Physiology & Behavior 96 (2009) 73–77

Contents lists available at ScienceDirect

Physiology & Behavior

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

Differential involvement of dopamine D_1 receptors in morphine- and lithium-conditioned saccharin avoidance

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ARTICLE INFO

Article history:
Received 13 December 2007
Received in revised form 6 August 2008
Accepted 19 August 2008

Keywords:
Conditioned taste avoidance
Dopamine
D_1 receptor
D_2 receptor
Lithium chloride
Morphine hydrochloride
Raclopride
Saccharin
SCH 39166

ABSTRACT

Conditioned saccharin avoidance (CSA) can be produced when either lithium chloride (LiCl) or a reinforcing drug, such as morphine, is administered following exposure to the taste of saccharin. In this study we investigated the involvement of dopamine (DA) transmission in the acquisition of morphine and LiCl-CSA. CSA was evaluated in a two-bottle choice paradigm with two conditioning pairings between saccharin and morphine or LiCl as unconditioned stimulus (US). Morphine hydrochloride (7.5 mg/kg s.c.) or LiCl (40 mg/kg i.p.), administered 45 and 120′ respectively after saccharin-drinking session, induced strong CSA. The DA D_1 receptor antagonist, SCH 39166 (0.1 mg/kg s.c.), impaired morphine-CSA if administered 15′ and, to a lesser extent, 30′ but not 45′ before the drug (i.e immediately after saccharin drinking). In contrast SCH 39166 reduced LiCl-CSA when administered 45′ before the drug and even more so when administered 105′ before LiCl i.e. immediately after saccharin drinking. Therefore SCH 39166 impaired morphine-CSA when given shortly before the drug, while it impaired LiCl-CSA when given shortly after saccharin. Raclopride, a specific antagonist of D_2 receptors, failed to affect LiCl- and morphine-CSA. These results are consistent with the idea that DA, acting on D_1 receptors, plays a differential role in morphine- and LiCl-CSA. In LiCl-CSA DA is necessary for the processing (consolidation) of the short-term memory trace of the saccharin taste to be associated with the lithium-induced aversive state, while in morphine CSA contributes to mediate the appetitive properties of the drug.

1. Introduction

Reinforcing drugs, similarly to lithium chloride (LiCl), can act as unconditioned stimuli (US) to induce avoidance of a saccharin solution (conditioned stimulus, CS) predictively paired with their systemic administration. This phenomenon, termed conditioned saccharin avoidance (CSA), has been viewed as a case of conditioned aversion and an expression of the double nature, appetitive/aversive of addictive drugs. Thus, it has been hypothesized that drugs like cocaine, morphine and nicotine have both appetitive and aversive properties and that, depending on the experimental conditions, can asymmetrically drive behavior and result in approach and positive reinforcement or in avoidance and negative reinforcement [1–3]. However, rats also learn to avoid saccharin predictively paired with a sucrose solution [4] and a less concentrated sucrose solution paired with a more concentrated one [5]. Since sucrose is devoid of aversive properties, these observations exclude that avoidance of the taste CS is the result of aversive conditioning. On this basis, this phenomenon has been interpreted as the result of an "anticipatory suppression", secondary to an "anticipatory contrast effect" (ACE), related to failure of saccharin to mimic the hedonic value of sucrose [5]. Indeed, comparative studies of drug- and lithium-CSA show the existence of several differences between drug- and lithium-CSA. Thus, drug-CSA, in contrast to lithium-CSA, does not result in aversive reactions (gapes, chin rubs, forelimb flails, paw tread) to saccharin, as shown in a taste reactivity paradigm [2,3], in response to the taste CS, it is sensitive to the incentive value of the CS (saccharin) being modulated by food and water deprivation [6–8] and it is impaired by lesions of the gustatory thalamus and cortex [9]. On this basis, the explanatory framework of anticipatory suppression utilized for sucrose-CSA has been extended to drug-CSA [10]. Accordingly, drug-CSA would be the result of the fact that the rewarding properties of saccharin do not correspond to those of the reward (reinforcing drug) it predicts. An advantage of the appetitive interpretation of the CSA properties of drugs is that it provides a paradigm for the study of the neurochemical mechanism of the appetitive properties of drugs [11,12].

A long standing issue in the field of drug reinforcement is that of the role of DA [13–17]. Wise original anhedonia hypothesis, assigning to DA a primary role in food and drug reward, has been more recently contrasted with incentive-motivational and activational theories that explicitly negate a DA role in reward and hedonia [13,15]. This paradigm shift has involved not only food reward but also drug reward

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doi:10.1016/j.physbeh.2008.08.017

including, paradoxically, amphetamine and cocaine reward. For example, Berridge and Robinson [13] do exclude that amphetamine and cocaine psychostimulants produce reward and hedonia ('liking' in their terminology) by stimulating DA transmission and rather suggest that their rewarding effects are eventually related to stimulation of NA and 5HT transmission. Recently we have reported that nicotine and morphine CSA are prevented by systemic administration of a DA D_1 receptor antagonist (SCH 39166) given immediately after saccharin and 15 min before the drug. In contrast, under the same conditions, SCH 39166 failed to affect lithium-induced CSA [12]. These observations indicate that DA is involved in the motivational properties of morphine and nicotine but not of lithium. However, LiCl-CSA is impaired if the administration of LiCl is delayed by 60 min from saccharin drinking session and SCH 39166 is given immediately after saccharin (i.e. 60 min before lithium). Therefore, while not important for the motivational properties of lithium, DA D_1 receptors appear essential for the processing (consolidation) of the short-term memory trace of the taste CS (saccharin) when a 60 min CS–US delay is introduced [18]. As indicated by the ineffectiveness of SCH 39166 on LiCl-CSA at 15 min CS–US delays, a DA-dependent consolidation of the saccharin taste is not operative at 15 min CS–US delays [12]. However, in the case of morphine and nicotine CSA, a 15 min CS–US delay does not allow to establish whether D_1 blockade impairs drug-CSA by acting on the saccharin taste consolidation or whether by acting on the drug motivational properties. In the present study this issue has been investigated by testing the effects of DA D_1 and D_2 antagonists on the acquisition of morphine CSA by allowing a 45 min CS–US delay, administered at different time points after saccharin, i.e. immediately, 15 min or 30 min thereafter. For comparative purposes the delay-dependent effects of SCH 39166 and raclopride on LiCl-CSA were also investigated.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (n=172)(Harlan, San Pietro al Natisone, Udine, Italy) weighing 200–225 g were housed in group of six per cage with standard food (Global Diet 2018, Harlan Italy) and water ad libitum, for at least 1 week in the central animal room, under controlled environmental conditions: constant temperature (23 °C), humidity (60%) and a 12 h light/dark cycle (light from 7 a.m. to 7 p.m.). After this period rats were housed one per cage in the behavioral test room at the same controlled environmental conditions. All experiments were performed in their home cage and carried out during daylight hours (starting 10 a.m.). In all CSA experiments rats had access to fluid (0.1% saccharin or water depending of the stage of the experiment) for 20 min each day starting the day before the beginning of the Experimental procedures and throughout its entire duration. Animals drank fluid from two special bottles (50 ml capacity), put inside the home cage by metallic support. All animal experiments were conducted in accordance with the statement revised and approved by the Society for Neuroscience in January 1995 and with the guidelines for care and use of experimental animals of the European Communities Directive (86/609; D.L.:27.01.1992, No. 116).

3. Experimental procedures

The experiments were performed for 8 days and consisted of three phases: training, conditioning and test.

3.1. Phase 1: training

Following 24 h of water deprivation, all subjects were given 20-min access to water daily for 5 consecutive days and the intake was recorded for each rat.

3.2. Phase 2: conditioning (CSA acquisition)

The conditioning phase lasted 2 days. In this phase, all subjects were given access to a novel saccharin solution (0.1% in tap water) during the scheduled 20 min fluid-access period and the amount drunk was recorded for each rat and assigned to various experimental groups, such that saccharin consumption was comparable among groups. Immediately (Experiments 1 and 2), 15 or 30′ (Experiment 1), 45 or 105′ (Experiment 2) following this exposure rats were injected with saline, D_1 (SCH 39166) or D_2 (raclopride) DA receptor antagonists. Animals were injected with morphine or LiCl or saline respectively, 45 min (Experiment 1) or 120 min (Experiment 2) later (see below for details).

3.2.1. Phase 3: test (CSA expression)

This phase lasted 1 day without any drug treatment. All animals were given access to both 0.1% saccharin and water for 20 min in a two-bottle choice paradigm (one bottle contained 0.1% saccharin and one bottle tap water). The degree of conditioned taste aversion was determined by calculating the percentage of saccharin consumption on the test day relative to the total fluid intake (saccharin plus water).

3.3. Experiment 1: morphine hydrochloride (45′ CS–US delay)

During conditioning 90 rats were given access to saccharin and divided in two main experimental groups and administered, 45′ after saccharin intake, with saline s.c. (n=33) or morphine hydrochloride 7.5 mg/kg s.c. (n=57) as US. Saline or SCH 39166 was administered immediately, 15 or 30′ after saccharin (CS) withdrawal, while raclopride was administered immediately or 30′ after CS withdrawal; see Fig. 1 for details.

3.4. Experiment 2: lithium chloride (120′ CS–US delay)

During conditioning 82 rats were given access to saccharin and divided in two main experimental group and administered, 120′ after saccharin intake, with saline i.p. (n=38) or LiCl 40 mg/kg i.p. (n=44) as US. Saline, SCH 39166 or raclopride was administered immediately, 45 or 105′ after saccharin (CS) withdrawal; see Fig. 1 for details.

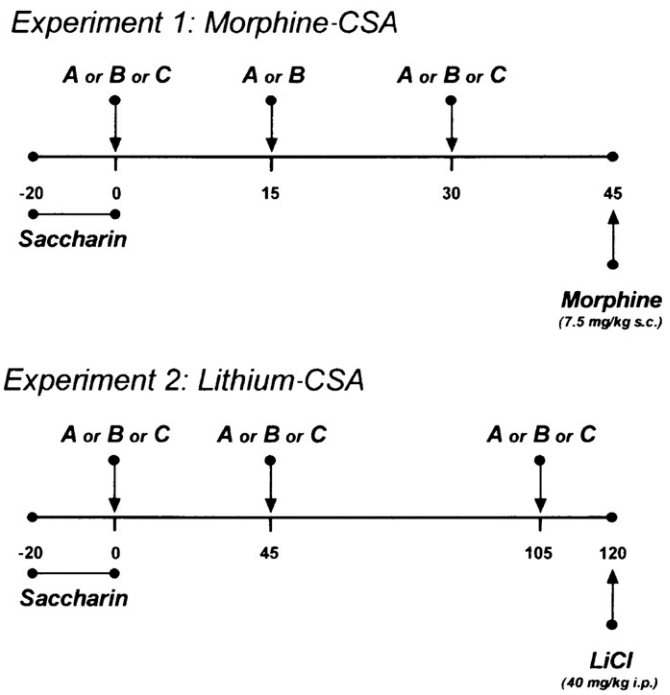

Fig. 1. Timeline of Experiments 1 and 2 showing the time of saccharin availability and of the injections (arrows). [(A, saline; B, SCH 39166 (0.1 mg/kg s.c.); C, raclopride (0.3 mg/kg s.c.)].