Behavioural Brain Research 279 (2015) 1–8

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Deep brain stimulation of the inferior colliculus: A possible animal model to study paradoxical kinesia observed in some parkinsonian patients?

Liana Melo-Thomas[a,b,c,*], Uwe Thomas[d]

[a] Departamento de Biociências, Universidade Federal de São Paulo, Av. D. Ana Costa, 95, Vila Mathias, Santos, SP 11060-001, Brazil
[b] Instituto de Neurociências & Comportamento – INEC, Av do Café, 2450, Ribeirão Preto, SP 14050-220, Brazil
[c] Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany
[d] Thomas RECORDING GmbH, Winchester Strasse 8, 35394 Giessen, Germany

ARTICLE INFO

Article history:
Received 4 July 2014
Received in revised form 20 October 2014
Accepted 24 October 2014
Available online 8 November 2014

Keywords:
Inferior colliculus
Paradoxical kinesia
Catalepsy
Deep brain stimulation
Parkinson disease
Haloperidol

ABSTRACT

The inferior colliculus (IC) plays an important role in the normal processing of the acoustic message and is also involved in the filtering of acoustic stimuli of aversive nature. The neural substrate of the IC can also influence haloperidol-induced catalepsy. Considering that (i) paradoxical kinesia, observed in some parkinsonian patients, seems to be dependent of their emotional state and (ii) deep brain stimulation (DBS) represents an alternative therapeutic route for the relief of parkinsonian symptoms, the present study investigated the consequence of DBS at the IC on the catalepsy induced by haloperidol in rats. Additionally, we investigated if DBS of the IC can elicit motor responses in anesthetized rats and whether DBS elicits distinct neural firing patterns of activity at the dorsal cortex (DCIC) or central nucleus (CNIC) of the IC. A significant reduction of the catalepsy response was seen in rats previously given haloperidol and receiving DBS at the IC. In addition, electrical stimulation to the ventral part of the CNIC induced immediate motor responses in anesthetized rats. The neuronal spontaneous activity was higher at the ventral part of the CNIC than the dorsal part. DBS to the ventral part but not to the dorsal part of the CNIC increased the spike rate at neurons a few hundred microns away from the stimulation site. It is possible that the IC plays a role in the sensorimotor gating activated by emotional stimuli, and that DBS at the IC can be a promising new animal model to study paradoxical kinesia in rats.

1. Introduction

The inferior colliculus (IC) has long been implicated as part of a brain system mediating aversive states [1–5]. Electrical stimulation of this structure or intracollicular microinjection of NMDA induces defensive responses, such as defensive alertness, freezing, and escape that mimic the fearful behavior elicited by environmental challenges [2–5]. The IC also integrates acoustic information from many auditory nuclei and then projects to the auditory thalamus, to lower auditory nuclei, and to nuclei at the sensorimotor interface [6].

Deep brain stimulation (DBS) has provided dramatic clinical benefit for patients with a variety of neurologic conditions including Parkinso's disease (PD). Electrical stimulation of specific brain areas such as subthalamic nucleus or the internal segment of the globus pallidus can substantially reduce the motor symptoms in patients with PD [for review see 7,8]. In an experimental setting, DBS also serves as a tool to selectively modulate neuronal function of brain regions and associated networks in order to delineate (patho)physiological circuitry [9]. Patients with PD are often rigid, they move with extreme difficulty, and typically they suffer tremor in several muscles when at rest. Nevertheless, despite these severe motor symptoms, these patients can occasionally perform unexpectedly rapid, accurate, and even skilled movements. This phenomenon is called paradoxical kinesia and in some cases appears to be provoked by intense emotion such as fear or anger [10].

PD is characterized by selective cell loss of the dopaminergic nigrostriatal tract of the brainstem, with corresponding decrease in striatal dopamine (DA) concentration [11]. The antipsychotic haloperidol blocks dopaminergic receptors in the nigrostriatal pathway leading to extrapyramidal motor side effects [12]. In

* Corresponding author at: Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany. Tel.: +49 15153136332; fax: +49 6419441414.
E-mail address: melothomas@staff.uni-marburg.de (L. Melo-Thomas).

http://dx.doi.org/10.1016/j.bbr.2014.10.035
0166-4328/

animal models, haloperidol induces a behavioral state known as catalepsy defined as the animals remaining immobile over a horizontal bar for at least 30 s [13]. For this reason haloperidol-induced catalepsy has long been used as an animal model for screening drugs for parkinsonism [14]. Studies conducted in our laboratory have shown that both systemic and intrastriatal haloperidol-induced catalepsy can be significantly reduced by prior microinjection of the NMDA glutamate receptor antagonist MK-801 into the IC [15,16]. We also demonstrated that microinjection of bicuculline, a GABAergic antagonist, directly into the IC induced a biphasic effect progressing from attenuation to potentiation of catalepsy induced by systemic haloperidol [17].

Taking into account that (i) aversive/sensory neural substrate by the IC can drive the modulation of catalepsy in rats and (ii) paradoxical kinesia can be provoked by intense emotion, the goal of the Experiment 1 was to investigate the effect of intracollicular DBS in an animal model of parkinsonism. The Experiment 2 was motivated by two goals: (i) to investigate if electrical stimulation of the IC can elicit motor responses in anesthetized rats as it does for classical motor structures like the striatum [18,19] and globus pallidus [20]; (ii) to monitor spontaneous neural activity in the dorsal cortex (DCIC) and central nucleus (CNIC) of the IC, and investigate whether electrical stimulation changed activity levels or elicited distinct firing patterns in these regions of the IC in anesthetized rats.

2. Materials and methods

2.1. Animals

Thirty-two male Wistar rats, weighing 250–300 g, from the animal house of CEDEME – Federal University of São Paulo, were used, and had free access to food and water throughout the experimental period. The animals were maintained in Plexiglas-walled cages in a 12:12 dark/light cycle (lights on at 07:00 am) under standard conditions in a temperature ($22 \pm 1\,^{\circ}C$) and humidity ($55 \pm 5\%$) controlled room. All protocols were in accordance with the recommendations of the Brazilian Society for Neuroscience and Behavior (SBNeC), which are based on the guidelines of the American National Institute of Health for the Care and Use of Laboratory Animals (Publication No.85-23, revised 1985) and were approved by the ethics committee of the Federal University of São Paulo (CEP: 0091/12).

2.2. Drugs

Haloperidol (Janssen Pharmaceutica, Beerse, Belgium) was obtained in a commercial form for intravenous use, in which the drug is dissolved in 1 ml of vehicle solution containing 6 mg lactic acid. This solution was diluted with physiological saline to obtain the required concentration of 1 mg/ml.

2.3. Experiment 1 – Behavioral study

2.3.1. Surgery

The animals were anesthetized with xylazine/ketamine (20 mg/kg and 100 mg/kg respectively) and fixed in a stereotaxic frame (Thomas RECORDING GmbH, Germany). The upper incisor bar was set at 3.3 mm below the interaural line such that the skull was horizontal between bregma and lambda. One group of 10 rats was implanted with one electrode (platinum electrode, iridium oxide coated, 250 μm outside diameter) introduced vertically into IC using the following coordinates, with lambda serving as the reference [21]: anteroposterior (AP) = −1.2 mm; mediolateral (ML) = −1.5 mm; and dorsoventral (DV) = 4.5 mm, and fixed to the skull with acrylic resin and two stainless steel screws.

2.3.2. Measurement of aversive threshold

One week after the surgery, the animals were placed in a circular arena (60 cm in diameter and 50 cm high with the floor divided in 12 sections) with the experimental compartment illuminated with a 40-W fluorescent lamp (350 lx at the arena floor level). The animals were allowed a 10 min period of habituation. Afterwards, the electrode implanted in the midbrain was connected to a stimulus generator (STG3008-FA, Multichannel Systems, Germany) which allowed to apply current pulses (cathode pulse width 100 μs, pulse interval 100 μs and anode pulse width 100 μs, repeated during 20 s). Brain stimulation was presented at 1 min intervals with the current intensity increasing by steps of 20 μA for measurements of the aversive thresholds. The current intensity producing running (gallop) or jumping in two successive trials was considered to be the escape threshold.

2.3.3. Catalepsy test

One day after the escape threshold had been determined, the catalepsy test was performed. The rats were divided into two groups (Halo or Halo + DBS, $n = 5$ for each group) and tested for catalepsy 20 min after haloperidol injection (1 mg/kg, i.p.) by carefully positioning their forepaws on a horizontal wooden bar at a height 8 cm above the floor, while their hind paws remained on the floor [22]. The latency for stepping down from the horizontal bar was measured. While the Halo group remained undisturbed (cutoff time, 5 min), the Halo + DBS group received electrical stimulation at the escape threshold previously defined in the IC, via the implanted electrode, 1 min after being positioned on the bar. The catalepsy test was performed again 30 min after haloperidol injection but in this case no electrical stimulation was performed. Each rat was used in only one session and received haloperidol and DBS only once during the catalepsy test. The experiments were conducted in a quiet room and the experimental session was recorded with a video-recording system.

2.4. Experiment 2 – electrophysiological recordings and stimulation

Electrophysiological experiments were performed in a sound-attenuating chamber. Experimental sessions lasted no more than 3 h, and each animal was used in only one session. The level of anesthesia was monitored by frequently checking response to tail pinch, and ketamine + xylazine were supplemented as necessary to maintain the depth of anesthesia.

The microdrive and microelectrodes in use in these experiments have been described in detail by Eckhorn and Thomas [23]. Briefly, the microdrive (minimatix, Thomas Recording GmbH, Germany), fixed to the stereotaxic equipment, carries up to five stainless-steel tubes (305 μm outside diameter and 152 μm inside diameter). In our experiment, one microelectrode (impedance ranged from 0.3 to 2.3 MΩ) was placed inside each tube with the tip of each microelectrode ≈1 mm back from the distal end of the tube. One electrode was used for stimulation (platinum/tungsten alloy, coated with iridium oxide, IROX, impedance 300 kΩ) and 3 electrodes were used for multiunit recording (platinum/tungsten alloy, impedance 1–2 MΩ). The animals were anesthetized, fixed in a stereotaxic frame and the scalp was opened as described above (see Section 2.3). The microdrive was lowered until the tip of each tube rested just over the dural surface. The electrodes were introduced and their tips brought to the same depth and aligned parallel at a distance of 305 μm from each other. Under computer control (Software TREC) each microelectrode was moved independently at a speed of 20 μm/s, crossed the dura, and aimed at the DCIC and