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Paradoxical kinesia induced by appetitive 50-kHz ultrasonic vocalizations in rats depends on glutamatergic mechanisms in the inferior colliculus

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ABSTRACT

Paradoxical kinesia is a sudden transient ability of akinetic patients to perform motor tasks they are otherwise unable to perform. This phenomenon is known to depend on the patient's emotional state and external stimuli. Paradoxical kinesia can be induced by appetitive 50-kHz ultrasonic vocalizations (USV) in rats displaying catalepsy following systemic haloperidol. We investigated the role of the inferior colliculus (IC) in paradoxical kinesia induced by 50-kHz USV, since the IC modulates haloperidol-induced catalepsy. We focused on glutamatergic and GABAergic neurotransmission, with male rats receiving intracollicular NMDA or the GABA receptor agonist diazepam 10 min before systemic haloperidol. Catalepsy time was assessed by means of the bar test, during which rats were exposed to playback of 50-kHz USV, white noise, and background noise. Our results show that playback of 50-kHz USV induced paradoxical kinesia by reducing haloperidol-induced catalepsy in rats which had received saline intracollicular microinjection. This paradoxical kinesia effect of 50-kHz USV playback on haloperidol-induced catalepsy was prevented by intracollicular NMDA administration. Although intracollicular diazepam microinjection potentiated haloperidol-induced catalepsy, it did not affect the response to 50-kHz USV playback. Together, NMDA receptor agonist suppressed the effectiveness of 50-kHz USV playback, whereas diazepam did not. These findings suggest that the IC is a key structure involved in paradoxical kinesia, with relevant processes being glutamatergic rather than GABAergic. Our approach thus appears useful for uncovering neural mechanisms of paradoxical kinesia and it might help identifying novel therapeutic targets for Parkinson's disease.

1. Introduction

Patients with Parkinson's disease (PD), a neurodegenerative basal ganglia disease, present a global deterioration in motor function with bradykinesia – slowness of movement – as one of the most characteristic clinical features, which, in extreme cases, can lead to an almost complete loss of movement, termed akinesia (Schilder et al., 2017). Such states can also occur in response to drug toxicity, high-dosed neuroleptics, such as haloperidol, or in other neurological diseases, especially multiple system atrophy (Wenning et al., 2004), progressive lacunar cerebro-sclerosis, or post-encephalitis (Schilder et al., 2017; Satterthwaite et al., 2008). It is known that akinesia depends on the emotional state of the subject and certain external stimuli (Jankovic, 2008). For instance, akinetic parkinsonian patients, when properly stimulated by visual or auditory stimuli, can be able to perform tasks, such as catching a ball, riding a bicycle or running, which they were otherwise unable to perform. This intriguing phenomenon, called paradoxical kinesia was first named by Souques in 1921 (Souques, 1921) to describe "a sudden and brief period of mobility typically seen in response to emotional or physical stress" in patients with advanced PD. Interestingly, paradoxical kinesia is not restricted to stressful or even life-threatening events, since familiar music can also induce

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paradoxical kinesia in patients (Sacks, 1973; Rubinsten et al., 2002). Clinical application of this intriguing phenomenon is somehow limited, especially since the neural mechanisms underlying it are largely unknown in humans. Therefore, animal models are required and akinesia is commonly studied in rodents in terms of catalepsy, that is, a state of immobility in which the animals are unable to correct externally imposed postures. Such a state can be induced in rats, for example, by systemic or intrastriatal administration of haloperidol which mainly acts by blocking striatal post-synaptic dopamine (DA) D2 receptors (Hornykiewicz, 1973; Wadenberg et al., 2001), and this state mimics the lack of spontaneous motor activity that is commonly seen in some PD patients.

Using the haloperidol-induced catalepsy model in rats, we recently showed for the first time that playback of 50-kHz ultrasonic vocalizations (USV) can be used as an emotionally and motivationally relevant appetitive auditory stimulus to reproduce paradoxical kinesia in cataleptic rats (Tonelli et al., 2018). In general, USV are a prominent component of the behavioral repertoire displayed by rats and serve important communicative functions as situation-dependent socio-affective signals (Brudzynski, 2013; Wöhr and Schwarting, 2013). Specifically, 50-kHz USV are typical for social situations with positive valence, like juvenile play (Knutson et al., 1988) or sexual encounters (Barfield and Geyer, 1972), and are believed to reflect a positive affective state ("rat laughter"; Panksepp, 2005). As repeatedly shown by means of our 50-kHz USV radial arm maze playback paradigm, appetitive 50-kHz USV lead to social approach behavior in the recipient (Wöhr and Schwarting, 2007; Engelhardt et al., 2017). At the neurobiological level, this is accompanied by reduced neural activity in the amygdala (Parsana et al., 2012) but enhanced DA activity in the nucleus accumbens (Willuhn et al., 2014), a brain area implicated in reward processing (Choi and Brown, 2003).

On the other hand, it is known, that catalepsy in rats can be modulated by glutamatergic and GABAergic mechanisms in the inferior colliculus (IC; Melo et al., 2010; Tostes et al., 2013), a midbrain structure not only implicated in auditory processing, but also motor outputs, probably mediated by its connections with motor systems (Casseday and Covey, 1996). The IC is a relay station integrating descending and ascending auditory information; the latter is known as the main auditory thalamic relay, projecting from the IC to the medial geniculate body and thus to the auditory cortex (Cappe et al., 2009). Previously, we have shown that intracollicular microinjections of glutamatergic drugs can modulate haloperidol-induced catalepsy. Specifically, administration of the NMDA glutamate receptor antagonist MK-801 into the IC significantly reduced catalepsy time, whereas the agonist NMDA potentiated it (Melo et al., 2010). In addition, we showed that intracollicular microinjection of the GABAergic agonist midazolam potentiated haloperidol-induced catalepsy whereas the GABAergic antagonist bicuculline produced a biphasic effect (Tostes et al., 2013). Finally, we obtained evidence indicating that catalepsy induced by haloperidol can be reduced by high frequency electrical deep brain stimulation in the IC, representing an animal model of paradoxical kinesia induced by aversive stimulation, since this stimulation led to flight responses (Melo-Thomas and Thomas, 2015).

Together, the IC represents a prime candidate target to investigate paradoxical kinesia mechanisms induced by appetitive 50-kHz USV, since it not only relays auditory information (Casseday and Covey, 1996), but also modulates catalepsy. Here, we addressed the question whether the IC is involved in paradoxical kinesia induced by appetitive 50-kHz USV and whether such 50-kHz USV might become ineffective in counteracting haloperidol-induced catalepsy once microinjections of the glutamate agonist NMDA or the GABAergic agonist diazepam are delivered into the IC.

2. Material and methods

2.1. Subjects

N = 44 male Wistar rats (Charles River Deutschland), weighing between 200 and 250 g, were used. They had 7 days of acclimatization before surgery during which they were kept in groups (maximum of five animals per cage). All experimental procedures were approved by the ethical committee of the local government (Regierungspräsidium Gießen, Germany, TVA Nr: 124–2014).

2.2. General overview

Two experiments were performed, each consisting of two parts. In Experiment 1, we focused on glutamatergic neurotransmission and delivered the glutamate agonist NMDA into the IC through microinjection. In the first part of Experiment 1, we determined the effects of NMDA on haloperidol-induced catalepsy. In the second part, the effects of NMDA on paradoxical kinesia induced by 50-kHz USV playback were assessed, and compared to acoustic control stimuli. In Experiment 2, we focused on GABAergic neurotransmission and delivered the GABA agonist diazepam into the IC. Again, we first determined the effects of GABA on haloperidol-induced catalepsy without 50-kHz USV playback. Then, in the second part, the effects of GABA on paradoxical kinesia induced by 50-kHz USV playback were assessed.

2.3. Surgery

The animals were anesthetized with isoflurane (Baxter Deutschland GmbH, Germany) and mounted in a stereotaxic frame (TSE Systems, Bad Homburg, Germany). The upper incisor bar was set at 3.3 mm below the interaural line so that the skull was horizontal between bregma and lambda. Each animal was implanted unilaterally with guide cannulae (gauge 22, length 13 mm; Thomas Recording GmbH, Gießen, Germany) aimed at the IC using the following coordinates, with lambda serving as reference: anteroposterior = −1.2 mm; mediolateral = +1.5 mm; and dorsoventral = 4.5 mm (Paxinos and Watson, 2007). The guide cannulae were fixed to the skull with acrylic resin and three stainless steel screws. A stylette inside the guide cannula prevented obstruction. All animals were allowed a recovery period of 7 days after surgery with *ad libitum* access to food and water. During this period, they were kept in pairs.

2.4. Drug and doses

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 diluted with physiological saline to obtain the required concentration of 1 mg/ml. In Experiment 1, N-methyl-D-aspartic acid (NMDA; Sigma-Aldrich, Darmstadt, Germany) was dissolved in physiological saline, obtaining a dose of 30nmol/0.5 μl, which had previously been shown to increase haloperidol-induced catalepsy (Melo et al., 2010). In Experiment 2, 7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (Diazepam; Sigma-Aldrich, Darmstadt, Germany) was dissolved in propylene glycol (10%), obtaining doses of 10μg/0.5 μl and 20μg/0.5 μl.

2.5. Microinjection procedure

A given microinjection was delivered using a 30 gauge stainless steel cannula introduced through the guide cannula until its lower end was 1 mm below the cannula tip. This infusion cannula was