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Differential role of dopamine in drug- and lithium-conditioned saccharin avoidance

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Abstract

Rats learn to avoid palatable saccharin solutions that predict the systemic administration of reinforcing drugs as well as malaise-inducing lithium chloride (conditioned saccharin avoidance, CSA). In the present study the involvement of dopamine (DA) transmission in the acquisition of morphine, nicotine and lithium-conditioned CSA was investigated in a two-bottle choice paradigm. Nicotine tartrate (0.2 and 0.4 mg/kg s.c.) administered 15 min after saccharin presentation induced CSA, with a maximum effect at 0.4 mg/kg. The DA D_1 receptor antagonist, SCH 39166 (0.1 mg/kg s.c.) and the DA D_2 receptor antagonist raclopride (0.3 mg/kg s.c.), administered immediately after saccharin, prevented CSA induced by the lower but not by the higher dose of nicotine. However, combined administration of the two antagonists prevented CSA induced by the higher dose of nicotine. SCH 39166 prevented CSA induced by all morphine doses while raclopride prevented only CSA induced by the lowest dose of morphine (1.75 mg/kg). CSA induced by different doses of lithium given by the same schedule of drug-CSA (i.e. two pairings, 15 min after saccharin) was not affected by SCH 39166. However SCH 39166 impaired the acquisition of lithium-CSA when lithium was given 60 min after saccharin. In contrast, raclopride failed to affect lithium-CSA independently from the delay between saccharin and lithium. These results suggest that DA can play different roles in drug- and in lithium-CSA and are consistent with a different mechanism of drug- as compared to lithium-CSA.

Keywords: Conditioned taste avoidance; Dopamine; D_1 receptor; D_1 receptor; D_2 receptor; Lithium; Morphine; Nicotine; Raclopride; Saccharin; SCH 39166

1. Introduction

A puzzling issue in the psychobiology and in the behavioral pharmacology of drug reinforcement is the notion that drug reinforcers, with no exception, induce avoidance of a saccharin solution that has been predictively paired with their systemic administration in a response-non-contingent manner (conditioned saccharin avoidance, CSA) [1–3]. The initial explanation of this property assumed that drugs have mixed appetitive/aversive properties which, depending on the experimental conditions, can asymmetrically drive behavior and result in approach and positive reinforcement or in avoidance and negative reinforcement [3]. Evidence independent from CSA studies that this might be the case applies to at least three drugs, namely, cocaine, nicotine and morphine [4,5]. In the case of amphetamine, however, such independent evidence is lacking. On the other hand, comparative studies of drug- and lithium-CSA show the existence of a number of differences, namely, that drug-CSA, in contrast to lithium CSA, does not result in aversion to saccharin taste, as shown in a taste reactivity paradigm [4,5]; that drug-CSA, in contrast to lithium-CSA, is sensitive to the incentive value of the taste of the conditioned stimulus (CS) (saccharin) and therefore to the food and water deprivation state of the animal [6–8]; that lesions of the gustatory thalamus and of the gustatory cortex impair drug- but not lithium-CSA [9]. Saccharin avoidance can be also obtained if saccharin is predictively associated with purely rewarding sucrose solutions [10]. This phenomenon has been termed “anticipatory suppres-

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sion" or "anticipatory contrast effect" and is explained as the result of the development of a preference for the stronger reward (sucrose) at the expenses of the milder one (saccharin) that predicts it [11]. These observations indicate that CSA is not necessarily related to the aversive properties of the unconditioned stimulus (US) but can take place also with a highly appetitive US. On this basis, the explanatory framework of anticipatory suppression has been extended to drug CSA [12]. Accordingly, drug-CSA is viewed as related to the highly rewarding properties of the drug that make the animal to become less motivated towards the relatively poor saccharin reward that predicts it. There is no doubt that from the epistemological point of view such appetitive hypothesis of drug-CSA is more satisfactory than the aversive hypothesis. In fact, by providing a unitary explanation for the reinforcing and for the CSA properties of drugs it satisfies the logical principle of parsimony (Occam's Razor). Another advantage of the appetitive interpretation of the CSA properties of drugs is that it provides an additional paradigm, namely, the CSA paradigm, for the study of the neurochemical mechanism of the appetitive properties of drugs [13].

A long-standing issue in the field of drug reinforcement is that of the role of DA [14–18]. While the role of DA in the reinforcing properties of psychostimulants is well accepted, in the case of non-psychostimulant drugs is highly debated and has been the topic of an almost innumerable series of studies. In the present study we have utilized drug-CSA to investigate the role of DA in the motivational properties of nicotine and morphine. For this purpose we have studied the effect of two antagonists of DA receptors, SCH 39166 and raclopride, specific for D_1 and, respectively, D_2 DA receptors, on the acquisition of nicotine and morphine CSA. For comparative purposes the effect of SCH 39166 and raclopride on lithium-CSA was also studied.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (Harlan, Italy) weighing 200–225 g were used. All animals were individually housed in Plexiglas cages placed in a temperature- and humidity-controlled room with food and water ad libitum. Light were on from 0700 to 1900 h. All experiments were performed in their home cage. 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 procedure and throughout its whole duration. Each animal was used only for one experiment and all animal experimentation was conducted in accordance with the statement revised and approved by the Society of Neuroscience in January 1995 and with the guidelines for care and use of experimental animals of the European Commission (86/609; D.L. 27.01.1992, no. 116).

2.2. Experimental procedures

The experiments were performed for 8 days and consisted of three phases.

2.2.1. 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.

2.2.2. 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 was recorded for each rat and assigned to various experimental groups, such that saccharin consumption was comparable among groups. Immediately following this exposure rats were injected with saline, D_1 or D_2 DA receptor antagonists. After 15 min (experiments 1, 2 and 3) or 60 min (experiment 4) animals were injected with various doses of an aversion-inducing agent or saline (see below for details).

2.2.3. 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 contain 0.1% saccharin and one bottle tap water). The degree of conditioned taste aversion was determined by calculating the percentage of saccharin consumption on test day relative to the total fluid intake (saccharin plus water).

2.3. Experiment 1: nicotine

During conditioning 72 rats were given access to saccharin and treated as follows: saline s.c.+saline s.c. ($n=6$); saline s.c.+nicotine (0.2 mg/kg s.c., $n=7$; 0.4 mg/kg s.c., $n=11$); SCH 39166 0.1 mg/kg s.c.+saline s.c. ($n=4$); SCH 39166 0.1 mg/kg s.c.+nicotine (0.2 mg/kg s.c., $n=6$; 0.4 mg/kg s.c., $n=6$); raclopride 0.3 mg/kg s.c.+saline s.c. ($n=4$); raclopride 0.3 mg/kg s.c.+nicotine (0.2 mg/kg s.c., $n=6$; 0.4 mg/kg s.c., $n=7$); SCH 39166 0.1 mg/kg s.c.+raclopride 0.3 mg/kg s.c.+saline s.c. ($n=6$); SCH 39166 0.1 mg/kg s.c.+raclopride 0.3 mg/kg s.c.+nicotine 0.4 mg/kg s.c. ($n=9$).

2.4. Experiment 2: morphine

During conditioning 69 rats were given access to saccharin and treated as follows: saline s.c.+saline s.c. ($n=6$); saline s.c.+morphine (1.75 mg/kg s.c., $n=7$; 7.5 mg/kg s.c., $n=6$; 15 mg/kg s.c., $n=6$); SCH 39166 0.1 mg/