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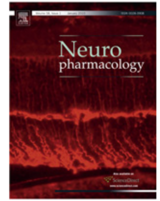

Cocaine reverses the naltrexone-induced reduction in operant ethanol self-administration: The effects on immediate-early gene expression in the rat prefrontal cortex

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A B S T R A C T

Naltrexone is a clinically approved medication for alcoholism. We aimed to investigate the effectiveness of naltrexone co-administered with cocaine and the association of these substances with immediate-early gene expression in the rat prefrontal cortex. We used chronic operant ethanol self-administration and oral treatments prescribed for alcoholism and available in pharmacies to maximise the predictive validity in humans. We performed real-time PCR analysis to determine gene expression levels in the prefrontal cortex. Only the highest dose of naltrexone (1, 3, and 10 mg/kg, p.o.) reduced the response to ethanol. Cocaine increased ethanol self-administration in a dose-dependent manner (2.5, 10, 20 mg/kg, i.p.) and reversed the naltrexone-induced reduction. Naltrexone failed to prevent the cocaine-induced increase in locomotor activity observed in these animals. Chronic self-administration of ethanol reduced the expression of the *C-fos* gene 4- to 12-fold and increased expression of the *COX-2* (up to 4-fold) and *Homer1a* genes in the rat prefrontal cortex. Chronic ethanol self-administration is prevented by naltrexone, but cocaine fully reverses this effect. This result suggests that cocaine may overcome naltrexone's effectiveness as a treatment for alcoholism. The ethanol-induced reduction in *C-fos* gene expression in the prefrontal cortex reveals an abnormal activity of these neurons, which may be relevant in the compulsive consumption of ethanol, the control of reward-related areas and the behavioural phenotype of ethanol addiction.

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1. Introduction

Alcoholism is a disabling addiction disorder (WHO, GISAH, 2011). An effective treatment for alcoholism remains elusive despite the advances that have been made including the development of naltrexone (i.e., Antaxone®) and acamprosate (i.e., Campral®), two clinically approved medications to treat binge ethanol consumption, ethanol abuse and dependence and to prevent relapse (Fuller and Gordis, 2001; Johnson, 2010; Mason, 2003; O'Brien et al., 1996; Spanagel and Zieglgänsberger, 1997). Treatment with oral naltrexone has been associated with a significant reduction in alcohol-related healthcare costs (Kranzler et al., 2010). Naltrexone is a non-selective opioid antagonist theorised to reduce ethanol consumption by blocking central opioid receptors that subsequently directly or indirectly modulate the effects of ethanol (Hillemacher et al., 2011; Hubbell and Reid, 1990). The mechanism of action of acamprosate is less well understood. Acamprosate is hypothesised to reduce neuronal hyperexcitability through its putative agonist-like effects at GABA receptors and its antagonist effects at the glutamate N-methyl-D-aspartate (NMDA) receptor (Kiefer and Mann, 2010; Littleton, 1995; Stromberg et al., 2001). The effects of combining the two compounds on ethanol consumption have also been assessed. Stromberg et al. (2001) reported no evidence of an additive or synergistic effect resulting from such a combination nor

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was it more effective than naltrexone alone in reducing ethanol consumption by rats.

The co-abuse of ethanol and cocaine occurs with high frequency and persistence in human populations worldwide. For example, Miller et al. (1989) reported that 94% of the American patients diagnosed as cocaine-dependent were also diagnosed with an ethanol dependence. In another study, approximately 12 million members of the general population had used both ethanol and cocaine within the previous twelve months (Grant and Harford, 1990). In a more recent study in Europe, 64% of the cocaine powder users (excluding crack cocaine users) reported frequent ethanol consumption (Gossop et al., 2006), and the concomitant use of ethanol was evident by analyses of blood and urine samples in 76% of cocaine-related cases of sudden death (Lucena et al., 2010). Finally, heavy chronic alcohol use is linked to a three-fold increased risk of cocaine use (Kulaga et al., 2010). These data support the idea that cocaine use could increase the vulnerability to the development of ethanol dependence (Rubio et al., 2008) and vice versa. A careful examination of the clinical data indicates that the concurrent use of ethanol and cocaine is associated with increased mortality and morbidity resulting from cerebro- and cardiovascular complications (Cami et al., 1998; O'Connor et al., 2005; Randall, 1992; Vroegop et al., 2009) as well as hepatotoxicity and compromised mental status (Odeleye et al., 1993; Vanek et al., 1996). Taken together, these facts underscore the urgency and necessity to develop pharmacotherapeutic interventions for alcoholism and the comorbidity of alcoholism with cocaine use.

Currently, despite the increasing number of studies investigating the effects of naltrexone or acamprosate on ethanol/cocaine co-consumption (Hersh et al., 1998; Oslin et al., 1999; Pettinati et al., 2008a, 2008b; Sable et al., 2004; Schmitz et al., 2004, 2009; Stromberg et al., 2002; Suh et al., 2008), knowledge in this area remains incomplete. For example, a high dose of naltrexone modestly reduced heavy ethanol consumption in individuals dependent on both cocaine and ethanol (Schmitz et al., 2009). Therefore, the aim of this study was to gain deeper knowledge regarding the treatment of alcohol addiction with naltrexone and acamprosate when cocaine is co-administered. For this purpose, we used chronic operant ethanol self-administration in rats, an animal model with one of the highest levels of predictive validity in humans (Koob et al., 2003) for the development of pharmacological treatments for substance abuse disorders. Furthermore and important in this study, we investigated the expression of immediate-early genes as biomarkers of neural stimulation in the prefrontal cortex. We focused on the prefrontal cortex because of its contribution to addictive behaviour (Lüscher and Malenka, 2011), its involvement in compulsive ethanol drinking, its demonstrated sensitivity to naltrexone and acamprosate treatment (Burattini et al., 2008; Li et al., 2010; Yu et al., 2011), and its critical role in integrating and regulating cognitive behaviour in rodents and in humans (e.g., Abernathy et al., 2010; Dayas et al., 2007; Vengeliene et al., 2009).

2. Methods

2.1. Subjects

Ninety-two male Wistar rats (Harlan, Barcelona, Spain) weighing 375–425 g at the start of the pharmacological experiments were housed in groups of 4 per cage in a temperature- and humidity-controlled environment on a 12 h reverse light/dark cycle (lights off at 07:00 h). Experimental sessions were performed during the dark phase (Fig. 1). Food and water were available ad libitum except as specified below. All research was conducted in strict adherence to the European Community Council Directive (91/414/EEC). All efforts were made to minimise animal suffering and to reduce the number of animals used.

2.2. Drugs

Ethanol solution was prepared daily as a 10% ethanol v/v solution from 99% ethanol. Acamprosate (3-Acetamidopropane-1-sulfonic acid, Campral®, Merck Santé S.A.S., Lyon, France) and naltrexone (17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one, Antaxone®, Pharmazam S.A., Barcelona, Spain) were dissolved in water and administered by oral gavage (p.o.) at a volume of 3 ml/kg. Cocaine hydrochloride (Sigma–Aldrich Co., U.S.A.) was dissolved in physiological saline and injected intraperitoneally at a volume of 1 ml/kg.

2.3. Ethanol self-administration and motor experiments

2.3.1. Apparatus and procedure

The ethanol operant sessions were conducted in modular chambers enclosed in sound-attenuating cubicles (Letica, LE 850 model; Panlab, Barcelona, Spain and Med Associates Inc., St. Albans, VT, USA). The association of visual or auditory cues with lever presses or dipper presentations was avoided. The exhaust fans were inactivated because they increase the rate of ethanol evaporation. The chambers were equipped with two retractable levers located 7 cm above a grid floor on either side of a drinking reservoir positioned in the centre of the front panel of the chamber and 4 cm above the grid floor. The levers were counterbalanced to respond as the active lever (delivering 0.1 ml) or as the inactive lever. The contents of the dipper were accessible to the animal until the next lever press, at least 2.5 s later, to avoid measuring dipper presentations as lever presses.

Training was conducted using a modification of the method used by López-Moreno et al. (2004). Briefly, the rats were placed on a restricted water intake schedule ranging from 2 to 4 days to facilitate the training in lever pressing. The length of the water restriction depended on the animal's rate of learning; animals that did not learn the first or second day were restricted for 4 days. During the first 4 days of training, 76 animals received a 1% saccharin solution in the dipper. Thereafter, the following sequence was followed on a fixed-ratio schedule of

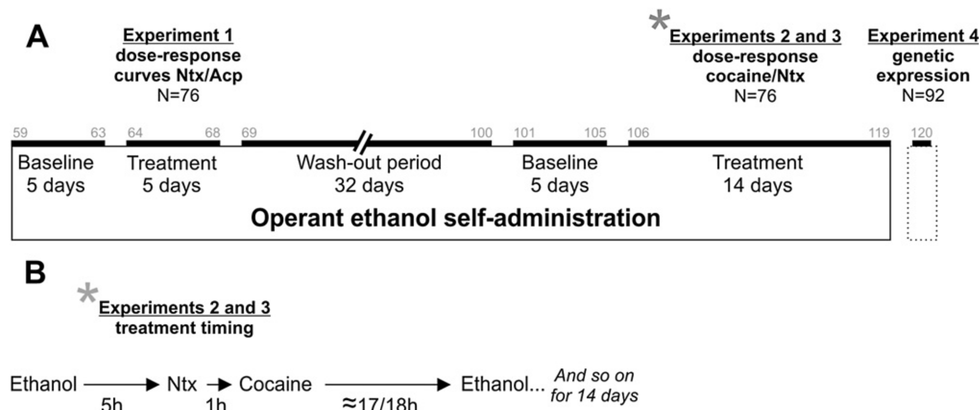

Fig. 1. A brief schematic representing the protocol used. Panel A, naltrexone and acamprosate were administrated for 5 consecutive days 1 h before the operant ethanol self-administration session (experiment 1). After a wash-out period, experiments 2 and 3 were conducted for 14 consecutive days. On the 15th day, the animals were sacrificed by decapitation for RTqPCR experiments at the time that they would have been placed in the ethanol operant chamber (experiment 4). A group of 16 rats responding to saccharin were used as the calibrator group. The numbers in grey indicate the cumulative number of operant ethanol sessions. Panel B shows the details of the treatment schedule of experiments 2 and 3. Ntx = Naltrexone; Acp = Acamprosate.

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