Research article

Effects of LY466195, a selective kainate receptor antagonist, on ethanol preference and drinking in rats

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HIGHLIGHTS

• We examined the effects of a novel kainate receptor antagonist on ethanol drinking and preference in rats.
• Administration of LY466195 significantly reduced ethanol preference in Long Evans rats.
• Administration of LY466195 produced a non-significant trend towards decreased ethanol preference in Sprague Dawley rats.
• Further studies are needed to more fully characterize the role of kainate receptors in drinking behaviors.

ABSTRACT

There is evidence that variation in the gene encoding a kainate receptor subunit contributes to alcohol dependence risk. Further, there is suggestive evidence that alcohol consumption is mediated, in part, by kainate receptors. In this study, we used a novel kainate receptor antagonist, LY466195, to examine the potential role of kainate receptors in alcohol drinking behavior using a rodent model of voluntary ethanol consumption. Male Sprague Dawley and Long Evans rats were given access to 20% ethanol using the intermittent two-bottle choice paradigm. Following 6 weeks of ethanol consumption, rats were pretreated with an acute dose of LY466195 (0, 4.0 and 10.0 mg/kg, i.p.) prior to a two-bottle choice test session. Acute administration of LY466195 did not significantly affect ethanol-drinking behavior in Sprague Dawley rats. In contrast, Long Evans rats pretreated with 10.0 mg/kg LY466195 showed a significant reduction in alcohol preference compared to vehicle-treated controls. Decreased alcohol preference in the Long Evans rats was associated with increased water intake and no change in the amount of ethanol consumed. Taken together, these results suggest that systemic administration of a selective kainate receptor antagonist reduces ethanol preference in rats, an effect that could be due to non-specific effects on overall drinking behavior.

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1. Introduction

Alcohol abuse disorder (AUD) is a significant public health concern in the United States. A recent epidemiologic survey showed that the lifetime prevalence of AUD in the United States is 36.0% in men and 22.7% in women [10]. The frequency of heavy drinking is a key risk factor for developing an AUD [6]. In 2014, 24.7% of individuals over the age of 18 reported consuming five or more drinks on a single occasion during the past month. Additionally, 6.8% of individuals over the age of 18 reported consuming five or more drinks on at least five occasions during the past month [1]. Despite these high rates of heavy drinking and the associated health risks, only 7.8% of adults who fit the criteria for an AUD seek treatment [10]. Moreover, current medications to treat AUD have limited efficacy and can produce significant adverse effects [3,19].
Based on preclinical studies showing that topiramate reduces ethanol consumption and reinforcement in rats \[4,18\], recent clinical trials have examined the efficacy of topiramate in alcohol dependence \[25\]. In a recent study, 12 weeks of topiramate treatment was sufficient to reduce the number of heavy drinking days among heavy drinkers \[15\]. Unfortunately, topiramate’s adverse effects, which include paresthesia, anorexia (with weight loss), difficulties with memory or concentration, and mild-to-moderate taste disturbances, limit its clinical utility \[20\]. Topiramate has several pharmacological mechanisms of action including antagonism of AMPA/kainate receptors \[9,21\]. A recent study showed that the efficacy of topiramate in reducing the number of heavy drinking days in human patients was moderated by a polymorphism in GLUK1, the gene that encodes the GluK1 kainate receptor subunit \[15\]. These results suggest that the efficacy of topiramate is mediated, in part, by pharmacological inhibition of GLUK1 kainate receptors.

Kainate receptors are ionotropic glutamate receptors \[17,23\] that show distinct expression patterns in the brain with high levels in the hippocampus and striatum, brain regions known to play important roles in alcohol reinforcement \[7,8\]. Recently, a potent and selective kainate receptor antagonist was developed for in vivo studies \[24\]. Because previous studies of glutamate receptors in preclinical models of ethanol consumption used the nonselective AMPA/kainate receptor antagonist CNQX to reduce ethanol intake \[2\], the precise role of kainate receptors in ethanol drinking remains to be determined. Here, we used the novel antagonist LY466195, which is highly selective for kainate receptors containing the GluK1 receptor subunit \[24\], to investigate the role of kainate receptors in a rodent model of voluntary ethanol consumption. Our hypothesis was that pharmacological inhibition of GluK1-containing kainate receptors would decrease ethanol drinking and preference in rats.

2. Materials and methods

2.1. Animals and housing

Male Sprague Dawley rats and male Long Evans rats weighing 250–300 g were obtained from Taconic Laboratories (Germantown, NY, USA). Rats were individually housed with food and water available ad libitum. A 12-h reverse light/dark cycle (lights off 07:00, lights on 19:00) was used throughout the experiments. All procedures were consistent with the ethical guidelines of the U.S. National Institutes of Health and were approved by the University of Pennsylvania School of Medicine Institutional Animal Care and Use Committee.

2.2. Drugs

Eli Lilly and Co. (Indianapolis, IN, USA) donated LY466195. The drug was dissolved in bacteriostatic 0.9% saline (bio-layer Veterinary Supply, Norristown, PA) for administration. The doses and time course of LY466195 pretreatment were based on preliminary studies demonstrating in vivo effects of LY466195 in behavioral models of addiction (data not shown) as well as rodent and human studies that identified efficacious and selective doses of LY466195 in models of migraine \[14,24\]. Doses of LY466195 as high as 100 mg/kg were shown to maintain selectivity for GluK1-containing kainate receptors and do not produce changes in locomotor activity \[24\].

2.3. Intermittent-2-bottle choice

The intermittent-2-bottle choice paradigm was used to assess ethanol consumption in rats as described previously \[5\]. Briefly, rats were acclimated to having two water bottles present in their home cage continuously for one week prior to the first ethanol exposure. Every Monday, Wednesday and Friday, two hours after the onset of the dark cycle (09:00), one water bottle was replaced with a bottle containing an ethanol solution and rats were allowed to drink freely. After two hours of exposure, the ethanol bottle and water bottle were taken out, weighed, and put back into the cage. Following 24-h of exposure, the ethanol bottle and water bottle were weighed a second time and the ethanol bottle was replaced with a bottle containing normal drinking water. During the first week, rats were exposed to progressively greater concentrations of ethanol (one day each of 3%, 6% and 10% ethanol (vol/vol)). For subsequent weeks, rats received 20% ethanol (vol/vol) on Mondays, Wednesdays and Fridays. A total of 20 acquisition sessions of 24-h ethanol exposure were conducted prior to testing. To prevent the development of a side preference or bias, water and ethanol bottle positions were counterbalanced across days. An empty cage containing one water bottle and one ethanol bottle was used to measure evaporation and bottle leakage. Rats were weighed weekly, including prior to acute LY466195 administration, to provide the denominator for calculating ethanol consumption (g/kg). Ethanol preference was calculated as the total amount of ethanol consumed/(total ethanol + water consumption) × 100. All measurements were made immediately before the introduction of the ethanol bottle on test days.

2.4. Acute administration of LY466195

For the final three of 20 total sessions involving 24-h ethanol exposure, all rats were injected with saline (1 ml/kg, i.p.) prior to the introduction of the ethanol bottle in order to habituate them to the injection procedures. On subsequent test days, rats received 0, 4.0 and 10.0 mg/kg LY466195 (i.p.) 10 min before a 24-h two-bottle choice exposure. A within-subjects design was used with doses of LY466195 counterbalanced across the three test sessions.

2.5. Data analyses

The effect of LY466195 on ethanol consumption, ethanol preference, and total fluid intake were analyzed using separate one-way ANOVAs. Following a significant main effect of treatment, post hoc analyses were conducted using Tukey’s HSD.

3. Results

3.1. Acquisition of ethanol drinking and ethanol preference in male Sprague Dawley and male Long Evans rats

The intermittent two-bottle choice paradigm was used to study ethanol drinking and ethanol preference in the two strains of rats. Total ethanol intake and ethanol preference (mean ± S.E.M.) at the two-hour time point for 19 days of intermittent ethanol exposure are displayed in Fig. 1. Male Sprague Dawley rats consumed 1.60 ± 0.27 g/kg of ethanol (Fig. 1A) and displayed an ethanol preference of 68.04 ± 5.46% (Fig. 1B) prior to the testing phase (i.e., Day 19). Male Long Evans rats consumed 1.75 ± 0.35 g/kg of ethanol (Fig. 1C) and displayed an ethanol preference of 75.32 ± 7.87% (Fig. 1D) following 19 days of intermittent ethanol exposure (i.e., Day 19).

3.2. Acute systemic administration of LY466195 had no effect on ethanol intake and ethanol preference in male Sprague Dawley rats

Following 20 days of intermittent ethanol access, rats were pretreated with the selective GluK1 kainate receptor antagonist
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