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Relationship between ethanol preference and sensation/novelty seeking

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HIGHLIGHTS

- RHA-I rats respond to novelty more than RLA-I rats.
- RHA-I rats show higher preference for ethanol than RLA-I rats.
- Several responses to novelty exhibit independence from each other.
- Two factors were identified—for low and high ethanol concentrations.
- Sensation/novelty seeking may help identify risk factors in ethanol preference.

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ABSTRACT

High- and low-avoidance Roman inbred rat strains (RHA-I, RLA-I) were selected for extreme differences in two-way active avoidance. RHA-I rats also express less anxiety than RLA-I rats. This study compared male Roman rats in ethanol preference and sensation/novelty seeking. Rats were first exposed in counterbalanced order to the hole-board test (forced exposure to novelty) and the Y-maze and emergence tests (free choice between novel and familiar locations). Then, rats were tested in 24-h, two-bottle preference tests with water in one bottle and ethanol (2, 4, 6, 8, or 10% in successive days). Compared to RLA-I rats, RHA-I rats showed (1) higher frequency and time in head dipping, (2) higher activity, and (3) lower frequency of rearing and grooming in the hole-board test, and (4) remained in the novel arm longer in the Y-maze test. No strain differences were observed in the emergence test. RHA-I rats exhibited higher preference for and consumed more ethanol than RLA-I rats at all concentrations. However, both strains preferred ethanol over water for 2–4% concentrations, but water over ethanol for 6–10% concentrations. Factorial analysis with all the rats pooled identified a two-factor solution, one grouping preferred ethanol concentrations (2–4%) with head dipping and grooming in the hole board, and another factor grouping the nonpreferred ethanol concentrations (6–10%) with activity in the hole board and novel-arm time in the Y-maze test. These results show that preference for ethanol is associated with different aspects of behavior measured in sensation/novelty-seeking tests.

1. Introduction

Sensation seeking [1]—a behavior tendency to search and prefer situations involving novelty, complexity, intensity and variety of stimulation, and the willingness to take physical, social, legal, and financial risks for the sake of such experiences—has been frequently linked to the acquisition of drug consumption and abuse in humans [2–5]. The parallel concept in research with nonhuman animals, *novelty seeking*, has been used to describe high levels of exploratory activity in response to novel environments and unknown objects or stimuli [6,7]. Animals that exhibit strong novelty-seeking behavior tend to self-administer and are more sensitive to the effects of such drugs of abuse as ethanol, nicotine, stimulants, and morphine, a fact suggesting that novelty seeking may indicate vulnerability to addiction [3,7–16]. The link between novelty seeking and addiction is suggested by higher dopamine release in the nucleus accumbens in situations involving both novelty and drugs of abuse, in individuals who exhibit vulnerability to addictive disorders [17–20].

Recent animal models suggest a distinction between the initial propensity to consume drugs and the transition to compulsive drug abuse,

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indentifying some behavioral traits that contribute differentially to the stages characterizing addiction [3]. It has been proposed that exploratory behavior in forced/inescapable novelty tests (known as "sensation-seeking," "response-to-novelty," or "novelty-responder" tests) is a good predictor of the proneness to take drugs [21], whereas preference for novelty in free-choice tasks (labeled "novelty-seeking" tests) correlates with compulsive drug taking and severity of addictive behavior (e.g., persistence in drug seeking, inability to stop taking drugs, enhanced relapse, reinstatement following abstinence, etc.) [22,23]. Examples of inescapable tests include exposure to a circular corridor or an open-field arena for a variable period varying between 5 min and 2 h [11,13,17,19,24,25]. Examples of free-choice tests include several place preference procedures based on exposure to one of two or more compartments (or arms in which an object can be found and explored) for one or more trials, followed by a trial in which animals are allowed to freely explore the familiar vs. the novel environment/object [10,12,16,22,26]. The hole-board test seems to have both inescapable and free-choice components [27], although it has been frequently considered an inescapable novelty test [7,15]. Consistent with this distinction, impulsivity, a behavioral trait associated to substance-use disorders, is related to preference for novelty in free-choice tests. Rats selected on the five-choice serial reaction time task for high impulsivity showed more preference for novel objects and contexts, and were also faster to initiate exploratory behavior in novel environments, compared to low impulsivity rats [28]. This evidence suggests that novelty seeking in animals is not a unitary behavioral trait, but one that includes some behaviors that differentially predict vulnerability to addiction [3,10,27].

Selectively-bred rat strains with differential propensity for novelty seeking may provide insights on the relationship between novelty seeking and addiction [3,6,29–31]. The Roman high- and low-avoidance rat strains (RHA and RLA, respectively) stand as an example of selectively bred lines that show extreme differences in behavioral traits related to sensation/novelty seeking and addiction [32,33]. Although initially selected for their performance in two-way active avoidance, these Roman strains have shown a host of correlated behavioral traits, including anxiety/emotional reactivity [32], impulsivity [34–38], coping styles in novel/stressful environments [24,39–46], consumption of palatable tastes [41,47], and vulnerability to addiction [33,48]. This experiment was designed to test RHA-I and RLA-I rats in a battery of tests assessing ethanol preference and sensation/novelty-seeking behavior, aiming at understanding (1) whether novelty seeking (as assessed by the hole-board test) can be dissociated from sensation/novelty responses (as assessed by the emergence test and the Y-maze test), and (2) whether this distinction relates to the acquisition of drug-taking behavior.

Ethanol preference (modeling the initial propensity to take drugs) was assessed by an increasing-dose series in two-bottle tests against water. Using this procedure, Manzo et al. [49] observed that both inbred RHA and inbred RLA (RHA-I, RLA-I) rats prefer ethanol over water at low concentrations (e.g., 2–4%), but switch over to water at higher ethanol concentrations (e.g., 8–10%). However, RHA-I rats showed consistently higher preference for ethanol than RLA-I rats across all concentrations (2–10%). Sensation/novelty seeking was measured in three tests: hole-board test (forced/inescapable; animals are placed in a novel environment), emergence test (free choice; animals choose to either stay in the familiar location or move out of it), and Y-maze novelty test (free choice; animals are given a choice between two familiar arms and a novel arm). Based on the evidence reviewed above, we predicted that (1) RHA-I rats would exhibit greater preference for ethanol than RLA-I rats at all concentrations, although both strains would switch from ethanol to water preference as the ethanol dose increases to 10%; (2) RHA-I rats would tend to exhibit higher sensation and novelty-seeking behaviors than RLA-I rats in all three tests; and (3) preference for ethanol would correlate with sensation-seeking behaviors in the forced/inescapable hole-board test, but not with novelty-seeking behaviors in the free-choice Y-maze novelty and emergence tests.

2. Method

2.1. Subjects

The subjects were 48 inbred male rats (24 RHA-I, 24 RLA-I) obtained from the Autonomous University of Barcelona, Spain, when they were approximately 3.5 months old. Rats were 4 months old and weighed an average of 406 g (±5.19) for RHA and 399 g (±8.91) for RLA rats at the start of the experiment. Animals were housed individually with free access to food and water throughout the experiment, in a room kept at 22–23 °C, and subjected to a 12:12 h light cycle (lights on at 08:00 h). The experiment was conducted following the European Union directive guidelines for the use of animals in research (2010/63/EU) and the Spanish Law (RD 53/2013).

2.2. Apparatus

Access to ethanol was provided in the home cage, in 24-h cycles. Home cages were 32 × 15 × 30 cm (L × H × W), made of acrylic, with a wire lid. The floor was covered with saw dust. Each cage was equipped with two glass bottles and an area to store food pellets on the wire lid. Each bottle had a stainless steel sipper tube equipped with a ball to minimize spillage (Bioscape, Castrop-Rauxel, Germany). Fluid consumption was measured by weighing the bottles before and after each 24-h cycle with a Cobos JT-300C digital scale. The different concentrations of ethanol used during the experiment were diluted (v/v) in tap water from an original concentration of 96% (Panreac, Castellar del Vallés, Spain). Animals were weighed daily with a Baxtran scale (model BS3, Girona, Spain).

The apparatus for the three novelty tests were placed in a sound-attenuated room under dim illumination. Numerous visual cues were placed on the walls of the testing room and were kept constant across tests. The hole-board apparatus was a white 66 × 66 × 47 cm (L × H × W) wooden box divided into 16 equal squares, containing four holes (diameter: 3.7 cm) in the floor. Partially hidden objects (small metallic toys) were located below the holes; this procedure has been reported to specifically induce novelty-seeking, rather than exploratory behavior or locomotor activity [39].

The Y-maze apparatus was similar to the one previously described by Dellu et al. [26]. The Y-maze was made of acrylic; arms were 50 × 32 × 16 cm (L × H × W). The floor was black and the walls were transparent. The floor of the maze was covered with odor-saturated sawdust.

The apparatus used for the emergence test (adapted from Dellu et al. [26]) consisted of a box with two equal compartments measuring 27 × 28 × 25 cm (L × H × W). A door (9 × 9 cm) enabled the rats to pass from one compartment to the other. One of the compartments was completely enclosed by black opaque plastic sides with a lid of the same material, while the other was made of white plastic and had no lid. The white compartment was illuminated by a 60 W lamp placed 100 cm above it.

2.3. Procedure

The three sensation/novelty tests were conducted in the early part of the light cycle, between 09:30–13.30 h, to reduce the possible influence of diurnal variation in activity. The order of these tests was counterbalanced across rats. There were 7 days between successive tests. Dependent variables for each test were video recorded and then processed with JWatcher (http://www.jwatcher.ucla.edu) by two observers. These observers received training from a senior researcher (MJG) until all discrepancies were resolved. Then, each observer was assigned half the sessions. Both observers were blind to the strain of the animal being observed. Frequency variables were measured on a ratio scale with an absolute zero and unbounded upper limit. Time variables were measured in seconds with a manual chronometer (Extech, Madrid, Spain).

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