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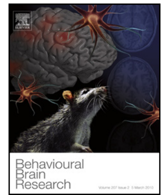

Research report

Ethanol-related behaviors in mice lacking the sigma-1 receptor

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HIGHLIGHTS

- Sig-1 receptor knockout mice (Sig-1R KO) display elevated alcohol drinking.
- Consumption of sweet or bitter solutions is unaltered in Sig-1R KO mice.
- Sig-1R KO mice show lower sensitivity to the ethanol locomotor stimulant effects.
- Sigma-1R KO mice are more sensitive to ethanol taste aversive and hypothermic effects.
- Ethanol-induced sedation does not differ in Sigma-1R KO and WT mice.

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ABSTRACT

Rationale: The Sigma-1 receptor (Sig-1R) is a chaperone protein that has been implicated in drug abuse and addiction. Multiple studies have characterized the role the Sig-1R plays in psychostimulant addiction; however, fewer studies have specifically investigated its role in alcohol addiction. We have previously shown that antagonism of the Sig-1R reduces excessive drinking and motivation to drink, whereas agonism induces binge-like drinking in rodents.
Objectives: The objectives of these studies were to investigate the impact of Sig-1R gene deletion in C57Bl/6J mice on ethanol drinking and other ethanol-related behaviors.
Methods: We used an extensive panel of behavioral tests to examine ethanol actions in male, adult mice lacking Oprs1, the gene encoding the Sig-1R. To compare ethanol drinking behavior, Sig-1 knockout (KO) and wild type (WT) mice were subject to a two-bottle choice, continuous access paradigm with different concentrations of ethanol (3–20% v/v) *vs.* water. Consumption of sweet and bitter solutions was also assessed in Sig-1R KO and WT mice. Finally, motor stimulant sensitivity, taste aversion and ataxic effects of ethanol were assessed.
Results: Sig-1R KO mice displayed higher ethanol intake compared to WT mice; the two genotypes did not differ in their sweet or bitter taste perception. Sig-1R KO mice showed lower sensitivity to ethanol stimulant effects, but greater sensitivity to its taste aversive effects. Ethanol-induced sedation was instead unaltered in the mutants.
Conclusions: Our results prove that the deletion of the Sig-1R increases ethanol consumption, likely by decreasing its rewarding effects, and therefore indicating that the Sig-1R is involved in modulation of the reinforcing effects of alcohol.

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1. Introduction

Alcoholism constitutes one of the most serious global public health problems. The World Health Organization estimates that about 2 billion people worldwide consume alcoholic beverages [1], 76.3 million of which have alcohol use disorders. Hallmarks of alcohol addiction include a compulsion to seek and drink alcohol, a loss of control to limit intake, and the emergence of a negative emotional state when access is prevented [2,3]. Although significant

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progress has been made to better understand the neurobiology of alcoholism, effective treatments remain elusive.

Originally, and mistakenly, categorized as members of the opiate receptor family or high-affinity phencyclidine binding sites [4,5], sigma receptors have been proposed to play a role in the etiopathology of many psychiatric conditions. Today, two different isoforms are known, sigma-1 (Sig-1R) and sigma-2 (Sig-2R), which differ in binding profile and molecular weight [6,7]; however, only Sig-1R has so far been cloned. Sig-1Rs are intracellular chaperones residing at the endoplasmic reticulum–mitochondrion interface [8–10] where they regulate calcium signaling. Sig-1Rs have been shown to translocate to other parts of the cell [10,11] where they can bind to various ion channels, receptors and kinases, resulting in the modulation of multiple neurotransmitter systems such as glutamate, acetylcholine, and dopamine [12–17]. The existence of an endogenous ligand for Sig-1R is still under debate, although certain neurosteroids and the trace amine *N*,*N*-dimethyltryptamine have been proposed [18]. Sig-1Rs are predominantly expressed in the central nervous system, in particular in limbic regions and brainstem nuclei [19,20].

Recent findings have suggested that compounds targeting Sig-1Rs may represent a new class of therapeutics aimed at treating alcohol use disorders. *In vivo* preclinical studies are starting to reveal that Sig-1R ligands can ameliorate the behavioral effects of many drugs of abuse including cocaine, methamphetamine, and alcohol [21–26]. Sig-1R antagonists have been shown in rodent models to reduce ethanol consumption, the motivation to work to obtain ethanol, and the alcohol deprivation effect selectively in animal models of excessive drinking [27–29]. Demonstrating selectivity of action, Sig-1R antagonists were shown not to affect the intake of sweet solutions [27,28], suggesting that the Sig-1R may not be involved in the motivation for natural rewards. Sig-1 antagonists have also been shown to attenuate ethanol-induced locomotion and ethanol-induced place and taste conditioning in mice [30]. On the other hand, Sig-1R agonists have been shown to induce alcohol binge-like drinking [31], suggesting bi-directionality of action. In addition, inbred mouse strains with greater ethanol preference display increased Sig-1R expression relative to more ethanol-averse mouse strains [32]. In humans, an association has been demonstrated between functional polymorphisms in the Sig-1R gene and alcoholism [33].

In light of the above-cited findings, the aim of the present study was to investigate the role of endogenous Sig-1Rs in the regulation of ethanol-related behaviors using a genetic approach. For this purpose, we used mutant mice lacking the *Oprs1* gene, which encodes for the Sig-1R, to investigate ethanol drinking behavior, as well as sensitivity to ethanol-induced motor stimulation, aversion and ataxia.

2. Materials and methods

2.1. Animals

Mice lacking the *Oprs1* gene were generated as previously described in [34]. Mice, originally of a mixed background, were backcrossed onto a C57BL/6J strain for >10 generations to obtain a background pure null mutant mice (*Oprs1*$^{-/-}$, Sig-1R KO). For control wild types (WT), age-matched C57BL6/J male mice were purchased from Jackson Laboratories (Bar Harbor, ME, USA). 9–13-week old mice were group-housed with food and water *ad libitum*, unless otherwise specified, in a humidity- and temperature-controlled AAALAC-approved vivarium on a 12 h reverse light/dark cycle. All experiments were performed during the mice dark cycle. Procedures adhered to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*, the Principles of Laboratory Animal Care, and were approved by the Institutional Animal Care and Use Committee (IACUC) of Boston University.

2.2. Drugs

The ethanol solution for injections (20% v/v, administered intraperitoneally -*i.p.*-) was prepared diluting 200-proof ethanol (Pharmco-Aaper Inc., Brookfield, CT) in isotonic saline. Ethanol solutions for drinking experiments (3%, 6%, 10% and 20% v/v) were prepared using 190-proof ethanol and tap water. Saccharin (0.02% and 0.07% w/v), quinine (0.03 and 0.1 mM) and sodium chloride (NaCl, 0.2 M) solutions were prepared dissolving saccharin sodium salt hydrate, quinine hemisulfate salt monohydrate (both from Sigma, St. Louis, MO), and sodium chloride (Fisher Scientific, Agawam, MA), respectively, in tap water.

The partial inverse agonist of the benzodiazepine (BDZ) receptor Ro 15-4513 (R&D Systems, Inc., Minneapolis, MN) was dissolved in DMSO (10% v/v) and then diluted with isotonic saline. Ro 15-4513 was injected *i.p.* in a volume of 10 ml/kg.

2.3. Voluntary drinking of ethanol

Ethanol naïve WT and Sig-1R KO mice were allowed to acclimate to single-housing in their home cage. After acclimation, the mice learned to drink water from two 50 ml conical tubes with rubber stoppers and metal double-ball sipper tubes, which produce negligible spillage. Mice body weights were recorded every 6 days.

A first set of WT and Sig-1R KO mice (body weight 26.9 ± 0.4, mean ± SEM) was exposed to escalating concentrations of an ethanol solution for 6 days each (3%, 6%, and 20% v/v), in their home cage in a continuous access (24 h/day), two-bottle choice paradigm *vs.* water. The two tubes were weighed daily and offered right before the dark cycle onset. Bottle positions were alternately changed to avoid development of place preference (ethanol on the right side on days 1, 3 and 4); data from the first two days of access to each solution were excluded from data analysis in order to avoid bias due to the novelty of each tastant and the stress of cage changing.

A second set of WT and Sig-1R KO mice (body weight 30.1 ± 0.7, mean ± SEM) was exposed to a 10% v/v ethanol solution in their home cage in a continuous access (24 h/day), two-bottle choice paradigm *vs.* water for 2 consecutive weeks.

Throughout the experiments, spillage estimates were calculated by weighing two bottles placed in empty cages, one filled with water and the other containing the appropriate solution. Spillage, however, was negligible. Solution intake was recorded by weighing the bottles before and after every access (precision 0.01 g). Solution intake was normalized to body weight; preference was calculated as the ratio percentage between the volume of tastant solution consumed and the total fluid intake.

2.4. Voluntary drinking of sweet and bitter solutions

Ethanol naïve WT and Sig-1R KO mice (body weight 28.9 ± 0.3, mean ± SEM) were tested for their preference for either sweet (saccharin) or bitter (quinine) solutions. The same two-bottle choice protocol used for ethanol was copied here, instead offering 6 days each of escalating concentrations of either saccharin (0.02% and 0.07%) or quinine (0.03 mM and 0.1 mM) solutions *vs.* water. Between tastants, mice were given a washout period of water for two weeks. Solution intake was recorded by weighing the bottles before and after every access (precision 0.01 g) and intake was normalized to body weight.

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