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Anxiety and ethanol consumption in victorious and defeated mice; effect of κ-opioid receptor activation

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Abstract Alcohol consumption and addiction have been related to anxiety and the anxiolytic effect of ethanol. It has been shown in mice that losers with repeated experience of social defeats are more anxious than winners with repeated experience of victories. Mice with a different social status were tested for their oral ethanol consumption using a free two bottle choice paradigm and for their social approach behaviour after ethanol consumption using the partition test, in which anxiety is an important component. In addition, the sensitivity of the animals for the κ-opioid receptor agonist U-50,488H (2.5 mg/kg, s.c.) was assessed using the partition test, in which this drug has been shown to induce anxiolytic-like effects. Further, the effect of daily treatment with U-50,488H for 8 days on ethanol consumption was tested in animals that had consumed ethanol and were subjected during these 8 days to a period of 5 days of interruption of ethanol supply and subsequently to a period of 3 days of renewed access to ethanol.

Losers consumed more ethanol than winners. Consumption of ethanol was accompanied by a decrease of anxiety level, as evidenced by an increased approach behaviour in the partition test. U-50,488H stimulated ethanol consumption after a period of 5 days of interruption of ethanol supply and drug treatment in the losers, but not in the winners. U-50,488H increased approach behaviour in the losers not consuming ethanol and decreased this behaviour in the winners, especially in those that had consumed ethanol. It is postulated that U-50,488H acts as a partial agonist in this respect. The increased anxiety may be related to the enhanced ethanol consumption in the losers, which may be of relevance for the etiology of alcohol addiction.

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1. Introduction

Anxiety has been implicated in alcohol consumption and addiction. According to the 'tension reduction' hypothesis (Cappell and Herman, 1972), elevated levels of anxiety or stress may lead to an increased predisposition to alcohol addiction. More anxious individuals could benefit more from the anxiolytic effect of alcohol and therefore consume more alcohol than less anxious individuals. Both humans and animal studies have reported an association between increased anxiety states and alcohol consumption and/or addiction (Kushner et al., 1990; Kudryavtseva et al., 1991; Pohorecky, 1981; Spanagel et al., 1995). Moreover, anxiety and stress have been suggested to play a role in relapse and reinstatement of alcohol consumption in humans and animals (Brown et al., 1995; Lê et al., 1998). However, in rats chronic consumption of alcohol was not accompanied by an anxiolytic-like effect, as observed after the initial consumption, and increased inborn anxiety did not result in increased consumption of alcohol (Silvestre et al., 2002; Henniger et al., 2002). Thus, it is of interest to determine the interaction between anxiety-related processes and ethanol consumption in more detail. The sensory contact model (Kudryavtseva, 1991) in which male mice have agonistic interactions on a daily basis, allows animals to be identified as victorious (winners) and as defeated (losers) that have developed fear and anxiety. Therefore, this model in combination with voluntary ethanol consumption was used to study the interaction of anxiety and ethanol.

Recently, we observed that winners hardly responded to treatment with the κ-opioid receptor agonist U-50,488H in anxiety provoking situations (the partition and the elevated plus-maze tests), while losers responded dose dependently with an anxiolytic-like effect (Kudryavtseva et al., 2004). κ-Opioid receptor systems have been implicated in drug addiction. Treatment with U-50,488H decreased cocaine intake in rats and morphine intake in mice when offered in doses that readily initiated self-administration behaviour (Kuzmin et al., 1997). On the other hand, this drug facilitated initiation of cocaine and morphine self-administration while the κ-opioid receptor antagonist inhibited the initiation of drug self-administration (Kuzmin et al., 1997, 1998; Van Ree et al., 1999). U-50,488H reduced voluntary ethanol intake by animals (Nestby et al., 1999; Lindholm et al., 2001). Co-administration of U50,488H and ethanol reduced ethanol-induced place preference (Matsuzawa et al., 1999), which might reflect the anxiolytic effect of U-50,488H (Privette and Terrian, 1995). On the other hand, stimulation of κ-opioid receptors increased ethanol intake, at least in long-term ethanol-experienced rats (Hölter et al., 2000). The differential data obtained so far are complicated by the fact that κ-opioid receptors have been implicated in drug-induced behavioural sensitisation, which may interact with the outcome of drug self-administration experiments (Toyoshi et al., 1996; Shippenberg and Rea, 1997).

The present study was aimed to investigate the influence of positive and negative social experience (winners and losers) on voluntary ethanol consumption in male mice using a free bottle choice paradigm as related to anxiety processes. After a period of 15 days of voluntary ethanol consumption, the mice were subjected to a period of 5 days of interruption of ethanol supply and subsequently to a period of 3 days with renewed access to ethanol. During those 8 days the mice were daily treated with U-50,488H or placebo in order to investigate the influence of this drug on ethanol consumption after deprivation, mimicking drug treatment during abstinence in alcoholics. On the last day of the deprivation period the mice were tested for their social approach behaviour using the partition test as index for anxiety. At the end of the experiment the sensitivity to U-50,488H was assessed in winners and losers that have consumed ethanol as compared to controls that have not consumed ethanol. We hypothesized that 1) losers (more anxious) voluntarily drink more ethanol than winners, 2) increased ethanol consumption is accompanied by decreased anxiety, 3) stimulation of the κ-opioid receptors modulates anxiety, and this effect may be dependent on the social status and/or chronic ethanol consumption.

2. Methods

2.1. Animals

Adult male mice of the C57BL/6J strain (24—27 g) from the stock maintained at the Institute of Cytology and Genetics SD RAS (original from Stolbovaja, Moscow) were used. The animals were housed under standard conditions (12:12 h light/dark regime; food (pellets) and water available ad libitum). Mice were weaned at one month of age and housed in groups of 8—10 in plastic cages (36 × 23 × 12 cm). Experiments were performed at 10—12 weeks of age. All procedures were in compliance with the European Communities Council Directive of November 24, 1986 (86/609/EEC).

2.2. Procedure obtaining winners and losers

Winners and losers were generated using the model of sensory contact (Kudryavtseva, 1991). Pairs of animals were placed in steel cages (28 × 14 × 10 cm) divided in two compartments by a perforated transparent partition allowing the animals to see, hear and smell their neighbour, but not to contact them physically. Test sessions commenced 2 days after adaptation of the animals to these new housing conditions (sensory contact). Every afternoon (between 2.00 p.m. and 5.00 p.m.) the steel cover of the cage was replaced by a transparent one, and 5 min later (the period needed for adaptation to the lighting condition) the partition was removed for 10 min to allow agonistic interactions. Superiority of one of the partners was evident within 2—3 daily test sessions. One partner attacked, bit, and chased the other, who displayed defensive behaviour only (sideways, upright postures, withdrawal, lying on the back or freezing). Agonistic interactions were discontinued by lowering the partition if intensive attacks lasted more than 3 min. Every day after the test session, each defeated mouse was placed in another two compartment cage with a partition, in which another winner was present in the other compartment. The winners remained in their own compartments. The procedure yielded equal numbers of males with an opposite social experience of aggression, evidenced by victories (aggressors, winners) and defeats (defeated mice, losers) in agonistic interactions.

2.3. Partition test

The partition test (Kudryavtseva, 1994) was employed as a tool for estimating behavioural reactivity of mice to the conspecific