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Anti-anxiety self-medication induced by incentive loss in rats

Lidia Manzo [a], M. José Gómez [a], José E. Callejas-Aguilera [a], Alberto Fernández-Teruel [b], Mauricio R. Papini [c,*], Carmen Torres [a]

[a] Universidad de Jaén, Spain
[b] Universitat Autònoma de Barcelona, Spain
[c] Texas Christian University, USA

HIGHLIGHTS

- Animals can control disease symptoms via food selection-self-medication.
- Ethanol administration is known to ameliorate the effects of reward loss.
- Roman strains selected for high/low avoidance learning differ in self-medication.
- Only low rats self-medicated with the anxiolytic ethanol after reward loss.
- Reward loss did not induce water consumption in either strain.

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ABSTRACT

Ethanol can be used to ameliorate negative emotion in anxiety-inducing situations. Two experiments tested whether rats would increase preference for ethanol immediately after anxiogenic sessions of appetitive extinction. It was predicted that preference for ethanol would be greater in inbred Roman low-avoidance rats (RLA-I) than in inbred Roman high-avoidance rats (RHA-I), given previous research demonstrating that the former strain exhibits greater sensitivity to incentive loss. Experiment 1 used a consummatory extinction task (22-to-0% sucrose downshift), whereas Experiment 2 used an instrumental extinction task (12-to-0 pellet downshift). In both experiments, postsession ethanol consumption was higher in RLA-I rats than in RHA-I rats. No strain differences in ethanol preference were found after acquisition sessions or in groups given postsession access to water. Because ethanol is an anti-anxiety drug, the present results suggest that rats are capable of changing their consummatory behavior to correct for an aversive emotional state induced by incentive loss.

1. Introduction

Animals afflicted by a variety of physical pathologies are known to select corrective dietary components that are not otherwise consumed in significant quantities. Field observations show that chimpanzees consume a variety of plant leaves that reduce endoparasite proliferation [1]. Using an experimental approach, Villalba, Provenza, and Shaw [2] induced three types of digestive discomfort by feeding sheep grain, tannin, and oxalic acid, and then gave animals a choice between different diets. Sheep preferred the diet containing a medication that corrected the internal discomfort—sodium bentonite for grain acidosis, polyethylene glycol for tannins, or dicalcium phosphate for the toxic effects of oxalic acid (see also Ref. [3]). Self-medication also occurs in relation to emotional states. For example, neuropathic pain induced by sciatic nerve ligation leads to enhance cannabinoid self-administration in rats [4]. In this experiment, rats lever pressed more when this behavior led to a carotid infusion of (R,S)-AM1241, a CB_2 cannabinoid-receptor agonist, but not when lever pressing caused vehicle self-administration. Moreover, rats exposed to inescapable shocks consumed ethanol (an anxiolytic drug) significantly more than water and more than rats exposed to avoidable shocks [5]. The parallels between physical pain (induced, e.g., by neuropathic pain or electric shock) and psychological pain (induced, e.g., by incentive loss) suggest that a similar type of self-medication should be demonstrable in rats exposed to loss-induced anxiety, such as appetitive extinction [6,7].

The present demonstration of anti-anxiety self-medication was constrained in three ways. First, ethanol was selected as the anti-anxiety medication because it has been repeatedly demonstrated that its systemic administration reduces the effects of incentive loss, acting much like benzodiazepine anxiolytics [8–11]. The issue in this case

* Corresponding author at: Department of Psychology, Texas Christian University, Fort Worth, TX 76129, USA.
E-mail address: m.papini@tcu.edu (M.R. Papini).

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was whether the withdrawal of an incentive (extinction) would cause a postsession increase in ethanol self-administration. Appetitive extinction and other incentive loss phenomena have been considered as animal models of anxiety because, among others, they support escape behavior, are influenced by anxiolytics, and trigger a release of stress hormones [12]. Second, self-medication would involve enhanced ethanol consumption during the period when anxiety is peaking, as different from substance abuse, which may be conceptualized as habitual consumption. Thus, the present experiments sought to tap into the potential anti-anxiety effects of ethanol, rather than its potential for substance abuse. Finally, rats from two genetically selected inbred strains were used, Roman high-avoidance (RHA-I, hereafter H) and Roman low-avoidance (RLA-I, hereafter L) rats, selectively bred for their high or low performance in a two-way active avoidance task [13]. Both outbred and inbred H rats have shown higher levels of novelty seeking behavior (including consumption of ethanol and other drugs of abuse) compared to L rats, but L rats demonstrate a higher level of anxiety/fearfulness than H rats [14–17].

2. Experiment 1

For the first demonstration of anti-anxiety self-medication, rats were exposed to a consummatory task involving access to 22% sucrose for 10 daily sessions, followed by access to water during 4 daily sessions. The 22-to-0% sucrose downshift was used to induce anxiety [12,18]. Following each consummatory session, rats had 2 h of access to either ethanol–water (E) or water–water (W) in a two-bottle preference test. Water was used to control for the possibility that drinking behavior, rather than ethanol preference, was enhanced after extinction sessions [19].

2.1. Method

2.1.1. Subjects

The subjects were 40 male inbred rats (20 H, 20 L), experimentally naïve, from the Universidad Autónoma de Barcelona, Spain. Rats were housed individually in polycarbonate cages with water continuously available, in a room with constant temperature (20 °C), and lights on between 08:00 and 20:00 h. At the start of the experiment, rats were approximately 90 days old and weighed 340–380 g. Animals were food deprived to 82% of their ad libitum weight and maintained by supplemental food whenever weight loss exceeded 18%, at least 30 min after the end of their daily protocol. Such daily protocol involved consummatory training sessions (lasting about 5 min) and postsession access to either ethanol and water, or only water, depending on the group (lasting 2 h).

2.1.2. Apparatus

Consummatory training involved six Plexiglas boxes, each measuring 30 × 15 × 30 cm (L × W × H). The front wall had a hole through which the sipper tube of a graduated cylinder was inserted. The 22% sucrose solution was prepared w/w by mixing 22 g of sucrose for every 78 g of distilled water. A magnetic mixer (Nahita Magnetic Stirrer 680-9, Beriáin, Spain) was used to dissolve the sucrose. Session length was measured with a manual stop watch (Extech, model 365510, Madrid, Spain),

The ethanol preference test was administered in the animal's home cage (32 × 30 × 15 cm, L × W × H). Two 50-ml bottles were introduced side by side through the metallic lid, one with tap water and the other with 2% ethanol. Two bottles containing tap water were used for controls. Fluid consumption for both consummatory training and preference testing was determined by weighing each bottle before and after the 2-h test with a digital scale (Cobos, JT-300C, Barcelona, Spain). The 2% ethanol concentration was prepared by mixing 62.5 ml of 96% alcohol (Panreac, Castellar del Vallés, Spain) for every 2,937.5 ml of tap water. The 2% ethanol concentration was selected because a previous study showed similar preference for this concentration in both H and L rats [20]. Daily animal weights were recorded with a Baxtran scale (model BS3, Girona, Spain).

2.1.3. Procedure

On Days 1–4, two bottles containing tap water were placed in the animal's home cage. On Day 5, animals were placed first in the conditioning box for a habituation session that lasted 5 min. No fluids were presented during this habituation session, which was intended to familiarize the animals with the conditioning box.

On Days 6–15 (10 sessions), acquisition sessions were administered in the conditioning box. In each session, animals received free access to 22% sucrose and the amount consumed was registered as described above. On Days 16–19 (4 sessions), extinction sessions were administered exactly as scheduled during acquisition, except that distilled water, rather than sucrose, was available in the conditioning box. The dependent variable during consummatory training was the amount of sucrose consumed (ml) per session. Each session lasted 5 min starting from the moment in which the animal made contact with the sipper tube. In preparation for sessions of consummatory training, rats were transported in squads of 6 animals, all from the same strain. The order of squads was counterbalanced across days during the entire experiment. Home cages were cleaned and the saw dust replaced every other day.

Immediately after each session of consummatory training (Days 1–19), animals were placed back in their home cage with two bottles. For one set of groups (W), both bottles contained tap water, whereas for a second set of groups (E), one bottle contained tap water and the other 2% ethanol. This test lasted 2 h and the amount of fluid (water and ethanol) consumed was registered. The position of the ethanol and water bottles was exchanged daily to minimize position preferences. The ethanol preference test was administered in the same manner after each session in the entire experiment.

Animals from each strain were matched by weight and randomly assigned to one of 2 groups ($n = 10$) depending on whether the preference test involved only tap water or water vs. 2% ethanol. Thus, four groups were established: H/E, L/E, H/W, and L/W. All analyses of variance reported were computed with the SPSS package, with an α value set at 0.05 level, and with LSD pairwise tests derived from the main analysis. F and p values are reported in the text only for significant results.

2.2. Results

A Strain (H, L) × Ethanol (E, W) factorial analysis of body weights averaged across the 14 days of the experiment (Table 1) indicated only a significant difference between the strains, $F(1, 36) = 11.76$, $p < 0.003$. Because consumption is in part related to body size, consumption was analyzed in absolute terms and in relation to body weight. The statistical results derived from absolute and relative measures were virtually identical; therefore, only the results for the absolute measures are reported below.

During the 10 daily acquisition sessions, a Strain × Session analysis of sucrose consumption indicated a significant interaction, $F(9, 324) = 2.66$, $p < 0.006$, and change across sessions, $F(9, 324) = 52.86$, $p < 0.001$ (Fig. 1, top). Pairwise LSD tests of the significant interaction derived from the main analysis indicated that L rats consumed more sucrose than H rats only on Session 10, $F(1, 36) = 67.26$, $p < 0.02$. During

Table 1
Mean (±SEM) weights (g) of each group during the entire experiment.

Postsession test	Experiment 1		Experiment 2	
	RHA-I	RLA-I	RHA-I	RLA-I
Ethanol	206.4 (±3.6)	188.2 (±4.4)	321.9 (±12.4)	295.0 (±9.3)
Water	202.4 (±5.2)	189.9 (±4.6)	323.2 (±10.4)	279.9 (±10.8)