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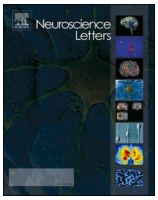

Conditioned catalepsy vs. Increase in locomotor activity induced by haloperidol

L.G. De la Casa *, M.A. Cintado, G. González-Tirado, L. Cárcel

Laboratory of Animal Behavior & Neuroscience, Seville University, Spain

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ABSTRACT

Previous research has revealed a high degree of complexity of the conditioned response that appears after associating a context with the effects of the dopaminergic antagonist haloperidol. Specifically, when a drug-free test is performed in the presence of the context, conditioned catalepsy is observed. However, if the test is extended over time, the opposite effect occurs, namely, a conditioned increase in locomotor activity. In this paper, we present the results of an experiment with rats that received repeated administration of haloperidol or saline before or after exposure to the context. Next, a drug-free test was performed to evaluate catalepsy and spontaneous locomotor activity. The results revealed, on the one hand, the expected conditioned response of catalepsy for those animals that received the drug prior to context exposure during conditioning. However, for the same group, an analysis of locomotor activity for an extended period of ten minutes after registering catalepsy revealed an increase in general activity and more faster movements compared to the control groups. These results are interpreted considering the possible temporal dynamics of the conditioned response that could induce changes in dopaminergic transmission responsible for the observed changes in locomotor activity.

1. Introduction

Previous studies have revealed that a neutral stimulus (such as an experimental context) repeatedly associated with the effects of a drug that acts as an Unconditioned Stimulus (US) becomes a Conditioned Stimulus (CS) that can acquire both the ability to elicit responses that are similar [1,2] or opposite [3,4] to those unconditionally induced by the drug. Such Conditioned Responses (CR) can be distinguished from the unconditioned effects of the drug by being tested in the presence of the CS but in absence of the drug [5].

Haloperidol is a typical antipsychotic drug with neuroleptic pharmacological action, which is part of butyrophenones [6]. During the last century, it was the main drug prescribed for the treatment of psychotic disorders [7], but mainly due to its numerous side effects, it has been replaced by atypical antipsychotics such as clozapine, olanzapine, quetiapine, or risperidone [8]. Neuroleptic drugs are potent antagonists of dopamine receptors in the central nervous system [9], and due to the repeated manifestation of motor problems derived from haloperidol, their evaluation and pharmacological analysis have received great attention in the scientific literature. Administration of haloperidol is followed by severe extrapyramidal effects in both non-human and humans such as akinesia, bradykinesia, catalepsy, or muscle rigidity [10,11].

In animal research, the haloperidol-induced cataleptic response, defined as the inability to correct an externally imposed posture [12], provides a simple and useful animal model to investigate motor alterations often observed in Parkinson's disease, and the antiparkinsonian potential of certain drugs [13]. In the more common experimental paradigm used to analyze haloperidol-induced conditioned catalepsy, the animals are placed in an unusual position. While untreated animals return to a normal position within seconds and proceed to explore the environment, animals in a state of catalepsy maintain the externally imposed posture for a relatively prolonged period [11,14]. The experimental procedure to quantify catalepsy that we employed in our experiment is the so-called "bar test", which consists of placing the animal's forelegs on an elevated horizontal bar and recording the time until the four legs touch the floor [15,16].

According to numerous studies with rodents, haloperidol-induced catalepsy and any reduction in behavioral activity resulting from its administration are related to the modulatory influence of the drug on the nigrostriatal dopaminergic pathway [17]. Due to the existence of anatomical and functional interactions between dopamine, GABA, and

* Corresponding author.at: Departamento de Psicologia Experimental, C/ Camilo Jose Cela, s/n, Universidad de Sevilla, 41018 Sevilla, Spain.
E-mail address: delacasa@us.es (L.G. De la Casa).

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acetylcholine in the striatum, it seems appropriate to assume that the extrapyramidal side effects observed after acute administration of haloperidol occur in response to an imbalance in these neurotransmitter systems [12].

On the other hand, the measurement of spontaneous locomotor and exploratory activity in laboratory rats has been considered an index of the animal's general behavior [18]. The traditional method for assessing the spontaneous activity of animals consists in observing movements in a limited space, usually an open field, registering total distance traveled or total percentage of time that the animal remains in motion [19]. However, other authors have indicated that a more detailed analysis of the different movements that integrate locomotor activity is needed to discriminate the effects of different pharmacological substances [20].

A review of those studies that have analyzed conditioning using haloperidol as a US reveals the existence of apparently contradictory results, since in some cases conditioned catalepsy responses have been observed [15,21], while in other cases a conditioned increase in locomotor activity has been reported [22,23]. To analyze in detail such discrepancies, we designed an experiment with the general aim of analyzing the associations established after repeated presentations of a novel context (the CS) and the effects of the dopaminergic antagonist haloperidol (the US). We registered two responses modulated by dopaminergic activity: catalepsy and spontaneous locomotor activity (including general activity time, total distance, fast movements, stereotyped movements, and rearing). Considering previous results, we expect to find a conditioned catalepsy response in a drug-free test. Furthermore, we expect to find a conditioned increase in locomotor activity, at least in general activity, when the drug-free test is extended over time.

2. Material and methods

2.1. Subjects

21 male Wistar rats, (n = 7 per group) with weights ranging from 320 to 434 g participated in this experiment. The animals were individually housed in 40 × 20 × 24 cm Plexiglas cages with wood shavings as bedding and maintained on a regular 12:12 h light / dark cycle (lights on at 07:00 A.M.). All behavioral tests were conducted during the light period of the cycle, starting at 9:00 am. All animals had access to food and water without restrictions throughout the duration of the experiment. The Ethics Committee for Animal Research of the University of Seville approved all experimental procedures (code number CEEA-US2015-28/4) that were carried out in accordance with the guidelines established by the EU Directive 2010/63/EU for animal experiments and the Spanish R.D. 53/2013.

2.2. Apparatus and drugs

Catalepsy was automatically registered in four automated catalepsy test chambers (Med Associates, Inc., St. Albans, VT, United States). The forepaws of the rat were placed on a horizontal cylindrical metal bar (diameter, 1 cm; length, 15 cm; 10 cm above the test platform), and the instrument measured the time that contact was maintained between the floor and the bar. A cut-off time of 60 s was used for all animals under all conditions. To record motor activity, each animal was placed in a transparent cage of 45 × 45 cm surrounded by 16 infrared light (spaced 2.5 cm) forming a double grid of infrared cells (Actitrack, Panlab, Barcelona, Spain). This system was connected to a computerized control unit that recorded the following parameters: (i) general activity time; (ii) total distance (ambulation); (iii) fast movements (speed > 5 cm/s); (iv) stereotyped movements; and (v) rearing.

The drug injected was haloperidol (Kern Pharma), administered subcutaneously in the nape of the neck at a dose of 0.5 mg/kg. A saline solution was used as a vehicle. All experimental procedures were initiated 20 min after the drug was injected.

2.3. Procedure

A schematic presentation of the experimental timeline is depicted in Fig. 1. The animals were divided into three groups: Hal/Sal, Sal/Hal, and Sal/Sal. On the first day, each animal was tested for catalepsy and locomotor activity for 60 min in a drug-free trial to obtain baseline activity. The context conditioning stage lasted from day 2 to 5, and began with the animals receiving the corresponding injection of haloperidol (Group Hal/Sal) or saline (Groups Sal/Hal and Sal/Sal) 20 min before being tested for catalepsy and locomotor activity. The animals were then tested in the catalepsy chambers to register descent latency (with a cut-off time of 60 s). Then they were translated into the chambers designed to assess locomotor activity, where they remained undisturbed for 60 min. After each experimental session, the rats were returned to their home cages and 20 min later the corresponding haloperidol (Group Sal/Hal) or saline (Groups Hal/Sal and Sal/Sal) dose was injected. After 2 days without treatment, to eliminate any possible residual drug in the animal's system, a single drug-free catalepsy and a 10-min spontaneous locomotor activity test were conducted (also initiated 20 min after saline administration).

3. Results

3.1. Analyses of mean descent latency (catalepsy)

3.1.1. Baseline

The mean descent latency at baseline was 2.09 s (SD = 2.8). An ANOVA with groups as the main factor conducted on mean descent latency on the day of baseline revealed the absence of significant differences, $F(2, 18) = 1.05$; $p > 0.37$, $\eta^2 = 0.11$.

3.1.2. Conditioning

A 4 × 3 repeated measures ANOVA (Trials × Groups) conducted on mean descent latency for the conditioning trials revealed significant main effects of Trials and Groups, $F(3, 54) = 8.79$; $p < 0.01$, $\eta^2 = 0.33$, and $F(2, 18) = 31.43$; $p < 0.01$, $\eta^2 = 0.78$, respectively. The main effect of Trials reflects an overall increase in descent latency across trials. Regarding the main effect of groups, Post-hoc comparisons (LSD, $p < 0.05$) revealed a significant increase in descent latency for the Hal/Sal Group (Mean = 37.16 s, SD = 11.81), as compared to the Sal/Hal and the Sal/Sal groups (Mean = 7.39 s, SD = 9.83, and Mean = 1.87 s, SD = 2.12, respectively). The Trials × Groups interaction was also significant, $F(6, 54) = 4.76$; $p < 0.01$, $\eta^2 = 0.35$. As can be seen in Fig. 2, the interaction was due to a progressive increase in descent latency across trials that was restricted to the Hal/Sal Group due to the haloperidol-induced catalepsy.

3.1.3. Test

A one-way ANOVA with main factor Groups conducted on mean descent latency on the free-drug test day revealed significant differences between Groups, $F(2, 18) = 3.66$; $p < 0.05$, $\eta^2 = 0.29$. Post-hoc comparisons (LSD, $p < 0.05$) revealed that the descent latency for the Hal/Sal Group (Mean = 26.63 s, SD = 17.81) was significantly higher compared to the Sal/Hal and Sal/Sal groups (Mean = 10.40 s, SD = 8.37, and Mean = 9.00 s, SD = 12.79, respectively), indicating the expected conditioned catalepsy response for the group that received haloperidol before context exposure at conditioning.

3.2. Analysis of spontaneous locomotor activity: Activity time, total distance, fast movements, stereotyped movements, and rearing

3.2.1. Baseline

Separate ANOVAs on each one of the five measures of spontaneous activity with main factor Groups for the baseline session revealed the absence of significant differences between groups for all measures, Fs $(2,18) < 2.79$; ps > 0.08.

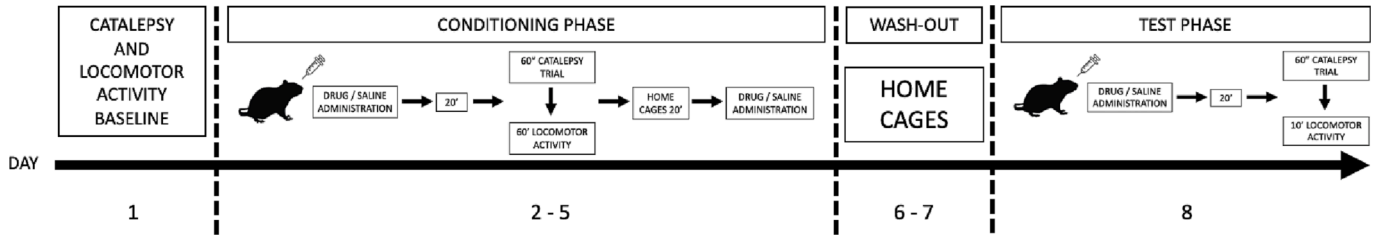

Fig. 1. Summary of the experimental timeline depicting all experimental procedures (see the section *Procedure* for additional details).

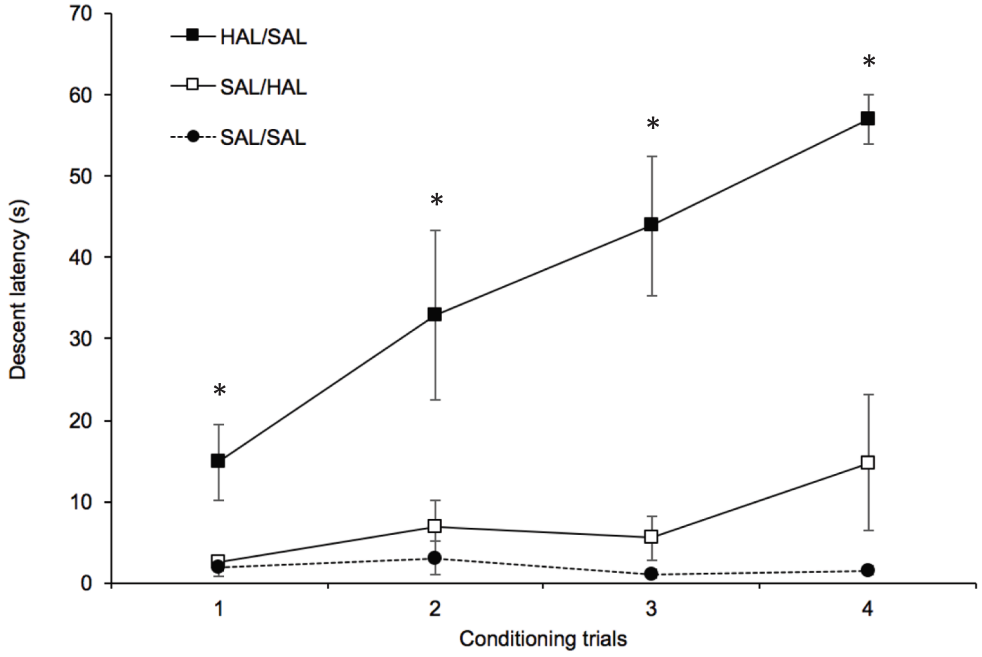

Fig. 2. Mean descent latency for catalepsy test during conditioning as a function of the drug injected before and after each experimental session. HAL: Haloperidol; Sal: Saline. Error bars represent standard error of the mean.

3.2.2. *Conditioning*

Table 1 shows the mean values for each measure of locomotor activity collapsed across conditioning trials as a function of groups. As can be seen in the table, there was a significant reduction in activity for all measures in the Hal/Sal Group (confirmed by ANOVAs that revealed a significant main effect of Groups for all dependent variables, ps < 0.01). These results confirmed the unconditioned reduction of locomotor activity induced by the drug. The differences between the control groups were non-significant (ps > 0.13).

3.2.3. *Test*

Table 2 shows the mean values for each measure of locomotor activity as a function of groups in the free drug test. As can be seen in the table, all measures for the Hal/Sal Group revealed an increase in locomotor activity compared to the control groups. However, independent one-way ANOVAs with main factor Groups conducted on each measure of locomotor activity at testing revealed significant differences only for activity time and fast movements, $F(2, 18) = 5.36$; $p < 0.05$, $\eta^2 = 0.37$, and $F(2, 18) = 4.18$; $p < 0.05$, $\eta^2 = 0.32$, respectively. Post-hoc comparisons (LSD, $p < 0.05$) revealed a significant increase in activity time and fast movements for the Hal/Sal Group compared to the Sal/Hal and Sal/Sal Groups. For the remaining measures, the differences were not significant (all ps > 0.06).

Table 1
Mean values for each measure of locomotor activity at conditioning stage collapsed across conditioning trials as a function of the drug injected before and after each experimental session. HAL: Haloperidol; Sal: Saline.

GROUP	Total distance	Stereotyped movements	Activity time	Fast movements	Rearing
HAL/ SAL	548.16 (192,60)	46.16 (16,25)	5.88 (1.89)	0.62 (0.32)	1.54 (1.36)
SAL/ HAL	8683.66 (2879,82)	406.32 (110.06)	39.40 (9.21)	15.73 (5.49)	95.78 (34.69)
SAL/ SAL	10267.33 (1154,30)	488.38 (81.87)	44.45 (4.19)	19.38 (2.78)	95.67 (17.26)

Table 2
Mean values for each measure of locomotor activity at test stage as a function of the drug injected before and after each experimental session. HAL: Haloperidol; Sal: Saline.

GROUP	Total distance	Stereotyped movements	Activity time	Fast movements	Rearing
HAL/ SAL	4874.38 (749.6)	202.57 (51.07)	87.71 (4.15)	59.14 (8.23)	62.71 (5.46)
SAL/ HAL	4147.94 (804.96)	169.00 (42.75)	78.71 (7.54)	47.11 (8.39)	47.71 (10.59)
SAL/ SAL	4149.61 (721.59)	153.14 (23.72)	77.87 (6.52)	47.87 (9.44)	56.00 (15.03)

4. Discussion

The results confirmed that when animals in the Hal/Sal group (that received haloperidol before context exposure) were submitted to the catalepsy bar test in a drug-free trial, conditioned catalepsy was evident compared to the Sal/Hal and Sal/Sal groups (that received haloperidol 20 min after context exposure or did not receive the drug, respectively). This conditioned catalepsy response has been consistently obtained using different procedures [15,24]. However, when following the catalepsy test bar, spontaneous locomotor activity of the animals was recorded for a prolonged period (10 min), it appeared a significant higher number of rapid movements, and an increase in activity time in the Hal/Sal as compared to the control groups. This conditioned increase in locomotor activity has also been previously reported in the literature [22,23], but, to our knowledge, this is the first experimental demonstration of both conditioned catalepsy and conditioned increase in locomotor activity in a single experiment.

A relevant aspect of our procedure is related to the time interval between the drug administration and the registration of catalepsy and locomotor activity responses. Different studies have evaluated the intensity of catalepsy using various intervals from haloperidol administration to response recording. For example, Bazyan et al. [25] injected the drug 30, 60, or 120 min before the test and reported a catalepsy effect for all the intervals, but found a positive correlation between the intensity of catalepsy response and the duration of the interval. In our experiment, the use of a 20-min interval between drug administration and the different tests is determined by previous studies carried out in our laboratory, in which this time interval was effective in inducing both conditioned catalepsy and a conditioned increase of locomotor activity [22–24].

To get an index of catalepsy we used the bar test, a widely used procedure in previous research in this field [21]. To analyze the conditioned increase in locomotor activity, unlike previous work in which only the mean percentage of activity was recorded, we registered several specific movements (total distance, number of stereotyped movements, activity time, number of fast movements and rearing), since several studies have shown specific locomotor activity patterns associated with the action of different pharmacological substances [26]. Therefore, for example, an increase in rearing responses has been found after high doses of d-amphetamine [27], and after repeated doses of morphine [28]. In the same vein, Barr et al. [29] found a higher frequency of rearing and an increase in horizontal crossing activity after cocaine administration. Other studies have reported different stereotyped responses associated with increased dopamine, such as turning, sniffing, and rearing [30]. Interestingly, an increase in general activity [31], and in fast movements [32] after amphetamine administration has also been found, similar to what we have found in our experiment. This could indicate that the underlying mechanism for the conditioned increase in haloperidol-induced activity is a change in dopaminergic activity similar to that produced by amphetamine administration.

Especially relevant for interpreting our results is the fact that the neurochemical response produced by haloperidol is related to the dose administered. Specifically, a low dose of haloperidol (0.03 mg / kg) has been observed to have an antagonist effect on presynaptic autoreceptors without affecting somatodendritic (postsynaptic) receptors, while a higher dose block both types of receptors [33]. Considering these mechanisms, we can offer an explanation, albeit speculative, of the results obtained in our experiment: The presence of the context associated with haloperidol would induce a CR that would initially be similar to that produced by the relatively high dose of drug injected in the test phase (0.5 mg/kg), blocking both autoreceptors and postsynaptic receptors and, consequently, inducing the conditioned catalepsy effect. However, the CR would decrease in intensity over time, in such a way that it would mimic the effect produced by a low dose of the drug. Therefore, the activity of the postsynaptic receptors would normalize, responding to the excess of dopamine accumulated by blockage of the autoreceptors, leading to the conditioned increase in locomotor activity.

A neuroscientific approach to the study of behavior should integrate factors from very diverse areas including, among others, chemistry, genetics, biology, or psychology. In our experiment, the main purpose was to collect behavioral data to evaluate the effects of the presence of a context associated with a dopaminergic antagonist on locomotor activity. Although we recognize that our study has some limitations due to the lack of neurochemical results regarding changes in brain areas associated with locomotor activity during conditioning, we consider that our data are relevant for behavioral neuroscience. In fact, we provided testable hypotheses supported by findings from other studies revealing that an increase in the extracellular concentration of dopamine appeared in the striatum after collecting brain fluid samples in a drug-free trial in the presence of a context repeatedly associated with amphetamine [34,35]. In addition, several studies have reported an increase in extracellular dopamine levels in the nucleus accumbens in the presence of CS [36], which reveals the ability of conditioning to modify not only observable behavior, but also the neural activity underlying such changes [37].

Future studies could use techniques like *in vivo* microdialysis to register changes in dopaminergic activity in response to different drug stimuli. This technique allows for the measurement of neurotransmitter concentrations in freely moving animals over prolonged periods and at different intervals [38]. Such a procedure will allow for the analysis of temporal changes in dopaminergic activity both when the drug is administered and when the CS is presented in the absence of the drug, which would help shed light on the physiological CR that would occur in parallel to behavioral changes.

Research on the CR supported by CS associated with the effects of different drugs has revealed valuable information related to drug use. Therefore, in the clinical setting, this type of conditioning is considered a relevant factor in the relapse process, mainly due to its involvement in the development of tolerance and sensitization of responses induced by drugs [39]. Furthermore, this research highlights the importance of context in any clinical intervention related to drug use [40], and can also be useful for identifying the neural structures and circuits that constitute the neurobiological basis of learning [5]. Specifically regarding the use of antipsychotic drugs as a US, these studies are relevant for drug prescription as they can help identify antipsychotics with greater affinity or effectiveness as antagonists of dopaminergic activity [41]. The study of CR has also proven to be a reliable screening tool with high predictive validity for identifying substances with antipsychotic properties and developing new antipsychotic drugs [42].

Our results demonstrate that the use of haloperidol can elicit different CR depending on the type of test used. These findings provide valuable information about the effects of drug conditioning on two different tasks and how these effects change over time. As such, they may be useful in assessing how continued haloperidol-based therapy affects patients in different tasks and over time. Additionally, our results suggest that the administration of the drug, in combination with contextual cues, can elicit effects similar to those of the drug itself, known as the placebo effect [43]. These findings may be related to the associative mechanisms of placebo [44], which have been shown to be effective in the treatment of pain, anxiety, and depression, as well as Parkinson's disease [45]. Although the exact mechanisms of placebo are still unknown, studies suggest that it may involve a combination of factors, including classical conditioning, patient expectations, and neurobiological factors [46]. Specifically, some research has linked the opioid and endocannabinoid systems with the analgesic effects of placebo [47], and the dopaminergic system appears to play a key role in the placebo effect in Parkinson's disease. Therefore, a better understanding of these mechanisms and their potential therapeutic applications could facilitate the use of pharmacological treatment in combination with placebo to reduce drug doses without compromising treatment efficacy [48].

In sum, our results confirmed that repeated pairings between a

context-CS and the effects of haloperidol administration supported a conditioning process that, depending on the type of test and the time at which the test was performed, generated apparently opposite CR (conditioned catalepsy versus conditioned increase in spontaneous locomotor activity). These data highlight the relevance of classical conditioning using drugs on behavioral changes and suggest new lines of research related to the role of associative processes on neurochemical changes as a result of previous experience with drugs.

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CRediT authorship contribution statement

L.G. De la Casa: Conceptualization, Supervision, Writing – original draft. **M.A. Cintado:** Investigation, Data curation, Writing – original draft. **G. González-Tirado:** Investigation, Visualization, Writing – review & editing. **L. Cárcel:** Investigation, Data curation, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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