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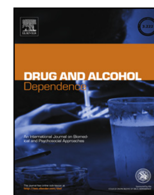

Short communication

Opioid antagonists block acetaldehyde-induced increments in dopamine neurons activity

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ABSTRACT

Background: Acetaldehyde is the main metabolite of ethanol ingested through alcoholic beverages. Traditionally considered aversive is presently being viewed as an activating agent of the mesolimbic dopamine system but underlying mechanisms are only partially known.
Methods: Through in vivo electrophysiology experiments in rats we have studied the role of endogenous opioids in acetaldehyde-induced increments in dopamine activity.
Results: Here we show that acetaldehyde-induced increase in firing rate, burst firing and spikes/burst of antidromically-identified ventro-tegmental area nucleus accumbens-projecting neurons are abolished by pretreatment with the opiate unselective antagonist naltrexone (0.4 mg/kg/ip). Similar effects are obtained after administration of naloxone (0.1 mg/kg/iv). These results indicate that endogenous opiate system(s) participate in acetaldehyde-induced increments in dopaminergic neuronal activity.
Conclusion: These data may explain the reduction in acetaldehyde-induced dopamine release in the nucleus accumbens after blockade of opiate receptors. Considering the paucity of efficacious therapies in alcoholism, and recent developments in ethanol-derived acetaldehyde effects, further experiments are warranted to further elucidate its role as a biomarker potentially useful to develop new strategies in the search for effective compounds aimed at reducing excessive alcohol intake, abuse and ultimately alcoholism.

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1. Introduction

Experimental evidence shows that acetaldehyde (ACD) is involved in the neurobiological mechanisms underlying the motivational effects of ethanol (EtOH; reviewed in Muggironi et al., 2013). ACD induces conditioned place preference (CPP; Peana et al., 2008), and maintains oral self-administration (Peana et al., 2010). Further, ACD is a potent reinforcer within the posterior VTA where is readily self-administered at concentrations 1000-fold lower than EtOH (Rodd-Henricks et al., 2002). In addition, electrophysiological studies observed that ACD stimulates the activity of VTA dopamine neurons projecting to the nucleus accumbens at doses 50 times lower than EtOH (Foddai et al., 2004; Melis et al., 2007). Consistent with a key role of ACD in the central actions of EtOH, blockade of alcohol dehydrogenase with 4 methyl-pyrazole (4-MP) prevents stimulation of dopamine neurons (Foddai et al., 2004; Melis et al., 2007), EtOH-induced CPP (Melis et al., 2007) whereas ACD-sequestering hampers EtOH-induced increase in microdialysate dopamine (Enrico et al., 2009) and oral ACD self-administration (Peana et al., 2012).

On the other hand, endogenous opioid systems appear to play a prominent role in the reinforcing properties of EtOH (Di Chiara et al., 1996). Accordingly, opioid receptor antagonists reduce voluntary EtOH intake and operant EtOH self-administration (Davidson and Amit, 1997) and block EtOH-induced CPP (Cunningham et al., 1998). In addition, naltrexone (NTX) is an effective adjunct to alcoholism treatment, particularly in preventing alcohol relapse (O'Brien et al., 1996; Volpicelli et al., 1992).

On the basis of these observations, we decided to study the effect of non-selective opioid receptor antagonists, NTX and naloxone (NLX), on the stimulating effect that ACD exerts on VTA dopamine neurons projecting to the NAc shell.

2. Materials and methods

2.1. Subjects and treatments

The study is in accordance with current Italian legislation [D.L. 116, 1992] that allows experimentation on laboratory animals only after submission and approval of a research project to the Ministry of Health (Rome, Italy), and in line with European

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Council directives on the matter [n. 2007/526/CE]. All efforts were made to minimize pain and discomfort and to reduce experimental subjects.

Male Wistar rats (275/350 g) were used. All subjects were kept on a 12 h/12 h light/dark cycle with food and water *ad libitum*. Rats were randomly assigned to the following groups: (1) Saline + ACD, that received exponentially increasing doses (5/5/10/20 mg/kg/i.v.) of ACD with intraperitoneal (i.p.) saline pretreatment. (2) NTX + ACD, identical to the previous group with i.p. naltrexone chloride (NTX) (0.4 mg/kg) substituting for saline. (3) ACD + NLX, which received a single dose of naloxone chloride (NLX) (0.1 mg/kg/i.v.) after ACD (40 mg/kg/i.v.).

Subjects were anesthetized with urethane (1.3 g/kg) i.p., the femoral vein was exposed, and a catheter inserted into the lumen to allow i.v. administration of pharmacological agents. All i.p. pretreatments were made 30 min before the i.v. administration of ACD. All substances used in these experiments were purchased from Sigma-Aldrich, Milan, Italy.

2.2. Electrophysiological recordings

Rats were mounted on a stereotaxic apparatus (Scientifica, UK) and prepared for the placement of a recording electrode (tip diameter, 2–3 μm; 2–5 MΩ) filled with 2% pontamine sky blue in 0.5 M sodium acetate, above the VTA (AP −5.3 mm from bregma; L 0.2/0.7 mm from midline) (Paxinos and Watson, 2005). A bipolar electrode was placed in NAc (AP +1.8 mm from bregma; L 1.1 mm from midline; V −7 mm from the surface) (Paxinos and Watson, 2005) to identify mesoaccumbens DA neurons by antidromic spikes elicited by the stimulation of the NAc (Fig. 1A–C). Stimuli consisting of monophasic rectangular pulses (0.1–2.0 mA; 0.1–0.5 ms; 0.8 Hz) were generated and the stimulating current monitored. The extracellular neuronal signal from single neurons was amplified (EXT-02F, NPI system, Germany) and displayed on a digital oscilloscope (Tektronix DPO 3012). Spikes of single neurons were discriminated, and digital pulses were sent to a computer for on-line data collection with a laboratory interface and software (CED 1401, Spike2; Cambridge Electronic Design, Cambridge, UK).

After 5 min of stable neuronal recording (basal activity), exponentially increasing doses of ACD (5/5/10/20 mg/kg) were injected i.v. every 2 min, so that the last administered dose was equal to the sum of the drug already received, and the cell activity was recorded. Only one cell was recorded per rat. Drug-induced modifications of the basal activity were calculated in percentage for the 2-min period following each administration and compared with the pre-drug baseline. Data are expressed as mean ± SEM. Statistical analysis was performed by one-way ANOVA. In the presence of overall significant main effects and interactions ($^* p < 0.05$), the Newman Keuls post-hoc test was performed. In the last experimental group ACD + NLX two means were compared, it was used a *T* Student test for statistical analysis ($^* p < 0.05$).

3. Results

The effect of ACD (with saline pretreatment) has been studied in 11 cases in which it was administered at cumulative doses of 40 mg/kg/iv. In additional 11 neurons the effect of the pretreatment with NTX (0.4 mg/kg), administered 30 min before ACD administration, was evaluated.

Baseline firing rate was 3.09 ± 0.45 Hz (mean ± SEM) and it was readily and dose-dependently increased in all neurons tested by i.v. ACD administration (5.61 ± 0.71 Hz; Fig. 1D). In contrast, In NTX-pretreated rats, no statistically significant difference was observed in firing rate pre- (2.65 ± 0.59 Hz) and post-ACD (2.67 ± 0.61 Hz; Fig. 1E). Further, ACD administration produced an increment in bursting activity (Fig. 1F). In particular, the baseline bursting rate was 0.12 ± 0.04 Hz and it was readily and dose-dependently increased in all neurons tested, at 20 mg/kg (0.33 ± 0.07 Hz) and 40 mg/kg (0.35 ± 0.08 Hz). Moreover, we observed an increase in the percentage of spikes delivered in bursts (%SIB) at cumulative does of 20 mg/kg (39.48 ± 2.46) and 40 mg/kg (44.70 ± 2.58) when compared to baseline pre-ACD (14.68 ± 5.41). Furthermore, the mean number of spikes contained in each burst (MSB) (2.36 ± 0.41) is significantly increased at a dose of 40 mg/kg (5.8 ± 0.64) whereas pretreatment with NTX blocks ACD-induced increments of all parameters evaluated (Fig. 1G).

For group saline + ACD, the one-way ANOVA showed a statistically significant effect of the treatment factor for each parameter measured: firing rate [F (3.863) = 10.64; $p < 0.05$], bursting rate [F (0.03259) = 0.11131; $p < 0.05$], %SIB [F (191.2) = 2401; $p < 0.0001$], MSB [F(3.947) = 16.35; $p < 0.03$]. NTX *per se* did not alter basal activity of VTA DA neurons. To further test the involvement of opiate receptors, we analyzed the effect of NLX (n = 4) on the changes induced by the maximal dose (40 mg/kg) of ACD on various electrophysiological parameters (Fig. 2). In particular, NLX reverted ACD-induced increments in bursting rate (from 0.36 ± 0.04 Hz to 0.10 ± 0.03 Hz); %SIB (from 40.91 ± 3.49 to 13.51 ± 4.78) and MSB (from 3.5 ± 0.29 to 1.25 ± 0.48) (Fig. 2C).

4. Discussion

These results confirm that ACD dose-dependently increases the spontaneous firing rate and bursting activity of antidromically-identified VTA dopamine neurons projecting to NAc shell, as previously described (Foddai et al., 2004). The main finding of the present study is that stimulation of the mesolimbic dopaminergic system induced by ACD is mediated by endogenous opioids. In fact, these data reveal that both antagonists, NTX and NLX, abolish the ACD-induced effects on VTA dopamine neurons, by preventing (NTX) and reverting (NLX) ACD-induced stimulation of electrophysiological parameters, respectively. These results are in line with behavioral observations showing that administration of opioidergic antagonists reduce oral ACD self-administration (Peana et al., 2011) and further add to the role of VTA neurons in the motivational properties of ACD. It has been shown that ACD regulates motivational properties of EtOH and possesses reinforcing properties *per se* (Foddai et al., 2004; Peana et al., 2010). In contrast, a recent study shows that ACD perfused locally in NAc does not increase accumbal dopamine levels (Clarke et al., 2014) and that pretreatment with D-penicillamine does not prevent the increase in NAc dopamine observed after local perfusion of EtOH (Clarke et al., 2014). Instead, intra-gastric ACD administration induces a significant increase on NAc shell extracellular dopamine levels (Enrico et al., 2009), and this effect was blocked by pre-treatment of D-penicillamine and L-cysteine, suggesting that the EtOH-induced extracellular DA increase in the NAc shell could be mediated by ACD (Enrico et al., 2009). In particular, these microdialysis studies indicate that ACD effect on dopamine release is more pronounced and long-lasting when compared to EtOH. Although reasons for this difference are unclear, it seems reasonable to speculate that differences in ACD bioavailability following administration of EtOH or ACD and the complexity of EtOH effects on the central nervous system are the two main mechanisms that may account for it. Indeed, peripheral EtOH metabolism into ACD, and then into acetate, keeps ACD blood levels extremely low (Deitrich et al., 2006). While administration of adequate doses of EtOH induces enough ACD production to affect brain function (Melis et al., 2007; Peana et al., 2008), the underlying kinetics of EtOH absorption, distribution, metabolism and excretion processes may well account for a slow entering of ACD in the brain (Deitrich et al., 2006). On the other hand, administration of a large amount of ACD as a single dose may saturate aldehyde-metabolizing capacity, allowing more ACD to enter the brain (Ward et al., 1997), inducing a more robust effect. Moreover, an increment in dopamine release after intra-VTA administration of ACD, suggests a key role for the VTA, where DA cell bodies reside (Melis et al., 2007). Therefore, a possible explanation for the observed lack of effect of ACD on NAc dopamine levels could be attributed to both concentrations and administration site of ACD used in the study of Clarke et al. (2014). Indeed, Melis and co-workers, reported an increase in NAc shell dopamine dialysate following intra-gastric ACD. These observations suggest that NAc dopamine release is increased due to activation of neuronal firing of VTA neurons, and that the doses used by Clarke in NAc could be so high to induce unspecific effects. A possible mechanism through which ACD enhances VTA DA neuronal firing, could be through action on two ionic currents: reduction of the A-type K^+ current and by activation of Ih current (Melis et al., 2007), which

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