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Short communication

Distinctive modulation of ethanol place preference by delta opioid receptor-selective agonists

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ABSTRACT

Background: Naltrexone is one of the few drugs approved by the Federal Drug Administration for the treatment of alcoholism. However, naltrexone is only effective in a subpopulation of treatment-seeking alcohol abusers, and suffers from compliance issues. The non-selective nature of this opioid antagonist likely contributes to its side effects and poor therapeutic efficacy. Drugs selectively targeting delta opioid receptor subtypes offer a potential way to treat alcohol abuse disorders. We have recently shown that delta subtype-selective agonists TAN-67 and SNC80 can have opposing effects on alcohol consumption, while having similar effects on alcohol withdrawal-induced anxiety.
Methods: We studied the ability of TAN-67 and SNC80 to induce place preference in naïve and ethanol exposed C57BL/6 mice and determined the effect of these agonists on the expression of ethanol place preference.
Results: We show that TAN-67 and SNC80 have opposing actions on ethanol place preference. However, neither of the drugs induces place preference by themselves at doses that are therapeutically effective in mice. Interestingly, SNC80, like naltrexone reduces ethanol place preference, however we have previously shown that SNC80 increases ethanol consumption at the tested dose. Similar to naltrexone, TAN-67 reduces alcohol consumption, but we show here that it may be due to an increase in ethanol place preference. Importantly, we found that chronic ethanol exposure does not increase the rewarding properties of the DOR subtype selective agonists.
Conclusions: Our results provide a better understanding of how DOR subtype selective drugs could potentially be used for treatment of alcohol abuse disorders.

1. Introduction

Alcohol use disorders pose a large burden on society (Rehm et al., 2009; Nutt et al., 2010). Currently only a small number of FDA-approved drugs are available for treatment seeking individuals. The non-selective opioid antagonist naltrexone is frequently prescribed to assist alcohol abusers in reducing their ethanol consumption. However, the efficacy of this drug is still under debate, and may only be effective in heavy drinkers (Pettinati et al., 2006; King et al., 2009) and those with a (genetic) predisposition/family history of alcohol use (Monterosso et al., 2001; Oslin et al., 2003; Krishnan-Sarin et al., 2007; Anton et al., 2008). Naltrexone has several side effects including limiting the utility of opioid analgesics in people actively taking the drug. Therefore, there is still a need to develop better therapeutics to treat alcohol use disorders. One potential mechanism is to selectively target delta opioid receptors (DORs). DORs are involved in ethanol consumption (Roberts et al., 2001) as well as anxiety (Filliol et al., 2000). Importantly, two DOR subtypes have been described *in vivo* (Zaki et al., 1996; Dietis et al., 2011). Moreover, DORs are upregulated after chronic exposure to stimuli including morphine (Cahill et al., 2001), stress (Commons, 2003) and inflammation (Cahill et al., 2003). Recently, we demonstrated that DOR subtypes have opposing effects on ethanol consumption (van Rijn and Whistler, 2009; van Rijn et al., 2010) and that ethanol exposure can reveal anxiolytic-like properties of the DOR-1 agonist TAN-67, that are absent in naïve mice (van Rijn et al., 2010). Also, we have shown that chronic ethanol exposure increases the potency of some DOR selective ligands in the spinal cord of mice (van Rijn et al., in press).

To further investigate the mechanism of action of DOR subtype-selective agonists on ethanol consumption we studied the effects of TAN-67 and SNC80 on ethanol place preference (PP). We find that these DOR agonists do not produce PP themselves but have a significant effect on ethanol place preference. Interestingly, we show for the first time that these two DOR agonists have opposite effects in the way that they modulate ethanol PP.

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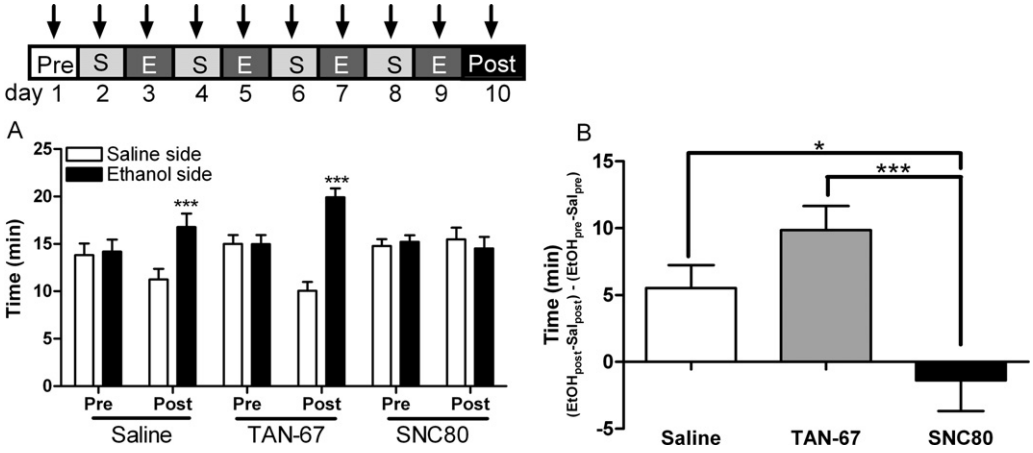

Fig. 1. The DOR agonists TAN-67 and SNC80 modulate ethanol place preference in opposite ways. C57BL/6 mice (n = 12–16) were conditioned to i.p. ethanol (2 g/kg, E) or saline (S) paired with one side of a 2-chamber CPP box for five minutes per session for eight sessions (see Section 2). On the days before (pre) and after (post) the conditioning sessions mice were allowed to freely explore both chambers of the CPP box for 30 min and time spent on each side was recorded. On the final test day mice were injected s.c. with either saline, 25 mg/kg TAN-67 or 20 mg/kg SNC80. Thirty minutes after injection, mice were injected i.p. with saline and placed in the CPP apparatus ($^{*}p < 0.05$; $^{***}p < 0.001$).

2. Methods

2.1. Ethanol place preference

Ethanol place preference was established by conditioning C57BL/6 mice (male, 18–22 g, Taconic) to 2 g/kg (15%) ethanol (Lim et al., 2011). A locomotor box (Med Associates, St. Albans, VT) was divided in two chambers. One chamber had plastic rod flooring and horizontally striped "wallpaper," the other chamber had plastic hole flooring and vertically striped "wallpaper." Mice were paired with ethanol or saline in an unbiased approach. Mice were injected intra peritoneally (i.p.) once daily with saline or ethanol and confined to one of two chambers for five minutes directly after injection. Each mouse received four pairings with ethanol and saline (days 2–8). On day one and day ten each mouse was placed in the saline-paired chamber and allowed to freely explore both chambers for 30 min. Time spent in both chambers was recorded on these days. Chambers were cleaned with 70% isopropanol between each measurement. Mice were injected with saline on day one and day ten to balance for any handling stress. To determine the effect of opioid selective ligands on the expression of ethanol PP mice were injected sub-cutaneously (s.c.) with drug 30 min prior to placement in the chamber.

2.2. Drug place preference

Drug place preference was performed as previously described (van Rijn and Whistler, 2009). On day one naïve or ethanol exposed (see below) C57BL/6 mice were placed randomly in one of two PP chambers and each mouse was allowed to freely explore both chambers for 30 min. An unbiased approach was used to determine in which chamber each mouse would receive drug or vehicle. Each mouse would be injected twice daily (morning and afternoon) with either vehicle or drug for three days (days 2–4) and con-

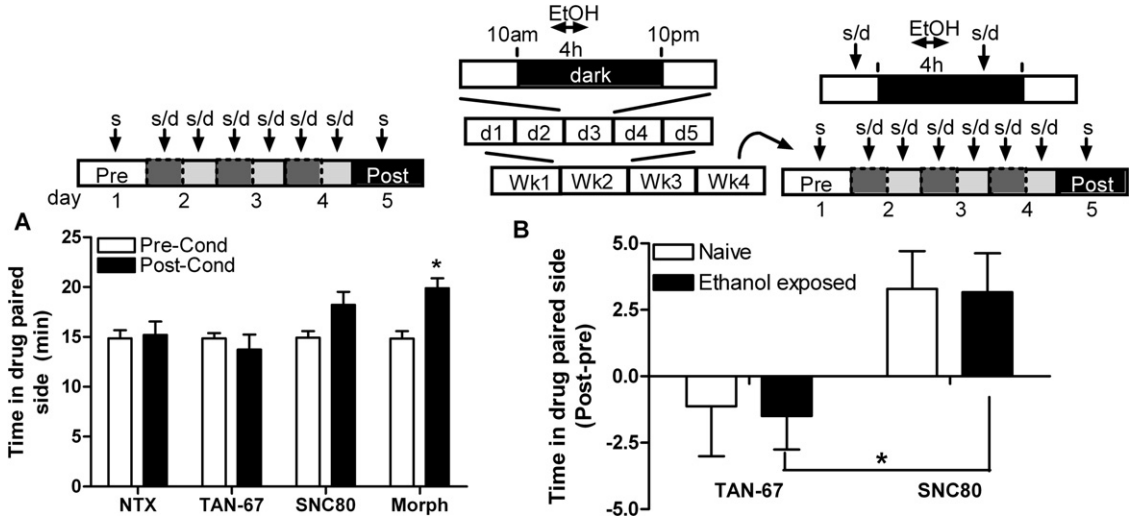

Fig. 2. DOR selective agonists do no produce place preference in naïve or ethanol exposed mice. (A) Naive C57BL/6 mice (n = 10–14) were conditioned by twice daily injection with saline (s) or drug (d) [TAN-67 (25 mg/kg), SNC80 (20 mg/kg), naltrexone (NTX, 1.5 mg/kg) or morphine (6 mg/kg)] for three days. On the days before (pre) and after (post) the conditioning sessions mice were allowed to freely explore both chambers of the place preference set up for 30 min and time spent on each side was recorded. (B) C57BL/6 mice (n = 12) were trained to self-administer ethanol in a limited access 2-bottle choice paradigm for three weeks. During the fourth week animals were conditioned in a place preference paradigm to TAN-67 (25 mg/kg) or SNC80 (20 mg/kg) as described above ($^{*}p < 0.05$).