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Suppression by baclofen of the stimulation of alcohol intake induced by morphine and WIN 55,212-2 in alcohol-preferring rats

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Abstract

Administration of morphine and cannabinoids stimulates alcohol intake in rats. The present study investigated whether the promoting effect of morphine and of the cannabinoid receptor agonist, WIN 55,212-2 [(*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone], on alcohol intake was prevented by the γ-aminobutyric $(GABA)_B$ receptor agonist, baclofen. Sardinian alcohol-preferring (sP) rats were given alcohol (10%, v/v) and water under the standard homecage two-bottle-free choice regimen with unlimited access for 24 h/day. Baclofen (0, 0.5 and 1 mg/kg; i.p.) was administered acutely 30 min before lights off. Morphine (0 and 1 mg/kg, s.c.) or WIN 55,212-2 (0 and 2 mg/kg, i.p.) was administered acutely 10 min after baclofen. Alcohol intake was recorded 60 min after lights off. As predicted, both morphine and WIN 55,212-2 produced a specific and marked increase in alcohol intake. Pretreatment with baclofen, which failed to alter alcohol intake when given alone, dose-dependently suppressed morphine- and WIN 55,212-2-induced promotion of alcohol drinking. These results suggest the involvement of the $GABA_B$ receptor in the neural circuitry mediating the stimulating effect of morphine and cannabinoids on alcohol consumption in sP rats.

Keywords: Alcohol intake; Baclofen; Morphine; WIN 55,212-2; Sardinian alcohol-preferring (sP), rat

1. Introduction

Low to moderate doses of morphine and cannabinoids have been repeatedly reported to stimulate appetite for alcohol in rats. Specifically, acutely and chronically administered morphine markedly promoted alcohol drinking behavior in rats tested under multiple experimental procedures (e.g.: Reid and Hunter, 1984; Linseman and Harding, 1990; Wild and Reid, 1990; Nichols et al., 1991; Hubbell et al., 1993; Hodge et al., 1995; Stromberg et al., 1997; Vacca et al., 2002). Similarly, the acute injection of the cannabinoid receptor agonists, anandamide, WIN 55,212-2 [(*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone] and CP 55,940 [(−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)-phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol], stimulated alcohol consumption in rats and mice (Colombo et al., 2002a,b; Wang et al., 2003) and enhanced alcohol motivational properties in rats (Gallate et al., 1999).

The neural substrate mediating this stimulation is at present not completely understood. Similarly to alcohol, both morphine and cannabinoids activate the mesolimbic dopamine system, i.e. the possible key neurochemical substrate mediating the reinforcing properties of drugs of abuse (see Di Chiara, 1995; Spanagel and Weiss, 1999). Specifically, microdialysis studies in rats have demonstrated that administration of low to moderate doses of morphine (e.g.: Di Chiara and Imperato, 1988; Pontieri et al., 1995), cannabinoids (Chen et al., 1990; Tanda et al., 1997) and alcohol (e.g.: Imperato and Di Chiara, 1986; Weiss et al., 1993) stimulated dopamine release in the nucleus accumbens, the terminal area of mesolimbic dopamine neurons arising in the ventral tegmental area. Consistently, electrophysiological data indicate an activation of the mesolimbic dopamine pathway by morphine (Gysling and Wang, 1983; Latimer et al., 1987),

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cannabinoids (French et al., 1997; Wu and French, 2000) and alcohol (Gessa et al., 1985; Brodie et al., 1990) in rats. It has been proposed that morphine and cannabinoids function as a "primer" for alcohol intake (Ulm et al., 1995; Colombo et al., 2002a,b); accordingly, it may be hypothesized that the stimulating action of morphine and cannabinoids on the mesolimbic dopamine system "primes" the additional stimulation of the system induced by alcohol, resulting in an increase in alcohol intake.

The function of mesolimbic dopamine neurons is controlled by multiple receptor systems, including serotonin, acetylcholine, opioid, glutamate and γ-aminobutyric (GABA) receptors (see Kalivas, 1993). Accordingly, pharmacological stimulation of $GABA_B$ receptors located in the ventral tegmental area (Bowery et al., 1987), on the cell body of dopamine neurons as well as on the terminals of glutamatergic afferent neurons, has been reported to exert an inhibitory action on basal and pharmacologically activated mesolimbic dopamine neurotransmission (Kalivas, 1993; Yoshida et al., 1994; Westerink et al., 1996).

It may be predicted that the pharmacological activation or blockade of $GABA_B$ receptors alters mesolimbic dopamine-related behavioral events. Accordingly, the present study was designed to investigate possible involvement of the $GABA_B$ receptor system in morphine- and cannabinoid-induced stimulation of alcohol intake. It was predicted that doses of the $GABA_B$ receptor agonist, baclofen, that do not alter alcohol intake per se, would suppress the promoting effect of morphine and WIN 55,212-2 on alcohol intake in selectively bred Sardinian alcohol-preferring (sP) rats.

2. Materials and methods

2.1. Animals

Male sP rats, from the 56th generation, were used. Rats derived from a population of sP rats had undergone caesarian derivation at Charles River (Lyon, France) for production of Specific Pathogen-Free individuals. Rats were individually housed in standard plastic cages with wood chip bedding. The animal facility was under an inverted 12:12-h light–dark cycle (lights on at 23:00), at a constant temperature of 22 ± 2 °C and relative humidity of approximately 60%. Standard rat chow (Mucedola, Settimo Milanese, MI, Italy) was always available. Rats were extensively habituated to handling and intraperitoneal and subcutaneous injection.

The experimental procedures employed in the present study were in accordance with the Italian Law on the "Protection of animals used for experimental and other scientific reasons".

2.2. Procedures

Starting from the age of 75 days, rats were continuously (24 h/day) offered two bottles containing alcohol (10% v/v, in tap water) and tap water, respectively. Bottles were refilled every day with fresh solution and their left–right positions interchanged at random to avoid development of position preference. Rats were maintained under the two-bottle choice regimen for 8 consecutive weeks before performing the pharmacological experiments. During this 8-week period, daily alcohol intake averaged approximately 6 g/kg.

Independent groups of rats were used in the "baclofen plus morphine" and "baclofen plus WIN 55,212-2" experiments. In each experiment, rats were divided into six subgroups ($n = 12$) matched for body weight and daily alcohol, water and food intake over the 3 preceding days. On the test day, rats were given baclofen (0, 0.5 and 1 mg/kg) 30 min before lights off. Morphine (0 and 1 mg/kg) or WIN 55,212-2 (0 and 2 mg/kg) were administered 10 min after baclofen injection. Baclofen (Sigma, St. Louis, MO, USA) was dissolved in saline and administered intraperitoneally (injection volume: 2 ml/kg). Morphine (sulfate; Salars, Como, CO, Italy) was dissolved in saline and administered subcutaneously (injection volume: 1 ml/kg). WIN 55,212-2 (Sigma) was suspended in saline with 0.1% Tween 80 and administered intraperitoneally (injection volume: 2 ml/kg).

Alcohol, water and food intake was monitored 60 min after lights off (0.1-g accuracy). This time interval was chosen on the basis of previous results indicating that morphine and WIN 55,212-2 exerted their maximal stimulating effect on alcohol intake in sP rats 60 min after their injection (Colombo et al., 2002a,b; Vacca et al., 2002). Alcohol, water and food intake was expressed in g/kg, ml/kg and g/kg, respectively, and analyzed by separate one-way analysis of variance (ANOVAs), followed by the Newman–Keuls test for multiple comparisons.

3. Results

In the "baclofen plus morphine" experiment, ANOVA revealed a significant effect of drug treatment on alcohol intake [$F(5;66) = 5.89$, $P < 0.0005$]. Post hoc analysis indicated that no dose of baclofen altered alcohol intake when given in combination with morphine vehicle ("0.5 mg/kg baclofen plus 0 mg/kg morphine" and "1 mg/kg baclofen plus 0 mg/kg morphine" vs. "0 mg/kg baclofen plus 0 mg/kg morphine" groups) (Fig. 1). Conversely, morphine stimulated alcohol intake by approximately 60% with respect to control rats ("0 mg/kg baclofen plus 1 mg/kg morphine" vs. "0 mg/kg baclofen plus 0 mg/kg morphine" groups) (Fig. 1). Finally, baclofen pretreatment dose-dependently suppressed the increasing effect of morphine on alcohol intake ("0.5 mg/kg baclofen plus 1 mg/kg morphine" and "1 mg/kg baclofen plus 1 mg/kg morphine" vs. "0 mg/kg baclofen plus 1 mg/kg morphine") (Fig. 1). Drug treatment failed to significantly alter water [$F(5;66) = 1.53$, $P > 0.05$] and food [$F(5;66) = 1.48$, $P > 0.05$] intake.

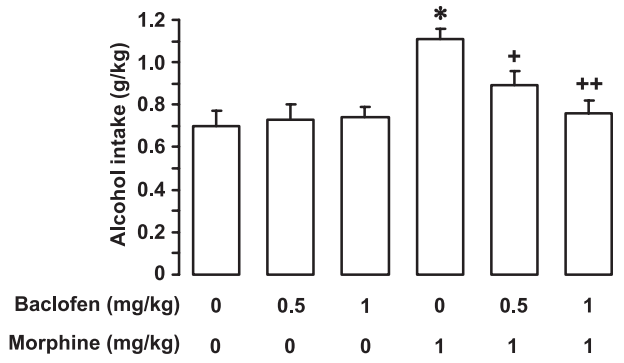

Fig. 1. Suppressing effect of the $GABA_B$ receptor agonist, baclofen, on the stimulating effect of morphine on alcohol intake in Sardinian alcohol-preferring (sP) rats. Alcohol (10%, v/v) was offered under the two-bottle, free choice regimen with water and unlimited access for 24 h/day. Food pellets were always available. Baclofen (0, 0.5 and 1 mg/kg, i.p.) was injected 10 min before morphine (0 and 1 mg/kg; s.c.) administration. Morphine was injected 20 min before lights off. Alcohol intake (expressed in g/kg) was monitored 60 min after lights off. Each bar is the mean ± S.E.M. of $n=12$ subjects. *$P<0.05$ with respect to "0 mg/kg baclofen plus 0 mg/kg morphine" rat group (Newman–Keuls test); $^{+}P<0.05$ and $^{++}P<0.005$ with respect to "0 mg/kg baclofen plus 1 mg/kg morphine" rat group (Newman–Keuls test).

In the "baclofen plus WIN 55,212-2" experiment, ANOVA showed a significant effect of drug treatment on alcohol intake [$F(5;66)=6.43$, $P<0.0001$]. No dose of baclofen affected alcohol intake when combined with WIN 55,212-2 vehicle ("0.5 mg/kg baclofen plus 0 mg/kg WIN 55,212-2" and "1 mg/kg baclofen plus 0 mg/kg WIN 55,212-2" vs. "0 mg/kg baclofen plus 0 mg/kg WIN 55,212-2" groups) (Fig. 2). WIN 55,212-2 induced an increase in alcohol intake by approximately 75% in comparison to control rats ("0 mg/kg baclofen plus 2 mg/kg WIN 55,212-2" vs. "0 mg/kg baclofen plus 0 mg/kg WIN 55,212-2" groups) (Fig. 2). Finally, combination of baclofen and WIN 55,212-2 resulted in a dose-dependent blockade of the stimulating effect of WIN 55,212-2 on alcohol intake ("0.5 mg/kg baclofen plus 2 mg/kg WIN 55,212-2" and "1 mg/kg baclofen plus 2 mg/kg WIN 55,212-2" vs. "0 mg/kg baclofen plus 2 mg/kg WIN 55,212-2") (Fig. 2). Water [$F(5;66)=0.50$, $P>0.05$] and food [$F(5;66)=0.59$, $P>0.05$] intake was not significantly modified by drug treatment.

4. Discussion

The acute administration of morphine and WIN 55,212-2 resulted in marked increase in voluntary alcohol intake in alcohol-preferring sP rats, confirming a large body of evidence on the capability of morphine and cannabinoids to stimulate alcohol drinking and alcohol motivational properties in rodents (see Introduction for references). The facilitatory action of morphine and WIN 55,212-2 on alcohol intake was completely blocked by pretreatment with the $GABA_B$ receptor agonist, baclofen. Indeed, doses of baclofen that did not alter alcohol intake when given alone dose-dependently suppressed the extra-intake of alcohol induced by morphine and WIN 55,212-2. These results extend to pharmacologically stimulated alcohol intake on the ability of baclofen to decrease alcohol consumption in rats; indeed, previous work has demonstrated that doses of baclofen higher than those used in the present study reduced acquisition and maintenance of alcohol drinking behavior and relapse like-drinking in alcohol-consuming, drug-naive rats (Colombo et al., 2000; Colombo et al., 2002a,b; Perfumi et al., 2002; Colombo et al., 2003).

The results of the present study indicate that the $GABA_B$ receptors are involved in the neural circuitry mediating the stimulating effect of morphine and cannabinoids on alcohol consumption. This circuitry might also include the mesolimbic dopamine system. Indeed, low to moderate doses of morphine, cannabinoids and alcohol share the capability to stimulate the activity of this system (see Introduction for references). Accordingly, it can be suggested that morphine- and WIN 55,212-2-induced stimulation of the mesolimbic dopamine system functioned as a "primer" on alcohol intake, by mimicking the effect of self-administered alcohol on dopamine release. In other words, the stimulating effect of morphine and WIN 55,212-2 on dopamine release in the nucleus accumbens may have triggered alcohol intake to further stimulate the system. Conversely, $GABA_B$ receptors located in the ventral tegmental area would offset—when stimulated—this stimulation and the extra-intake of alcohol induced by morphine and WIN 55,212-2. The observation that baclofen suppressed the increase in extracellular dopamine concentration induced by morphine (Fadda et al., 2003) and alcohol (this laboratory, unpublished results) in the rat nucleus accumbens strengthens the above hypothesis.

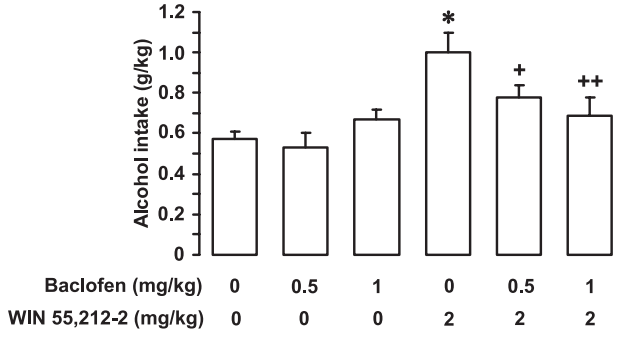

Fig. 2. Suppressing effect of the $GABA_B$ receptor agonist, baclofen, on the stimulating effect of the cannabinoid CB_1 receptor agonist, WIN 55,212-2, on alcohol intake in Sardinian alcohol-preferring (sP) rats. Alcohol (10%, v/v) was offered under the two-bottle, free choice regimen with water and unlimited access for 24 h/day. Food pellets were always available. Baclofen (0, 0.5 and 1 mg/kg, i.p.) was injected 10 min before WIN 55,212-2 (0 and 2 mg/kg; i.p.) administration. WIN 55,212-2 was injected 20 min before lights off. Alcohol intake (expressed in g/kg) was monitored 60 min after lights off. Each bar is the mean ± S.E.M. of $n=12$ subjects. *$P<0.05$ with respect to "0 mg/kg baclofen plus 0 mg/kg WIN 55,212-2" rat group (Newman–Keuls test); $^{+}P<0.05$ and $^{++}P<0.005$ with respect to "0 mg/kg baclofen plus 2 mg/kg WIN 55,212-2" rat group (Newman–Keuls test).

The activity of mesolimbic dopamine neurons is controlled—beside $GABA_B$ receptors—by different receptor systems, including serotonin, acetylcholine, opioid and glutamate receptors (see Kalivas, 1993). In agreement with the above hypothesis, administration of the 5-HT_3 receptor antagonist, tropisetron (known also as ICS 205–930), has been found to attenuate—similarly to the effect of baclofen in the present study—the increase in alcohol intake induced by morphine (Hodge et al., 1995) and WIN 55,212-2 (this laboratory, unpublished results) in alcohol-consuming rats offered the "alcohol vs. water" choice under the two-bottle regimen.

In conclusion, the results of the present study demonstrate that the $GABA_B$ receptor agonist, baclofen, inhibited the facilitatory effect of morphine and the cannabinoid receptor agonist, WIN 55,212-2, on alcohol intake in alcohol-preferring sP rats. A possible interpretation of these results is based on the ability of baclofen to suppress morphine- and cannabinoid-induced activity of the mesolimbic dopamine system, which would have otherwise functioned as a "primer" for alcohol intake.

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