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Acamprosate's ethanol intake-reducing effect is associated with its ability to increase dopamine

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ABSTRACT

Previous studies indicate that the anti-craving substance acamprosate modulates nucleus accumbens (nAc) dopamine levels via a dopamine-controlling nAc-VTA-nAc neurocircuitry. It was demonstrated that glycine receptors in the nAc are involved both in the dopamine-elevating effect and the ethanol intake-reducing effect of the drug. Here we wanted to explore the interaction of ethanol and acamprosate on nAc dopamine and investigate whether dopaminergic transmission may be related to the ethanol intake-reducing effects. In three separate studies we investigated nAc extracellular dopamine levels by means of in vivo microdialysis after administration of acamprosate and ethanol in 1) naïve rats, 2) rats pre-treated with acamprosate for two days or 3) ethanol medium- and high-preferring rats receiving ten days of acamprosate pre-treatment. In the first two studies, acamprosate elevated dopamine and simultaneously prevented ethanol from further increasing dopamine output. In the third study, long-term acamprosate pre-treatment produced a loss of the ethanol intake-reducing as well as the dopamine-elevating effects of acamprosate, and the dopamine elevating property of ethanol was restored. We suggest that acamprosate may partly substitute for the dopamine-elevating effect of ethanol but once tolerance develops to this effect, the ability to decrease ethanol intake is lost.

1. Introduction

Alcohol addiction is a chronic brain disorder manifested by neuronal alterations i.a. in the mesolimbic dopamine system, an important part of the brain reward pathway (Koob and Nestler, 1997; Wise and Rompre, 1989; Spanagel, 2009). It has been established that administration of alcohol (ethanol) activates the dopamine system, resulting in an increase of dopamine in various areas of the brain of which the nucleus accumbens (nAc) has gained most interest (Berridge et al., 2009; Wise, 2004). One of the pharmacotherapies used to treat alcoholism is acamprosate (calcium-bis(*N*-acetylhomotaurinate); Campral®) (Littleton, 1995; Mason, 2015). In the rat, acamprosate was demonstrated to increase nAc dopamine (Olive et al., 2002; Cano-Cebrián et al., 2003), an effect similar to that of ethanol, which was hypothesized to contribute to the drug's ethanol intake-reducing effect (Cowen et al., 2005). However, several mechanisms of action underlying acamprosate's anti-alcohol effect have been forwarded, including interaction with GABAergic neurotransmission (Boismare et al., 1984; Daoust et al., 1992) or interaction with glutamatergic neurotransmission by direct or indirect modulation of NMDA or mGluR receptors (al Qatari et al., 1998; Naassila et al., 1998; De Witte et al., 2005; Blednov and Harris, 2008). Recently it was suggested that *N*-acetylhomotaurinate is a biologically inactive molecule and that it rather is the calcium moiety of acamprosate (calcium-bis(*N*-acetylhomotaurinate) that is the active ingredient (Spanagel et al., 2014).

In the search for the mechanism underlying ethanol's ability to increase nAc dopamine we found the amino acid taurine, nAc glycine receptors (GlyR) and ventral tegmental nicotinic acetylcholine receptors (nAChR) to be key components (Ericson et al., 2006; Söderpalm et al., 2017, review; Adermark et al., 2011; Ericson et al., 2011). Since acamprosate is a homotaurine analogue sharing structural similarities not only with GABA, but also with taurine, an endogenous ligand of the GlyR, we explored in a series of studies whether the dopamine elevating properties of acamprosate and ethanol displayed any similarities. We found that acamprosate, either after systemic or local administration, increased nAc dopamine and that the effect involved GlyRs in the nAc and nAChRs in the VTA (Chau et al., 2010a). This was identical to what we previously had found when studying taurine (Ericson et al., 2006; Ericson et al., 2011) and ethanol (Blomqvist et al., 1993; Blomqvist et al., 1997; Ericson et al., 2003; Molander and Söderpalm, 2005)

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individually. When continuing to explore the functional importance of nAc GlyRs in the ethanol intake-reducing effect of acamprosate we were able to reverse the acamprosate-induced decrease in ethanol intake by pre-treatment with the competitive GlyR antagonist strychnine in the nAc (Chau et al., 2010b). This mechanism of action would then explain the effect of acamprosate also at the behavioral level in the rat. Thus, although several mechanisms of action have been suggested to underlie the ethanol intake-reducing effect of acamprosate, the link between ethanol, acamprosate and dopamine appears to be of importance.

Interestingly, the anti-alcohol effect of acamprosate appears to decline with long-term treatment, at least in rodents, and it was suggested that repeated administration produces tolerance towards the ethanol intake-reducing effect of the compound (Cowen et al., 2005; Vengeliene et al., 2010; Lidö et al., 2012). The underlying mechanism for this is currently unknown but was suggested to derive from interference either with dopaminergic or glutamatergic neurotransmission. Furthermore, acute administration of acamprosate was found to increase dopamine transporter binding and decrease dopamine D2-like binding in the nAc, whereas after repeated acamprosate administration the binding levels returned to normal (Cowen et al., 2005). If repeated administration of acamprosate induces neuronal adaptations diminishing its effect, it appears highly relevant from a clinical perspective to further address and understand these events.

In the present study we aimed to evaluate the effects of acute and repeated administration of acamprosate on ethanol-induced dopamine output in the nAc in relation to development of tolerance towards the ethanol intake-reducing effect of acamprosate. Three in vivo microdialysis experiments investigating the interaction between acamprosate and ethanol on dopamine output were performed. In the first experiment, we aimed to determine the nAc dopamine levels following acute local administration of both acamprosate and ethanol in drug-naïve rats. In the second experiment, we aimed to determine the nAc dopamine levels following systemic administration of both acamprosate and ethanol in animals pre-treated two days with acamprosate. And, in the last experiment, we aimed to determine the nAc dopamine response following systemic administration of both acamprosate and ethanol in ethanol medium- and high-preferring rats treated with acamprosate or vehicle for ten days.

2. Material and methods

2.1. Animals

In Experiment 1 and 2, male Wistar rats (n = 59, B&K Universal AB Scanbur, Sollentuna, Sweden or Taconic, Denmark) weighing 290-330 g, were used. Upon arrival, the rats were housed in groups of four in a humidity - (60%) and temperature - (21 °C) controlled room on a 12/12 h light/dark cycle (on 07:00 off 19:00), with free access to rodent chow (Harlan Teklad Europe, UK) and tap water. Animals were allowed to adapt for at least seven days to the animal maintenance facilities prior to the start of the experiments. In the third experiment male Wistar rats (n = 33, Taconic, Denmark) weighing 250–280 g were used. These rats were initially housed in groups of four and later in single cages in climate-controlled rooms as described above, except the light cycle was reversed (on 20:00 off 08:00). The reversed light cycle was used in order to monitor ethanol consumption (for details see below) during the rats' active period, performing in vivo microdialysis under these conditions has previously not been found to influence the dopamine output. As in the other experiments, the rats had free access to regular rodent chow and water and were allowed to adapt for at least a week prior to initiation of ethanol screening. All experiments were conducted according to the Declaration of Helsinki and were approved by the Ethics Committee for Animals Experiments (Gothenburg, Sweden).

2.2. Drugs and chemicals

Acamprosate (kindly provided by Merck, Lyon, France) was dissolved in Ringer solution when perfused into the nAc or in 0.9% NaCl when administered systemically (i.p.). 95% ethanol (Svensk sprit AB, Sweden) was diluted in Ringer solution when administered locally, 0.9% NaCl when administered systemically (i.p.) or in tap water, when administered intragastrically or in the drinking bottle. The content of the Ringer solution was (in mmol/l): 140 NaCl, 1.2 $CaCl_2$, 3.0 KCl, and 1.0 $MgCl_2$.

2.3. Microdialysis technique

Brain microdialysis experiments were performed in awake and freely moving animals, according to a protocol previously described (Lidö et al., 2009). Briefly, rats were anaesthetized by isoflurane (Apoteket AB, Sweden), mounted into a stereotaxic instrument (David Kopf Instruments) and put on a heating pad to prevent hypothermia during surgery. Holes were superficially drilled for placement of two anchoring screws and one I-shaped dialysis probe (for Experiment 1 and 2, custom made in the laboratory) or a pre-manufactured I-shaped guide cannula in order to allow for a longer period of recovery following surgery (Experiment 3; AgnTho's, Lidingö, Sweden). The dialysis probe or guide cannula were lowered into the nAc (coordinates for dialysis probe: A/P: +1.85, M/L: −1.4, D/V: −7.8; for guide cannula: A/P: +1.85, M/L: −1.4, D/V: −5.8; (Paxinos and Watson, 2007). The exposed length of the dialysis membrane was 2 mm.

The dialysis probe or guide as well as the anchoring screws were fixed to the scull with Harvard cement (DAB Dental AB, Sweden). After surgery, the rats were allowed to recover for two days (Experiment 1 and 2) before the dialysis experiment was initiated or seven to nine days before active systemic treatment was initiated (Experiment 3) (see Fig. 1 for experimental timeline). The longer period of recovery in experiment 3 was needed to minimize the influence of the surgical procedure on the voluntary ethanol consumption during repeated acamprosate treatment. On the experimental day, the sealed inlet and outlet of the probes were cut open and connected to a micro-perfusion pump

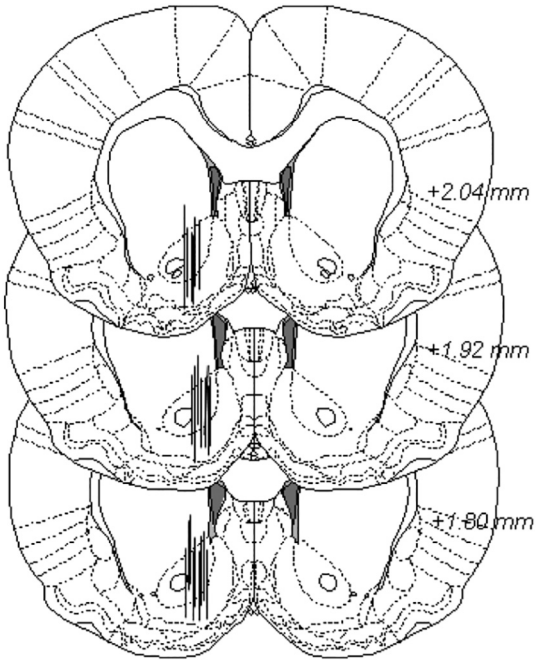

Fig. 1. Histology. Location of the microdialysis probes in the three separate experiments. The black lines indicate tracks of every fifth rat included in the study. Numbers beside each plate represent distance from bregma.