NeuroToxicology 65 (2018) 38–43

Contents lists available at ScienceDirect

NeuroToxicology

Full Length Article

Electrical stimulation or MK-801 in the inferior colliculus improve motor deficits in MPTP-treated mice

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ARTICLE INFO

Article history:
Received 17 October 2017
Received in revised form 16 January 2018
Accepted 17 January 2018
Available online 31 January 2018

Keywords:
Inferior colliculus
Deep brain stimulation
Parkinson's disease
MPTP
Rotarod
Open field
Mice

ABSTRACT

The inferior colliculus (IC) is an important midbrain relay station for the integration of descending and ascending auditory information. Additionally, the IC has been implicated in processing sensorimotor responses. Glutamatergic and GABAergic manipulations in the IC can improve motor deficits as demonstrated by the animal model of haloperidol-induced catalepsy. However, how the IC influences motor function remains unclear. We investigated the effects of either intracollicular deep brain stimulation (DBS) or microinjection of the glutamatergic antagonist MK-801 or the agonist NMDA in C57BL/6J mice chronically treated with saline or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). After DBS or microinjections, the mice were submitted to rotarod and open field tests, respectively. DBS in the IC was effective to increase the time spent on the rotarod in MPTP-treated mice. After unilateral microinjection of MK-801, but not NMDA, MPTP-treated mice increased the distance travelled in the open field ($p < 0.05$). In conclusion, intracollicular DBS or MK-801 microinjection can improve motor performance in parkinsonian mice suggesting the IC as a new and non-conventional therapeutic target in motor impairment.

1. Introduction

Besides being an important midbrain relay station for the integration of descending and ascending auditory information, the IC contributes to the descending control of acoustic-motor systems, a separate role from that in the core auditory system (Huffman and Henson, 1990). Accordingly, auditory abnormalities have been reported in patients with Parkinson's disease (PD) that seem to reflect pathological changes in the brain-stem (Shalash et al., 2017). In this sense, it seems plausible to assume that activation or inhibition of the IC could improve motor function in such patients with motor disturbances. In fact, rhythmic auditory stimulation can be used to improve motor function in PD patients (Rubinsten et al., 2002; Arias and Cudeiro, 2008). Reinforcing this assumption, we previously demonstrated that both, systemic and intrastriatal haloperidol-induced catalepsy was significantly reduced by prior microinjection of the NMDA glutamate receptor antagonist MK-801 into the IC in rats (Melo et al., 2010; Medeiros et al., 2014). In addition, a significant reduction of the catalepsy response was seen in haloperidol-treated rats when receiving high frequency deep brain stimulation (DBS) of the IC (Melo-Thomas and Thomas, 2015). Such catalepsy is probably due to impaired dopaminergic activity in the basal ganglia, which in case of haloperidol is induced by blockade of striatal postsynaptic dopamine D2 receptors (Hornykiewicz, 1973; Sanberg, 1980; Wadenberg et al., 2001). Although haloperidol-induced catalepsy is a classical animal model of human akinesia (Sanberg, 1980), it only induces a transient motor impairment. A chronic animal model of parkinsonism, as for instance 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) chronic intoxication, is more

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https://doi.org/10.1016/j.neuro.2018.01.004
0161-813X/

comparable to PD symptoms in humans than the haloperidol model and would be more suitable to investigate the influence of the IC in the motor system. This model has become an invaluable tool to produce experimental Parkinsonism, since it produces neurodegeneration in the dopaminergic nigrostriatal system and several PD symptoms (Langston et al., 1999; Barcia et al., 2005; Snow et al., 2000; Sedelis et al., 2001).

In the parkinsonian brain, the loss of dopaminergic modulation of striatal activity leads to an overall increase in excitatory drive in the internal globus palidus and substantia nigra (SN) pars reticulata. This hyperactivity is heavily implicated in the etiology of PD motor symptoms. Glutamatergic mediated excitation of neurons in the striatum (Gotz et al., 1997) can be reduced by antagonists of NMDA receptors through the indirect pathway, possibly by acting at both striatal and extrastriatal sites. Antagonists of NMDA receptors have been shown to have antiparkinsonian effects in MPTP-treated monkeys (Marino et al., 2003; Schmidt and Kretschmer, 1997), and mice (Fredriksson et al., 1994; Vaglini et al., 1994). However, whether this effect is at least in part mediated by the IC has never been investigated. In order to better understand how the IC can influence motor deficits, we investigated whether the glutamatergic neural substrate in the IC or high frequency DBS of this structure can improve motor impairments induced by MPTP intoxication in mice.

2. Methods

2.1. Animals

24 month-old male C57BL/6J mice, weighing 24–28 g, from the animal facility of Janvier (Le Genest Saint Isle, France) were used. The animals had free access to food and water throughout the experimental period and were maintained in Plexiglas-walled cages in a 12 h day-night cycle (lights on at 07:00 am) under standard conditions in a temperature ($21 \pm 1\,^{\circ}C$) and humidity ($55 \pm 5\%$) controlled room. All procedures related to animal maintenance, care and experimentation were conducted in accordance with the European Community Council Directive (2010/63/UE) for animals to be used in preclinical studies, and were approved by the Institutional Animal Ethics Committee of the University of Murcia.

2.2. Drugs

1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP, Sigma-Aldrich, St. Louis, MO) was dissolved in physiological saline solution and administered systemically in a volume of 1 ml/kg. For intracollicular microinjections, (+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)-cyclohepten-5,10-imine (MK-801; Sigma-Aldrich, St. Louis, MO, USA), and NMDA (Sigma-Aldrich, St. Louis, MO, USA) were dissolved in physiological saline solution shortly before being used. All intracollicular microinjections were performed in a volume of 0.1 μl. Controls received an equivalent volume of physiological saline.

2.3. MPTP treatment

Mice received a chronic treatment with MPTP (n = 5) that consisted of five intraperitoneal injections of MPTP-HCl (6.8 mg/kg) at 2 h intervals followed by a monthly injection (6.8 mg/kg) during 6 months (Annese et al., 2015; Jackson-Lewis and Przedborski, 2007). Control animals (n = 6) received physiological saline.

2.4. Surgery

After the intoxication period, a chemitrode was implanted into the IC under stereotaxic surgery. The chemitrode consisted of a stainless-steel guide cannula (gauge 22, length 10 mm) glued to a stimulation electrode (platinum/iridium wire: 90% platinum, 10% iridium, core diameter 125 μm, outer diameter 150 μm, impedance <10 k ohm; Thomas Recording GmbH, Giessen, Germany) and was built with the purpose of injecting drug at the same site that electrical stimulation is applied. Mice underwent general anesthesia induced and maintained by inhalation of isoflurane 2% (Baxter) and were fixed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA). The chemitrode was implanted in the midbrain, aimed at the IC according to the following coordinates with lambda serving as the reference (Paxinos and Franklin, 2004): anteroposterior (AP) = −1.0 mm; mediolateral (ML) = −1.0 mm; and dorsoventral (DV) = 2.8 mm, and fixed to the skull with acrylic resin and one stainless steel screw. At the end of the surgery, each guide cannula was sealed with a stainless steel wire to protect it from obstruction. After stereotaxic surgery, each mouse was treated with a subcutaneous injection of buprenorphine (0.1 mg/kg). After surgery, the mice were kept in a heated room during 24 h and were given a 5–7 days recovery period before the experiments started.

2.5. Electrical stimulation and microinjection procedure

2.5.1. Intracollicular high frequency DBS

One week after the surgery, the animals were placed into an arena (60 cm in diameter and 50 cm high) illuminated with a 40-W fluorescent lamp (350 lx at the arena floor level). The animals were allowed to a 5 min period of habituation. Then, the electrode was connected to a stimulus generator (STG3008-FA, Multichannel Systems, Germany) which allowed to apply current pulses (biphasic). Brain stimulation was presented at 15 s intervals with the current intensity increasing by steps of 20 μA. High-frequency 830 Hz stimulation (pulse width: 100 μs; pulse interval: 100 μs) was delivered to the IC in 1 min intervals during which the current intensity was increased by 20–50 μA steps. The minimum current intensity producing turning or running in two successive trials was considered to be the stimulation threshold (in the present study the current intensity ranged from 80 μA to 120 μA). The electrical stimulation procedure consisted of applying 20 times (3 s duration with 15 s intervals) the current at the stimulation threshold. Immediately after the electrical stimulation, the mice were placed on the rotarod. The same animals were submitted to the sham stimulation procedure two days later, in a counterbalanced way, but for that the stimulator was switched off.

2.5.2. Microinjection procedure

One week after the surgery, the microinjections were delivered using a thin stainless steel dental needle (30 gauge, outer diameter: 0.3 mm) introduced through the guide cannula until its lower end was 1 mm below the cannula tip. This infusion needle was connected to a 10 μl Hamilton syringe by a polyethylene tube, and a volume of 0.1 μl of drug solution or vehicle was delivered over 1 min by an infusion pump (World Precision Instruments-WPI, Sp101i, Germany). The needle was left in place for additional 2 min after injection. Each mouse was given an intracollicular microinjection of NMDA (0.04 nmol/0.1 μl), MK-801 (6 nmol/0.1 μl) or physiological saline (0.1 μl) 10 min before being placed into the activity box. The microinjections and the electrical stimulation were performed in the same animals with a 2 days interval as washout period.