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Role of the $GABA_B$ receptor in alcohol-seeking and drinking behavior

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Abstract

The present paper summarizes experimental data demonstrating the reducing effect of direct agonists and positive allosteric modulators (PAMs) of the γ-aminobutyric $acid_B$ ($GABA_B$) receptor on different alcohol-related behaviors. Different lines of evidence indicate that direct agonists, including baclofen, effectively suppress acquisition and maintenance of alcohol drinking behavior, relapse-like drinking, and alcohol's reinforcing, rewarding, stimulating, and motivational properties in rats and mice. More recently, the discovery of a positive allosteric modulatory binding site, together with the synthesis of in vivo effective ligands, opened a new avenue of research in $GABA_B$ pharmacology. Accumulating lines of evidence suggest that PAMs retain baclofen's capcity to suppress alcohol consumption and alcohol's reinforcing and motivational properties in rats; these effects occur at doses far from those producing behavioral toxicity.

Keywords: $GABA_B$ receptor; Direct agonists; Baclofen; Positive allosteric modulators; Alcohol intake; Operant alcohol self-administration; Reinforcing and motivational properties of alcohol; Alcohol-preferring rats

Recent lines of experimental and clinical evidence suggest that drugs activating the γ-aminobutyric $acid_B$ ($GABA_B$) receptor—one of the two receptor subtypes to which the major inhibitory neurotransmitter GABA binds—may constitute a novel class of potentially effective pharmacotherapies for alcohol dependence.

Direct agonists

It has been reported that administration of the prototypic direct agonist, baclofen, as well as of other direct agonists such as CGP44532 and SKF97541 suppressed several alcohol-related behaviors in rodents, including (1) acquisition (Colombo et al., 2002) and maintenance (Colombo et al., 2000; Daoust et al., 1987; Perfumi et al., 2002; Petry, 1997; Quintanilla et al., 2008) of alcohol drinking behavior in rats continuously exposed to the standard, home cage two-bottle ''alcohol versus water'' choice regimen; (2) the increase in alcohol intake, under the two-bottle regimen, occurring in rats after a period of forced abstinence from alcohol (the so-called ''alcohol deprivation effect,'' an experimental model of alcohol relapse) (Colombo et al., 2003a, 2006); (3) the increase in alcohol intake, under the two-bottle regimen, induced in rats by treatment with opioid and cannabinoid receptor agonists (Colombo et al., 2004); (4) the reinforcing properties of alcohol, assessed in rats and mice trained to press a lever to access alcohol under standard procedures of oral operant alcohol self-administration (Anstrom et al., 2003; Besheer et al., 2004; Janak and Gill, 2003; Liang et al., 2006; Maccioni et al., 2005; Walker and Koob, 2007); (5) the motivational properties of alcohol in rats, measured by (i) the extinction responding procedure (i.e., the total amount of unreinforced lever pressing that rats are willing to perform in seeking alcohol) (Colombo et al., 2003b; Leite-Morris and Czachowski, 2006; Leite-Morris et al., 2008) and (ii) the progressive ratio (PR) schedule of reinforcement (where the number of lever presses increases progressively over the session up to a breaking point) (Maccioni et al., 2008b; Walker and Koob, 2007); (6) reinstatement of alcohol-seeking behavior triggered in rats by the uncontingent presentation of a small, and pharmacologically irrelevant, amount of alcohol (another model of alcohol relapse) (Maccioni et al., 2008a); (7) alcohol-induced conditioned place preference (an index of alcohol's rewarding properties) in mice (Bechtholt and Cunningham, 2005). Furthermore, baclofen administration resulted in the blockade of alcohol-induced stimulation of locomotor activity (Boehm et al., 2002; Chester and Cunningham, 1999; Cott et al., 1976; Shen et al., 1998) and sensitization to the locomotor stimulant effects of alcohol (Broadbent and Harless, 1999) in mice; these results are of relevance in view of the facts

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that (1) locomotor stimulation induced by a psychoactive drug, including alcohol, has been proposed as an animal model of the drug's euphorigenic properties (see Wise and Bozarth, 1987) and (2) sensitization—defined as an increase in the effect of a drug after repeated exposure—is thought to play a central role in the development of drug addiction (see Robinson and Berridge, 1993). Finally, administration of baclofen has been reported to inhibit the intensity of different signs of alcohol withdrawal syndrome—including anxiety-related behaviors, tremors, and seizures—in rats made physically dependent on alcohol (Colombo et al., 2000; Knapp et al., 2007).

Of interest, preliminary clinical surveys with baclofen apparently extended to human alcoholics most of the results of the previously mentioned rodent studies as baclofen has been found to promote abstinence and decrease alcohol consumption, craving for alcohol, and severity of alcohol withdrawal symptoms and signs, including *delirium tremens*, in alcohol-dependent patients (Addolorato et al., 2000, 2002a, 2002b, 2003, 2006, 2007; Agabio et al., 2007; Ameisen, 2005; Bucknam, 2007; Flannery et al., 2004).

Positive allosteric modulators

Recent studies have demonstrated the existence in the $GABA_B$ receptor macroprotein of a binding site with positive allosteric modulatory activity (Urwyler et al., 2001, 2003). This binding site is topographically distinct from the orthosteric binding site of GABA, and its pharmacological activation—by compounds such as CGP7930, GS39783, BHF177, and *rac*-BHFF—increases the potency and efficacy of GABA (or direct agonists like baclofen) in activating the $GABA_B$ receptor (Cryan et al., 2004; Guery et al., 2007; Malherbe et al., 2008; Urwyler et al., 2001, 2003). Positive allosteric modulators (PAMs) of the $GABA_B$ receptor are devoid of substantial intrinsic agonistic activity in the absence of GABA (Urwyler et al., 2001, 2003). Thus, PAMs offer more physiological means of activating the $GABA_B$ receptor in vivo than direct agonists as they do not perturb receptor signaling on their own but potentiate the effect of GABA only where and when it is endogenously released.

When given alone, PAMs of the $GABA_B$ receptor reproduced several in vivo effects of baclofen, including anxiolysis (Cryan et al., 2004; Jacobson and Cryan, 2008; Malherbe et al., 2008) and suppression of (1) intravenous self-administration of cocaine in rats (Filip et al., 2007; Smith et al., 2004), (2) reinstatement of cocaine-seeking behavior induced in rats by a priming uncontingently delivered dose of cocaine or by the presentation of cues previously associated to cocaine availability (Filip and Frankowska, 2007), (3) cocaine-induced hyperlocomotion and locomotor sensitization in mice (Lhuillier et al., 2007), (4) cocaine-induced lowering of brain reward thresholds in rats (Slattery et al., 2005), (5) nicotine-induced conditioned place preference in rats (Mombereau et al., 2007), (6) intravenous self-administration of nicotine in rats (Paterson et al., 2008), and (7) nicotine-induced lowering of brain reward thresholds in rats (Paterson et al., 2008).

PAMs of the $GABA_B$ receptor also reproduced the suppressing effect of baclofen on different alcohol-related behaviors. Specifically, daily administration of CGP7930 (0, 25, 50, and 100 mg/kg, i.g.) or GS39783 (0, 6.25, 12.5, and 25 mg/kg, i.g.) for five consecutive days dose-dependently suppressed acquisition of alcohol drinking in alcohol-naive, Sardinian alcohol-preferring (sP) rats exposed to the home cage two-bottle alcohol (10%, vol/vol) versus water regimen with unlimited access for 24 h/day (Orrù et al., 2005). Similarly, daily administration for five consecutive days of CGP7930 (0, 50, and 100 mg/kg, i.g.) or GS39783 (0, 50, and 100 mg/kg, i.g.) dose-dependently reduced daily alcohol intake in alcohol-experienced sP rats exposed to the home cage two-bottle alcohol (10%, vol/vol) versus water regimen with unlimited access for 24 h/day (Orrù et al., 2005). In the latter study, some degree of tolerance to reducing effect of CGP7930 and GS39783 on daily alcohol intake tended to develop on continuing treatment.

Treatment with GS38793 was also found to attenuate alcohol's reinforcing properties in sP rats (Maccioni et al., 2007). In the study concerned, rats were initially trained to lever press to orally self-administer alcohol (15%, vol/vol) under a fixed ratio (FR) 4 schedule of responding in daily 30-min sessions. Tests with GS39783 (0, 25, 50, and 100 mg/kg, i.g.) were conducted when lever-pressing and self-administration behaviors reached stable levels (150–200 responses/session and 0.8–0.9 g/kg alcohol per session, respectively). Treatment with GS39783 resulted in a dose-dependent reduction in responding for alcohol and alcohol self-administration; in comparison to vehicle-treated rats, the number of lever responses for alcohol and the amount of self-administered alcohol were reduced by approximately 30, 40, and 50% in the rat groups treated with 25, 50, and 100 mg/kg GS39783, respectively. Notably, the effect of GS39783 on alcohol self-administration was specific as treatment with GS39783 failed to alter responding for an alternate nondrug reinforcer (sucrose) in an independent group of sP rats.

Consonant data were reported by Liang et al. (2006). In the latter study, Indiana P rats were initially trained to lever press for oral alcohol (10%, vol/vol) under an FR3 schedule of reinforcement in daily 40-min sessions. Once lever responding had stabilized, rats were exposed to test sessions with CGP7930 (0, 10, and 20 mg/kg, intraperitoneal). Treatment with CGP7930 dose-dependently reduced responding for alcohol; at the highest dose, the number of responses on the alcohol-associated lever was reduced by approximately 45% in comparison to vehicle-treated rats.

A final study (Maccioni et al., 2008b) investigated the effect of GS39783 on alcohol's motivational properties, measured by means of the PR schedule of reinforcement.