Published in final edited form as:

Neurosci Lett. 2008 October 10; 443(3): 236–240. doi:10.1016/j.neulet.2008.07.074.

Effects of baclofen on conditioned rewarding and discriminative stimulus effects of nicotine in rats

Bernard Le Foll^{1,2}, Carrie E. Wertheim¹, and Steven R. Goldberg¹

¹Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland, USA

²Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, 33 Russell Street, Toronto, Canada

Abstract

Neurochemical studies suggest that baclofen, an agonist at GABA_B receptors, may be useful for treatment of nicotine dependence. However, its ability to selectively reduce nicotine's abuse-related behavioral effects remains in question. We assessed effects of baclofen doses ranging from 0.1 to 3 mg/kg on nicotine-induced conditioned place preferences (CPP), nicotine discrimination, locomotor activity and food-reinforced behavior in male Sprague Dawley rats. The high dose of baclofen (3 mg/kg) totally eliminated food-reinforced responding and significantly decreased locomotor activity. Lower doses of baclofen did not have nicotine-like discriminative effects in rats trained to discriminate 0.4 mg/kg nicotine from saline under a fixed-ratio 10 schedule of food delivery. Lower doses of baclofen also did not reduce discriminative-stimulus effects of the training dose of nicotine and did not significantly shift the dose-response curve for nicotine discrimination. Rats treated with the high 3 mg/kg dose of baclofen did not express nicotine-induced CPP. These experiments, along with previous reports that baclofen can reduce intravenous nicotine self-administration behavior, confirm the potential utility of baclofen as a tool for smoking cessation.

Keywords

Conditioned place preferences – discrimination; Reward; Nicotine; Rats – GABA

1. Introduction

A common feature of addictive drugs such as cocaine, amphetamine, heroin and nicotine, is that they increase dopamine levels in the nucleus accumbens, which is thought to play a major role in the rewarding effects of these drugs [22]. Baclofen, an agonist at gamma-aminobutyric acid-B (GABA_B) receptors reduces the dopamine elevations produced by various drugs of abuse in the nucleus accumbens [15,41,47] and has been frequently proposed as a pharmacotherapy for drug dependence. Baclofen reduces intravenous cocaine self-administration by rats under fixed-ratio and progressive-ratio schedules of reinforcement [6,39,40,44] and cocaine-seeking behavior by rats under second-order schedules of reinforcement [9,13] (see Cousins et al. 2002 for a review). Such findings have been difficult to interpret since baclofen, which is used in clinics by neurologists as a muscle

relaxant, produces non-specific depressant effects on behavior that may partly explain the decreases in responding it produces with intravenous drug self-administration procedures. Nevertheless, findings from several studies using fixed-ratio schedules [4,33,39,44] suggest that baclofen and CGP44532, another GABA_B agonist, produce selective effects on drug-maintained responding relative to food-maintained responding at certain doses, although other studies using progressive-ratio schedules yielded less convincing findings [4,33].

More recently, ligands acting on GABA-ergic transmission have been proposed as novel candidates for the treatment of nicotine dependence [32]. Gamma-vinyl GABA, an indirect GABA receptor agonist, that acts through inhibition of GABA transaminase [21], reduces both the acquisition and expression of nicotine-induced conditioned place preferences (CPP) [12] and decreases intravenous self-administration of nicotine in rats [35]. Unfortunately, this compound has severe side-effects, such as restriction of visual field [14], that limit its clinical use. Baclofen appears to be a better tolerated GABA-ergic alternative for clinical treatment of nicotine dependence. Baclofen alters the sensory properties of smoked cigarettes in humans [10] and nicotine self-administration in rats [16,33]. Moreover, baclofen has recently been shown effective and safe for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis [1], suggesting that it would also be well tolerated in human smokers. To further investigate the potential utility of baclofen as a treatment for nicotine dependence, we used a CPP paradigm as an animal model of conditioned reward and a drug discrimination paradigm as an animal model of psychomotor and subjective effects of nicotine [26].

2. Materials and Methods

Subjects

Male Sprague-Dawley rats ($n = 203$ for CPP experiment and $n = 24$ for nicotine discrimination experiment; 230 – 260g) were obtained from Charles River (Wilmington, MA) and housed in a temperature- and humidity-controlled room. These facilities are fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and experimentations were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Intramural Research Program, National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals (National Research Council 1996). Experiments were conducted during the light phase of a 12-h/12-h light/dark cycle (lights on at 0700 hours). Rats were housed in groups of two per cage (CPP) or individually (discrimination). The rats were allowed to acclimate to the animal colony for at least 3 weeks before training and were repeatedly handled during this period. Water was available *ad libitum*. For discrimination, a diet restriction was maintained throughout the study (3 NIH07 biscuits /day).

Drugs

Baclofen [r(+)-baclofen hydrochloride] and Nicotine [(–)-nicotine hydrogen tartrate] were purchased from Sigma Chemical Company (St Louis, Mo., USA) and were diluted in saline. All drugs were administered in a volume of 1.0 ml/kg. Nicotine was administered subcutaneously (s.c., pH=7) and baclofen intraperitoneally (i.p.). Doses are expressed as free base. Baclofen was administered 30 min before the sessions.

Conditioned place preference

We used previously reported equipment and procedures [28,30]. Briefly, a pre-test session (15 min), conditioning sessions (two 20-min sessions of per day over three days; saline in the morning and 0.1 mg/kg nicotine in the afternoon), and a post-conditioning test session (15 min) were conducted over five consecutive days. Eighteen rats displaying a strong bias

(more than 600 sec in one compartment) were excluded from study. A “biased” stimulus assignment procedure was used, i.e. the compartment paired with nicotine was the initially non-preferred side of the apparatus, as measured during the pre-test. The baseline pre-test score was used to determine which side of the apparatus was associated with nicotine during the conditioning phase. Rats could move freely between compartments during pre-test and post-conditioning test sessions, but not during conditioning sessions. Rats were pre-treated acutely with baclofen (0.3, 1 or 3 mg/kg) or with saline only before the post-conditioning test session when expression of nicotine place preference was evaluated. Since, baclofen may impair movement of rats between compartments of the apparatus, rats that did not move from one side to the other after baclofen treatment (i.e. rats who stayed in one side of the apparatus during the entire duration of the test session) were excluded from data analysis (one rat treated with 0.3 mg/kg baclofen and two rats treated with 3 mg/kg baclofen).

Nicotine discrimination

Twelve standard operant-conditioning chambers (Coulbourn Instruments, Lehigh Valley, PA) were used using standard procedures (see [28,30] for details). Briefly, 24 rats were trained under a discrete-trial schedule of food-pellet delivery to respond on one lever after an injection of a training dose of 0.4 mg/kg nicotine and on the other lever after an injection of 1 ml/kg of saline vehicle ($n = 24$). Injections of nicotine or saline were given subcutaneously 10 min before the start of the session. Reaching the final level of accuracy (eight consecutive sessions with at least 90% of the responses on the correct lever and no more than four incorrect responses during the first trial) required 18 to 70 sessions with a mean value ($\pm$ SEM) of 36.6 ± 3.0 sessions. Then, a range of doses of baclofen, given 30 min before the session were substituted for the training dose of nicotine. Next, a range of baclofen doses was administered together with the training dose of nicotine. A dose of 1 mg/kg baclofen was also administered together with various doses of nicotine to assess effects on the dose-response curve for nicotine discrimination. The higher 3 mg/kg dose of baclofen was not tested against nicotine curves, because this dose, alone or in combination with the training dose of nicotine, completely eliminated food-reinforced responding in most subjects.

Data analysis

The outcome of the CPP experiment was determined by analyzing the raw time scores in the less preferred side of apparatus before and after conditioning. Distance traveled and number of crossings from one side to another during the test session were also analyzed. Repeated measures ANOVA and LSD-post-hoc test were used for analysis. For nicotine discrimination, the discrimination performance and the response rate (in responses/sec) were measured. For discrimination performance, the dose of nicotine predicted to produce 50% of responses on the nicotine-associated lever was calculated by a linear regression analysis of the log dose-effect function for nicotine. Results were considered significant while $P < 0.05$.

3. Results

Effect of baclofen on nicotine-induced CPP

No significant basal differences between times spent by the different groups of rats in the less preferred side of the apparatus during the pre-conditioning test were observed (Fig. 1, open bars, all $P > 0.56$). After six conditioning sessions (3 with 0.1 mg/kg nicotine, and 3 with saline), in agreement with previous studies [17,27,28,30], rats displayed a significant CPP for the compartment previously paired with nicotine injection during a post-conditioning test session when nicotine was not administered. Repeated measures of ANOVA indicated a significant effect of time ($F_{1,174}=20.2$, $P < 0.0001$), but no significant effect of nicotine treatment ($F_{1,174}=1.82$, $P=0.2$), and no significant effect of baclofen

($F_{3,174}=0.16$, $P=0.92$). Post-hoc analysis indicated that nicotine-induced CPP were present in rats receiving either saline ($P=0.02$) or the doses of 0.3 and 1 mg/kg baclofen on the test day ($P=0.049$ and $P=0.03$, respectively). In contrast, no significant nicotine-induced CPP was displayed by rats receiving the higher dose of 3 mg/kg baclofen on the test day ($P=0.26$) (Fig. 1A). However, there was no significant statistical interaction between nicotine and baclofen using the Repeated-measures ANOVA analysis. CPP 3 mg/kg baclofen increased time spent in the non-preferred side of the apparatus in controls rats (right panel of the Fig. 1, $P=0.04$), indicating a potential non-specific effect of the high dose of baclofen in time spent in the drug-paired compartment. However, any such non-specific effect (an increase) would counteract, rather than facilitate baclofen's reduction of the nicotine-induced CPP.

Distances traveled by the rats during test sessions are shown in Fig. 1B. Baclofen produced a biphasic effect on locomotor activity of the rats in these experiments. ANOVA analysis indicates no significant effect of nicotine conditioning ($F_{1,133}=0.01$, $P=0.92$), a significant effect of baclofen administration ($F_{3,133}=31.3$, $P<0.0001$), and no significant conditioning x treatment interaction ($F_{3,133}=1.1$, $P=0.35$). Post-hoc analysis indicated that 0.3 mg/kg baclofen stimulated locomotor activity ($P=0.04$ for both nicotine- and saline-conditioned rats), whereas 3 mg/kg of baclofen significantly decreased locomotor activity ($P<0.001$ for both nicotine- and saline-conditioned rats) (Fig. 2A).

Values for number of crossings from one side to the other of the apparatus during test sessions are shown in Fig. 1C. ANOVA analysis indicates no significant effect of nicotine conditioning ($F_{1,133}=1.3$, $P=0.26$), a significant effect of baclofen administration ($F_{3,133}=12.5$, $P<0.0001$), and no significant conditioning x treatment interaction ($F_{3,133}=1.1$, $P=0.35$). Post-hoc analysis indicated that 3 mg/kg of baclofen significantly decreased the number of crossings (Fig. 1C).

Generalization Tests and effect of baclofen on discrimination of the training dose of nicotine

Figure 2 (left panel) shows the percentage of responses made on the drug lever and overall rates of responding during sessions when different doses of baclofen were tested for their ability to substitute for the training dose 0.4 mg/kg of nicotine. Baclofen failed to generalize to nicotine over a large range of doses (less than 5% of responses emitted on the nicotine-associated lever with doses of baclofen ranging from 0.03 to 1 mg/kg). Increasing the dose of baclofen to 3 mg/kg completely inhibited rates of responding (Fig. 2, left bottom panels). Figure 2 (upper left panel) shows that various doses of baclofen did not block or significantly reduce the discriminative stimulus effects of the training dose of nicotine (all $P>0.8$).

Effects of 1 mg/kg baclofen on discrimination of various doses of nicotine

Figure 2 (right panel) shows the effects of baclofen on the dose-response curve for nicotine discrimination. ED50 values for drug-lever selection were 0.05 (0.04 – 0.06) mg/kg for nicotine alone and 0.07 (0.05 – 0.09) mg/kg for nicotine administered in combination with 1 mg/kg baclofen. The significant overlap of ED50 values indicates no significant shift of the nicotine discrimination. Two-way ANOVA indicated a significant effect of 1 mg/kg baclofen pretreatment on nicotine discrimination ($F_{1,135} = 4.8$, $P = 0.03$) and a significant effect of nicotine dose ($F_{3,135} = 119.1$, $P < 0.001$), but no significant interaction between baclofen pretreatment and nicotine dose ($F_{3,135} = 2.0$, $P = 0.11$). The 1 mg/kg dose of baclofen had no significant effect on responses rates of the rats, either alone or in combination with different doses of nicotine (Fig. 2, lower right panel).

4. Discussion

In agreement with a number of previous studies [17,27,28,30], a dose of 0.1 mg/kg nicotine induced significant CPP using a biased procedure. Acute administration of 3 mg/kg baclofen blocked the expression of this nicotine-induced CPP. In the drug discrimination procedure, acute administration of baclofen did not produce nicotine-like discriminative effects, did not reduce the discriminative effects of the training dose of nicotine and did not shift the dose-response curve for nicotine discrimination.

One limitation of the present CPP experiment is the use of a biased procedure, i.e. the rats were individually categorized based on their initial (pre-test) preference for one side of the apparatus. We have recently shown that the stimulus assignment procedure is a critical factor in the ability of nicotine to induce CPP (see [27], for a review). It is unlikely that the CPP were due to a shift in the basal preference for one side of the apparatus due to repeated testing, since no shift was observed in control rats receiving only saline injections during the conditioning phase (Fig. 1A, right panel). A 3 mg/kg dose baclofen did increase time spent in the non-preferred side of the apparatus, an effect that may reflect anxiolytic properties of baclofen. This effect would not contribute to the disruption of nicotine-induced CPP, since such an anxiolytic effect would increase time spent in the initially non-preferred side of the apparatus and, therefore, increase the magnitude of the CPP score. As expected, the CPP procedure was less sensitive to the motor disruptive effects of drugs than operant procedures, since 3 mg/kg baclofen totally eliminated food-reinforced operant behavior of rats in the drug discrimination experiment (lower left panel of Fig. 2) but only partially decreased locomotor activity of rats in the CPP experiment (Fig. 1B,C). Moreover, since rats that received 3 mg/kg baclofen continued to actively move from one side to the other of the CPP apparatus during the test session (Fig. 1C), the decrease in time spent in the nicotine-paired environment likely reflects a decrease in the motivational effects resulting from previous administrations of nicotine.

The present finding that expression of nicotine-induced CPP is blocked by baclofen is in agreement with previous reports that baclofen is effective in blocking the expression of methamphetamine-induced CPP [31] and conditioned motor effects associated with cocaine administration [19]. In addition, the present finding extends previous findings that increasing GABA-ergic neurotransmission blocks the expression of nicotine-induced CPP [2,12]. Together these findings suggest that baclofen can reduce the motivational effects of environmental stimuli repeatedly associated with nicotine administration.

Baclofen produced no nicotine-like discriminative effects in rats in the present study (Fig. 2, upper left panel), but this does not necessarily indicate a lack of potential as a novel agent for smoking cessation, since the cannabinoid CB₁ receptor antagonist, rimonabant, which appears to be efficacious in treating smoking dependence in humans [24], also does not produce any nicotine-like discriminative effects [7,28]. The discriminative stimulus effects of nicotine are mainly mediated by neuronal nicotinic acetylcholine receptors (nAChR) [23,38,43,45,46]. Therefore, it is not surprising that baclofen had no global effect on nicotine discrimination. Interestingly, the moderate shift to the right of the nicotine-dose response curve induced by baclofen (see upper right panel of Fig. 2 and statistical analysis using ANOVA), may reflect the blockade of dopamine-releasing effects of nicotine [15,20,36,37], since some authors have argued that there is a small dopaminergic component to the discriminative stimulus effects of nicotine [8,11,18,30]. In humans, a single dose of baclofen slightly alters ratings of subjective effects of tobacco, increasing ratings of 'harsh' and decreasing ratings of 'like cigarette's effects' [10]. Similarly, a blockade of the dopaminergic component of the discriminative stimulus effects of nicotine could produce a small shift of the nicotine discrimination curve.

Recent clinical findings suggest that baclofen may be effective in blocking reactivity to drug associated stimuli [3]. Indeed, a significant portion of relapses to tobacco use were reported to occur in the presence of environmental stimuli associated with previous episodes of tobacco smoking [42]. Moreover, ligands acting at GABA_B receptors are able to decrease both stimulus-controlled drug-seeking behavior [13] and reinstatement of nicotine-seeking behavior by drug-associated stimuli (cues) in rats [34]. The fact that baclofen produced a small but significant reduction in nicotine-induced CPP in the present study supports and extends previous findings that GABA_B ligands can attenuate responses to drug-associated environmental stimuli and demonstrates the selectivity of this effect. Further studies are needed to evaluate whether the effects of baclofen can be observed after chronic treatment in smokers, as already shown in alcoholics [1]. Nevertheless, in contrast to other pharmacological ligands with potential clinical utility for smoking cessation, such as CB₁ receptor antagonists [25,28] and dopamine D₃ receptor ligands [29,30], that are able to selectively block nicotine-induced CPP at doses well below those that disrupt locomotor activity or food-reinforced operant behavior, the present effects of baclofen on CPP are small and appear to be embedded in motor effects. However, clinical trial findings in alcoholics indicate good tolerability of baclofen, suggesting tolerance develops to its depressant effect during chronic treatment [1].

In conclusion, the present findings provide evidence that baclofen can reduce conditioned rewarding effects of nicotine using a place preference procedure. Although this effect occurred at a dose of baclofen that strongly depressed locomotor activity, it did not seem to be related to non-specific motor effects or to effects on nicotine discrimination. This supports and extends previous findings with cocaine that baclofen attenuates responses to drug-associated environmental stimuli. Since nicotine-associated environmental stimuli are particularly critical in the maintenance of smoking behavior and reports of desire to smoke in abstinent smokers [5], baclofen may be a useful tool for preventing relapse to smoking behavior in ex-smokers.

Acknowledgments

This study was supported by NIDA-IRP, DHHS. BLF has received the support of the CIHR-TUSP training program.

References

1. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet*. 2007; 370:1915–1922. [PubMed: 18068515]
2. Ashby CR Jr, Paul M, Gardner EL, Gerasimov MR, Dewey SL, Lennon IC, Taylor SJ. Systemic administration of 1R,4S-4-amino-cyclopent-2-ene-carboxylic acid, a reversible inhibitor of GABA transaminase, blocks expression of conditioned place preference to cocaine and nicotine in rats. *Synapse*. 2002; 44:61–63. [PubMed: 11891877]
3. Brebner K, Childress AR, Roberts DC. A potential role for GABA(B) agonists in the treatment of psychostimulant addiction. *Alcohol Alcohol*. 2002; 37:478–484. [PubMed: 12217943]
4. Brebner K, Phelan R, Roberts DC. Effect of baclofen on cocaine self-administration in rats reinforced under fixed-ratio 1 and progressive-ratio schedules. *Psychopharmacology (Berl)*. 2000; 148:314–321. [PubMed: 10755745]
5. Caggiula AR, Donny EC, White AR, Chaudhri N, Booth S, Gharib MA, Hoffman A, Perkins KA, Sved AF. Cue dependency of nicotine self-administration and smoking. *Pharmacol Biochem Behav*. 2001; 70:515–530. [PubMed: 11796151]

6. Campbell UC, Lac ST, Carroll ME. Effects of baclofen on maintenance and reinstatement of intravenous cocaine self-administration in rats. *Psychopharmacology (Berl)*. 1999; 143:209–214. [PubMed: 10326784]
7. Cohen C, Perrault G, Voltz C, Steinberg R, Soubrie P. SR141716, a central cannabinoid (CB₁) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. *Behav Pharmacol*. 2002; 13:451–463. [PubMed: 12394421]
8. Corrigan WA, Coen KM. Dopamine mechanisms play at best a small role in the nicotine discriminative stimulus. *Pharmacol Biochem Behav*. 1994; 48:817–820. [PubMed: 7938142]
9. Cousins MS, Roberts DC, de Wit H. GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. *Drug Alcohol Depend*. 2002; 65:209–220. [PubMed: 11841892]
10. Cousins MS, Stamat HM, de Wit H. Effects of a single dose of baclofen on self-reported subjective effects and tobacco smoking. *Nicotine Tob Res*. 2001; 3:123–129. [PubMed: 11403726]
11. Desai RI, Barber DJ, Terry P. Dopaminergic and cholinergic involvement in the discriminative stimulus effects of nicotine and cocaine in rats. *Psychopharmacology (Berl)*. 2003; 167:335–343. [PubMed: 12684733]
12. Dewey SL, Brodie JD, Gerasimov M, Horan B, Gardner EL, Ashby CR Jr. A pharmacologic strategy for the treatment of nicotine addiction. *Synapse*. 1999; 31:76–86. [PubMed: 10025686]
13. Di Ciano P, Everitt BJ. The GABA(B) receptor agonist baclofen attenuates cocaine- and heroin-seeking behavior by rats. *Neuropsychopharmacology*. 2003; 28:510–518. [PubMed: 12629530]
14. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. *BMJ*. 1997; 314:180–181. [PubMed: 9022432]
15. Fadda P, Scherma M, Fresu A, Collu M, Fratta W. Baclofen antagonizes nicotine-, cocaine-, and morphine-induced dopamine release in the nucleus accumbens of rat. *Synapse*. 2003; 50:1–6. [PubMed: 12872287]
16. Fattore L, Cossu G, Martellotta MC, Fratta W. Baclofen antagonizes intravenous self-administration of nicotine in mice and rats. *Alcohol Alcohol*. 2002; 37:495–498. [PubMed: 12217945]
17. Fudala PJ, Teoh KW, Iwamoto ET. Pharmacologic characterization of nicotine-induced conditioned place preference. *Pharmacol Biochem Behav*. 1985; 22:237–241. [PubMed: 2858867]
18. Gasior M, Shoaib M, Yasar S, Jaszyna M, Goldberg SR. Acquisition of nicotine discrimination and discriminative stimulus effects of nicotine in rats chronically exposed to caffeine. *J Pharmacol Exp Ther*. 1999; 288:1053–1073. [PubMed: 10027843]
19. Hotsenpiller G, Wolf ME. Baclofen attenuates conditioned locomotion to cues associated with cocaine administration and stabilizes extracellular glutamate levels in rat nucleus accumbens. *Neuroscience*. 2003; 118:123–134. [PubMed: 12676144]
20. Imperato A, Mulas A, Di Chiara G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. *Eur. J. Pharmacol*. 1986; 132:337–338. [PubMed: 3816984]
21. Jung MJ, Lippert B, Metcalf BW, Bohlen P, Schechter PJ. gamma-Vinyl GABA (4-amino-hex-5-enoic acid), a new selective irreversible inhibitor of GABA-T: effects on brain GABA metabolism in mice. *J Neurochem*. 1977; 29:797–802. [PubMed: 591956]
22. Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol. Sci*. 1992; 13:177–184. [PubMed: 1604710]
23. Kumar R, Reavill C, Stolerman IP. Nicotine cue in rats: effects of central administration of ganglion-blocking drugs. *Br J Pharmacol*. 1987; 90:239–246. [PubMed: 2880625]
24. Le Foll B, Forget B, Aubin HJ, Goldberg SR. Blocking cannabinoid CB₁ receptors for the treatment of nicotine dependence: insights from preclinical and clinical studies. *Addiction Biology*. 2008 in press.
25. Le Foll B, Goldberg SR. Cannabinoid CB₁ receptor antagonists as promising new medications for drug dependence. *J. Pharmacol. Exp. Ther*. 2005; 312:875–883. [PubMed: 15525797]
26. Le Foll B, Goldberg SR. Nicotine as a typical drug of abuse in experimental animals and humans. *Psychopharmacology(Berl)*. 2006; 184:367–381. [PubMed: 16205918]
27. Le Foll B, Goldberg SR. Nicotine induces conditioned place preferences over a large range of doses in rats. *Psychopharmacology (Berl)*. 2005; 178:481–492. [PubMed: 15765262]

28. Le Foll B, Goldberg SR. Rimonabant, a CB₁ antagonist, blocks nicotine-conditioned place preferences. *Neuroreport*. 2004; 15:2139–2143. [PubMed: 15486497]
29. Le Foll B, Schwartz J-C, Sokoloff P. Disruption of nicotine conditioning by dopamine D3 receptor ligands. *Molecular Psychiatry*. 2003; 8:225–230. [PubMed: 12610655]
30. Le Foll B, Sokoloff P, Stark H, Goldberg SR. Dopamine D3 ligands block nicotine-induced conditioned place preferences through a mechanism that does not involve discriminative-stimulus or antidepressant-like effects. *Neuropsychopharmacology*. 2005; 30:720–730. [PubMed: 15562293]
31. Li SM, Yin LL, Ren YH, Pan LS, Zheng JW. GABA(B) receptor agonist baclofen attenuates the development and expression of d-methamphetamine-induced place preference in rats. *Life Sci*. 2001; 70:349–356. [PubMed: 12005267]
32. Markou A, Paterson NE, Semenova S. Role of {gamma}-Aminobutyric Acid (GABA) and Metabotropic Glutamate Receptors in Nicotine Reinforcement: Potential Pharmacotherapies for Smoking Cessation. *Ann N Y Acad Sci*. 2004; 1025:491–503. [PubMed: 15542754]
33. Paterson NE, Froestl W, Markou A. The GABA(B) receptor agonists baclofen and CGP44532 decreased nicotine self-administration in the rat. *Psychopharmacology (Berl)*. 2004; 172:179–186. [PubMed: 14610636]
34. Paterson NE, Froestl W, Markou A. Repeated administration of the GABAB receptor agonist CGP44532 decreased nicotine self-administration, and acute administration decreased cue-induced reinstatement of nicotine-seeking in rats. *Neuropsychopharmacology*. 2005; 30:119–128. [PubMed: 15266350]
35. Paterson NE, Markou A. Increased GABA neurotransmission via administration of gamma-vinyl GABA decreased nicotine self-administration in the rat. *Synapse*. 2002; 44:252–253. [PubMed: 11984860]
36. Pidoplichko VI, DeBiasi M, Williams JT, Dani JA. Nicotine activates and desensitizes midbrain dopamine neurons. *Nature*. 1997; 390:401–404. [PubMed: 9389479]
37. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature*. 1996; 382:255–257. [PubMed: 8717040]
38. Pratt JA, Stolerman IP, Garcha HS, Giardini V, Feyerabend C. Discriminative stimulus properties of nicotine: further evidence for mediation at a cholinergic receptor. *Psychopharmacology (Berl)*. 1983; 81:54–60. [PubMed: 6415731]
39. Roberts DC, Andrews MM. Baclofen suppression of cocaine self-administration: demonstration using a discrete trials procedure. *Psychopharmacology (Berl)*. 1997; 131:271–277. [PubMed: 9203238]
40. Roberts DC, Andrews MM, Vickers GJ. Baclofen attenuates the reinforcing effects of cocaine in rats. *Neuropsychopharmacology*. 1996; 15:417–423. [PubMed: 8887996]
41. Schiffer WK, Gerasimov MR, Bermel RA, Brodie JD, Dewey SL. Stereoselective inhibition of dopaminergic activity by gamma vinyl-GABA following a nicotine or cocaine challenge: a PET/microdialysis study. *Life Sci*. 2000; 66:PL169–PL173. [PubMed: 10737423]
42. Shiffman S. Relapse following smoking cessation: a situational analysis. *J Consult Clin Psychol*. 1982; 50:71–86. [PubMed: 7056922]
43. Shoaib M, Gommans J, Morley A, Stolerman IP, Grailhe R, Changeux JP. The role of nicotinic receptor beta-2 subunits in nicotine discrimination and conditioned taste aversion. *Neuropharmacology*. 2002; 42:530–539. [PubMed: 11955523]
44. Shoaib M, Swanner LS, Beyer CE, Goldberg SR, Schindler CW. The GABAB agonist baclofen modifies cocaine self-administration in rats. *Behav Pharmacol*. 1998; 9:195–206. [PubMed: 9832934]
45. Stolerman IP, Chandler CJ, Garcha HS, Newton JM. Selective antagonism of behavioural effects of nicotine by dihydro-beta-erythroidine in rats. *Psychopharmacology (Berl)*. 1997; 129:390–397. [PubMed: 9085409]
46. Stolerman IP, Garcha HS, Pratt JA, Kumar R. Role of training dose in discrimination of nicotine and related compounds by rats. *Psychopharmacology (Berl)*. 1984; 84:413–419. [PubMed: 6440189]

47. Xi ZX, Stein EA. Baclofen inhibits heroin self-administration behavior and mesolimbic dopamine release. *J Pharmacol Exp Ther.* 1999; 290:1369–1374. [PubMed: 10454516]

Fig. 1.

A Effects of baclofen on expression of nicotine-induced conditioned place preferences (CPP). Expression of nicotine-induced CPP was only significantly blocked by the high 3 mg/kg dose of baclofen, which was given acutely 30 min before the post-conditioning test session ($n = 19-26$). Columns show mean ($\pm$ SEM) time spent in the initially non-preferred (i.e. drug-paired) compartment during preconditioning (open bar) and postconditioning test (closed bar) sessions. $*P < 0.05$ vs saline treated-animals. **B** Effects of baclofen on locomotor activity (distance traveled in meters $\pm$ SEM) and **C** on number of crossings ($\pm$ SEM) from one side to the other of the apparatus during CPP test sessions. Both distance travelled and

number of crossings were significantly reduced by only the high 3 mg/kg dose of baclofen. * $P < 0.05$; ** $P < 0.001$ vs saline treated-animals.

Fig. 2.

Effects of baclofen on nicotine discrimination and food-reinforced responding. The *upper panels* show the percentage of responses on the lever associated with nicotine administration as a function of baclofen and nicotine dose (mg/kg). *Upper left panels*: Baclofen doses up to 1 mg/kg did not produce nicotine-like discriminative effects and did not alter the discriminative effects of the 0.4 mg/kg training dose of nicotine ($n = 6$). *Upper right panels*: A 1 mg/kg dose of baclofen did not produce a significant shift of the dose-response curve for nicotine discrimination in rats trained to discriminate 0.4 mg/kg nicotine from saline ($n = 12-24$; upper right panel). In the *bottom panels*, response rates are expressed as responses per second averaged over the session. Doses of baclofen up to 1 mg/kg had no significant

effect on response rates, but a higher 3 mg/kg dose completely eliminated responding (*lower left panel*). A dose of 1 mg/kg baclofen had no significant effect on response rates when given together with different doses of nicotine (*lower right panel*). Data are means $\pm$ S.E.M.