experiments were performed. Experiment 1 was designed to assess the effects of the GABA–benzodiazepine complex agonist in rats which had received a prior microinjection of midazolam (MDZ; 10 or 20 nmol/0.5 μl) or physiological saline solution (0.5 μl) directly into the IC, followed 10 min later by an intraperitoneal injection of haloperidol (0.5 mg/kg) to induce catalepsy (MDZ10/Halo, MDZ20/Halo, and Sal/Halo, groups, $n = 8$, 8 and 9 respectively). Control groups received MDZ (10 or 20 nmol/0.5 μl) or physiological saline (0.5 μl) injected directly into the IC,

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