Pharmacological Reports
2008, 60, 755–770
ISSN 1734-1140

Review

$GABA_B$ receptors in drug addiction

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Abstract:
Preclinical studies and clinical trials carried out within the past few years have provided a premise that γ-aminobutyric acid (GABA) transmission and $GABA_B$ receptors play a modulatory role in the mechanism of action of different drugs of abuse. The present review summarizes the contribution of $GABA_B$ receptors to the rewarding, locomotor and discriminative stimulus properties of drugs of abuse and their withdrawal symptoms in laboratory animals. It also reviews the current knowledge about the $GABA_B$ receptor ligands in clinical trials, with a focus on their effects on presentation of the drug-associated cues and withdrawal-induced drug craving.

Key words:
addictive substances, discrimination, $GABA_B$ receptor ligands, locomotion, reward, reinstatement of seeking behavior, withdrawal, laboratory animals, clinical trials

Introduction

According to the World Health Organization (WHO), drug addiction is a chronic disease of the central nervous system that is characterized by a loss of control over impulsive behavior that leads to compulsive drug seeking and taking and to relapses even after many months of abstinence.

The clinical diagnosis of addiction is also defined by the use of a psychoactive substance for a longer period or at higher doses than initially prescribed, drug cravings or unsuccessful attempts to cease the drug use, use of the drug despite the negative effect on one's social and professional life, increasing tolerance, a withdrawal syndrome and desire to take the drug to alleviate these symptoms (according to DSM IV, American Psychiatric Society).

Recently published data (preclinical studies and clinical trials) have provided a premise that γ-aminobutyric acid (GABA) and $GABA_B$ receptors play a modulatory role in the mechanism of action of different drugs of abuse [4, 35, 70, 102, 132, 147, 158].

$GABA_B$ receptors

$GABA_B$ receptors, belonging to the metabotropic receptor family, were discovered at the end of the 1970s by the Bowery's research team [22] and were cloned in 1997 by Bettler et al. [81]. These receptors are composed of a heterodimer of $GABA_{B1}$ and $GABA_{B2}$ subunits [82, 116] (Fig. 1).

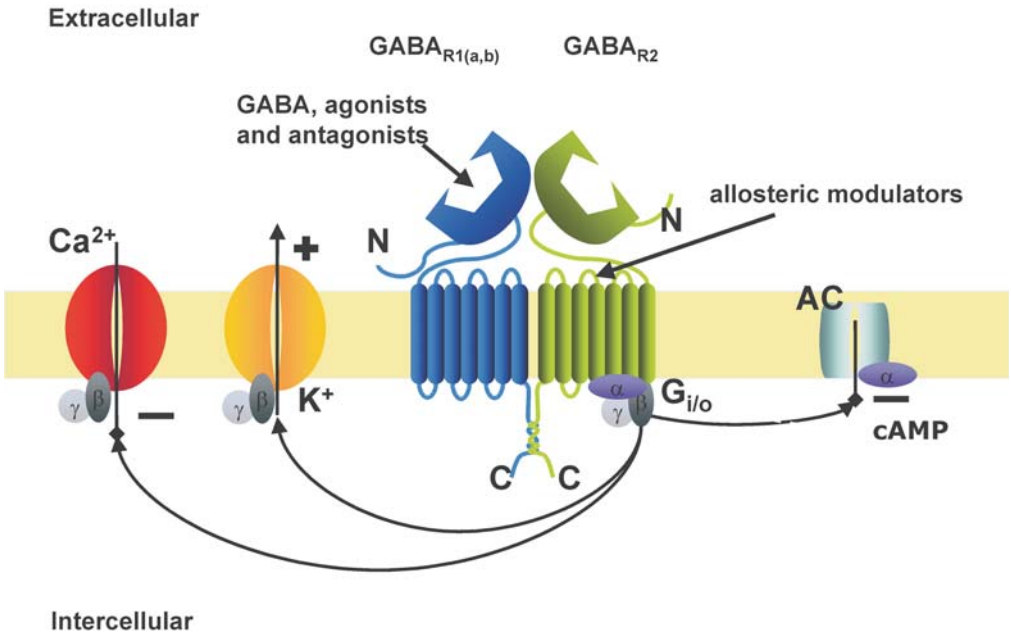

Fig. 1. Structure of the $GABA_B$ receptor and its intracellular signal effectors

Structure

The primary structure of both $GABA_B$ receptor subunits has been established. They are proteins with a molecular weight of 130 kDa and 110 kDa, respectively, and are composed of a chain of 961 ($GABA_{B1}$) and 940-941 ($GABA_{B2}$) amino acids. Both of them have a long, extracellular amino terminus, seven transmembrane domains and a short, intracellular carboxyl terminus forming a loop responsible for linking both subunits [14, 82]. The $GABA_{B1}$ subunit is encoded by a gene localized to chromosome 6p21.3 in humans [82, 113], 20p12 in rats [93] and 17B1 in mice [118]. It is interesting to note that molecular biology techniques (cloning) have allowed researchers to successfully distinguish at least eight biologically important isoforms of this subunit (a–h), with the a and b isoforms being indispensable for $GABA_B$ heterodimer formation [14]. The $GABA_{B1}$ subunit contains a long, extracellular amino acid chain, where binding sites for the endogenous neurotransmitter and ligands (agonists and antagonists) of $GABA_B$ receptors are located [87].

The $GABA_{B2}$ subunit is encoded by a gene localized to 9q22.1-22.3 in humans [116], 5q24 in rats [93] and 4B1 in mice [118]. It is known that this subunit (so-called „orphan") does not bind endogenous neurotransmitter or receptor ligands, but contains all the molecular determinants required for the recognition of G proteins and its activation [66, 123]. Moreover, the $GABA_{B2}$ subunit functions as a carrier of the $GABA_{B1}$ subunit and transports it from the endoplasmic reticulum to the cell surface [42]. The function of the $GABA_{B2}$ subunit is changed by so-called allosteric modulators, i.e., substances that can attach to the intramembrane domain of the $GABA_{B2}$ subunit [15, 154].

Interestingly, both $GABA_B$ receptor subunits interact with many intra- and extracellular proteins. Recently published studies on cell lines have demonstrated that the C-terminal domain of the $GABA_{B1}$ subunit binds ATF-4, 14-3-3 and tamalin, whereas the C-terminal of the $GABA_{B2}$ subunit binds the MUPP-1, CHOP (Gadd 153) and β-filamin proteins. These associated proteins fulfill different functions which include transcription factors (ATF-4, CHOP) that produce long-term metabolic changes implicating new protein synthesis after $GABA_B$ receptor activation, structural proteins and proteins that are engaged in migration (14-3-3, tamalin, MUPP-1), proteins responsible for receptor dimerization and synaptic localization, and proteins that anchor the $GABA_B$ receptor to the cell skeleton (β-filamin). Moreover, the

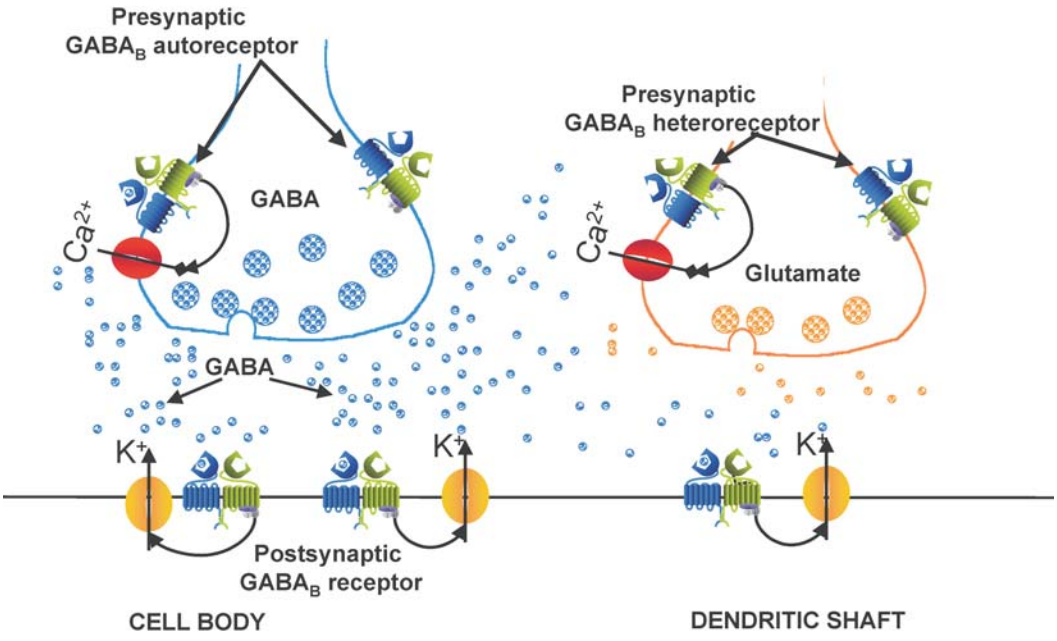

Fig. 2. Localization of $GABA_B$ receptors to synaptic sites

N-terminal of the $GABA_{B1}$ subunit has been shown to bind fibulin and HNK-1, i.e., extracellular proteins. The role of HNK-1 protein has not been elucidated, but fibulin has been suggested to participate in the synaptic localization of $GABA_{B1a}$ and $GABA_{B1b}$ isoforms [cf. 14].

Localization

$GABA_B$ receptors have been identified in both the central and peripheral nervous system. Within the central nervous system, the $GABA_B$ receptors are predominantly localized to neurons with their largest density in the thalamic nuclei, cerebellum, amygdala and cortex. Considerable densities of these receptors have also been detected in the hippocampus, habenula, substantia nigra, ventral tegmental area, nucleus accumbens septi, globus pallidus and hypothalamus [16, 23]. Other studies revealed that $GABA_B$ receptors are expressed in the spinal cord (ventral and dorsal horns) [99]. It is important to emphasize that the distribution pattern of the $GABA_{B1}$ and $GABA_{B2}$ subunit transcripts and proteins in many structures of the central nervous system are similar, except for the low expression of $GABA_{B2}$ mRNA in the basal ganglia (caudate nucleus, putamen), hypothalamus, olfactory bulb and spinal cord [34, 49].

Peripherally, $GABA_B$ receptors occur in the autonomic ganglia, in the spleen, urinary bladder, small intestine, lung, testis, stomach, pancreas, kidney, liver, oviducts, myocardium and skeletal muscles [120].

$GABA_B$ receptors are localized presynaptically on bodies and/or dendrites of GABAergic neurons (autoreceptors) and non-GABAergic neurons (heteroreceptors) or postsynaptically on non-GABAergic neurons [16, 82, 133] (Fig. 2). The presynaptic $GABA_B$ receptors are composed of the $GABA_{B1a}$ and $GABA_{B2}$ subunits, whereas the postsynaptic receptors are built with the $GABA_{B1b}$ and $GABA_{B2}$ subunits [16, 89].

Ligands

The discovery of the exogenous $GABA_B$ receptor ligand, baclofen, i.e., *p*-chlorophenyl-GABA, was a milestone in the characterization of these receptors. Baclofen, which was synthesized by Heinrich Keberle in 1962, 30 years before a $GABA_B$ receptor was cloned, is a lipophilic GABA derivative that is active after peripheral administration, and possesses a high affinity for the $GABA_B$ receptors and has a strong intrinsic activity. Baclofen is an optically active com-

pound, and its R isomer shows a three times greater affinity for $GABA_B$ receptors and has a more efficient action than the racemate. The next-generation $GABA_B$ receptor agonists, which are still structural baclofen analogues, were introduced in the 1980s and 1990s. These compounds, synthesized by the Swiss pharmaceutical company, NOVARTIS, and designated with the symbol CGP, exhibit a three- to sevenfold higher affinity for $GABA_B$ receptors compared to (R)-baclofen, high selectivity and easy penetration of the blood-brain barrier (Tab. 1) [62].

In the 1980s the first $GABA_B$ receptor antagonists, phaclofen, saclofen and 2-hydroxysaclofen, were synthesized. These compounds showed high receptor selectivity, but their low affinity for $GABA_B$ receptors (Tab. 1) and weak brain penetration after peripheral administration limited their use in pharmacological studies [84]. The first antagonists able to cross the blood-brain barrier and remain active after peripheral administration were compounds designated as CGP 35348, CGP 55845A and CGP 36742. However, their very low affinity for $GABA_B$ receptors limited their usability (Tab. 1) [63, 64]. Unlike the first-synthesized antagonists, another series of $GABA_B$ receptor blockers had a very high affinity for $GABA_B$ receptors, but did not cross the blood-brain barrier. Hence, they were used only for *in vitro* studies. The synthesis of SCH 50911 [17], a high-affinity (K_i = 6.42 nM), highly-selective and easily brain-penetrable (after oral treatment in animals) $GABA_B$ receptor antagonist was a breakthrough. Manipulations of the chemical structure of this antagonist yielded other derivatives (e.g., CGP 52432, CGP 54626, CGP 56999), which had similar binding characteristics and *in vivo* activity as SCH 50911 (Tab. 1).

It should be emphasized that like the endogenous neurotransmitter, all the above-described $GABA_B$ receptor ligands (either agonists or antagonists) bind to the $GABA_{B1}$ subunit and the binding site is localized to the extracellular domain (region) of the subunit [87]. Agonist binding closes and stabilizes this area and then activates the subunit, while antagonist binding prevents formation of the stable (closed) extracellular region of the $GABA_{B1}$ subunit [130].

$GABA_B$ receptor activity can be changed by so-called allosteric modulators, i.e., substances that bind to the intracellular domain of the $GABA_{B2}$ subunit and alter the $GABA_B$ receptor heterodimer in the open or high affinity confirmation [15, 154]. A number of compounds have been synthesized that fulfill the role of positive allosteric modulators. These compounds do not present with receptor affinity and intrinsic activity, but instead enhance both the affinity of the endogenous ligand for the $GABA_{B1}$ subunit and the signal transduction efficacy following agonist stimulation. GS 39783, CGP 7930 and its analogue, CGP 13501, as well as BHF177 and (+)-BHFF are ex-

Tab. 1. $GABA_B$ receptor ligands and their binding affinities

Drug	$GABA_B$ receptor affinity K_i (*IC_{50}) (nM)	References
Agonists		
(R)-Baclofen	4.57	cf. 129
(R,S)-Baclofen	14*	62
3-APPA (CGP 27492)	5	cf. 6
3-APMPA (SKF 97541, CGP 35024)	16*	cf. 129
CGP 44532	45*	cf. 65
CGP 47656	85*	62
Antagonists		
CGP 35348	4.92	cf. 129
CGP 36216	43000*	119
CGP 36742 (SGS 742)	4.84	cf. 129
CGP 46381	4900*	64
CGP 51176	6000*	64
CGP 52432	7.63	cf. 129
CGP 54626	8.85	cf. 129
CGP 55845	8.53	cf. 129
CGP 56999A	80*	cf. 67
CGP 62349	2*	cf. 6
CGP 64213	1.17*	cf. 67
CGP 71978	124*	121
CGP 71979	1460*	121
CGP 71980	326*	121
CGP 71982	8*	121
CGP 76290A	1.85*	121
CGP 76291A	69*	121
Phaclofen	13000*	cf. 20
2-OH-saclofen	11000*	cf. 6
NCS 382	2500*	cf. 129
Saclofen	26000*	cf. 20
SCH 50911	6.42	cf. 129

amples of such allosteric modulators [71, 100, 155, 156]. The allosteric modulators are devoid of the side effects typically associated with $GABA_B$ receptor agonists, and therefore, may offer an attractive and novel means to identify new leads for pharmacotherapy of several disorders, including drug addiction.

Functions

As mentioned above, the metabotropic $GABA_B$ receptors transmit intracellular signals *via* adaptor proteins of the G_i or G_o type (see Fig. 1). Ligand binding alters the conformation of the $GABA_{B1}$ subunit and then of the whole $GABA_{B1}$-$GABA_{B2}$ complex, which promotes the binding of a subunit of G_i or G_o protein to its intracellular domain, finally produces functional changes in the respective effectors, including intracellular enzymes (adenylate cyclase and phospholipase C) and ion channels (potassium and calcium channels). $GABA_B$ receptor stimulation usually inhibits adenylate cyclase activity and blocks cAMP synthesis [112]. Such an effect has been described for type I, II or V adenylate cyclase. $GABA_B$ receptor stimulation and adenylyl cyclase type III, IV or VII activation produces the opposite effect, namely, it raises the intracellular cAMP level. There is also evidence that the further activation of phospholipase C-coupled $G_{i\alpha}/G_{o\alpha}$ proteins by $GABA_B$ receptor agonists increases Ca^{2+} release from intracellular stores and enhances metabotropic glutamate receptor function.

Apart from the functional alterations of intracellular enzymes, $GABA_B$ receptor stimulation modifies ion channel function. In particular, the ligand-$GABA_B$ receptor-$G_{i/o}$ protein interaction promotes changes in neuronal membrane permeability to potassium ions. K^+ ions exit neuronal cells *via* different routes, including Kir3 potassium channels, SK calcium-activated potassium channels, and barium-sensitive Kir3 potassium channels. The most characteristic change induced by $GABA_B$ receptor stimulation is cell membrane hyperpolarization and IPSP generation [115, 131, 139]. The next group of $GABA_B$ receptor effectors comprises calcium ion channels [82]. As demonstrated in many *in vitro* systems, $GABA_B$ receptor stimulation and activation of the $G_{\beta\gamma}$ subunit of the $G_{i/o}$ protein led to both the blockade of Ca^{2+} influx into the cell through voltage-dependent N-type and P/Q-type calcium channels [167], and the modulation of voltage-dependent L- and T-type calcium channel activity [105, 141]. The former mechanism leads to a reduced release of different neurotransmitters from the presynaptic membrane.

Presynaptic $GABA_B$ receptors inhibit the release of GABA (as presynaptic autoreceptors) or acetylcholine, noradrenaline, serotonin, glutamic acid and dopamine (as presynaptic heteroreceptors) [18, 22, 75, 76, 85]. Most data have focused on the regulatory effect of presynaptic $GABA_B$ heteroreceptors on dopaminergic neuronal activity. It has been demonstrated that iontophoretically administration of the $GABA_B$ receptor agonist, baclofen, or peripheraly blocked the ventral tegmental area dopaminergic neuronal activity and its inhibitory effects were reversed by the $GABA_B$ receptor antagonist, CGP 35348 [50]. Similar inhibitory effects of baclofen on dopaminergic neuronal activity were observed in rat substantia nigra slices cultured *in vitro* [160]. A microdialysis study proved the inhibitory effect of baclofen on the release of dopamine in the striatum, nucleus accumbens septi and frontal cortex in mice [117] and rats [168], whereas a selective $GABA_B$ receptor antagonist, SCH 50911, increased dopamine release in the substantia nigra [51].

$GABA_B$ receptors control many other physiological functions in mammals. Experimental studies on animals have revealed that $GABA_B$ receptor agonists (but not their allosteric modulators) decrease muscular tension, suppress locomotor activity, lower body temperature and cause memory deficits [14, 21]. The contribution of the $GABA_B$ receptors in the above effects was corroborated by the lack of myorelaxation and hypothermic effects after baclofen administration to $GABA_B$ receptor knockout mice. Moreover, these animals showed spontaneous seizures leading to premature death, a decreased pain threshold, increased locomotor activity when exposed to a novel environment, cognitive deficits and retardation [14, 157]. Other studies have documented that the $GABA_{B1}$ or $GABA_{B2}$ subunit knockout had an antidepressant effect, but the anxiety level was elevated [106, 107].

The $GABA_B$ receptor is implicated in different pathological states associated with GABAergic neurotransmission deficits (e.g., status epilepticus, anxiety) [24, 41, 44, 59, 68, 125] and dopaminergic neurotransmission disruption (e.g., schizophrenia, addiction) [41]. By causing appropriate changes in animals' organisms, $GABA_B$ receptor agonists can also play the role of a stimulus in the discrimination test [32].

Baclofen is the most widely used $GABA_B$ receptor ligand. It acts on the spinal cord nerves and decreases the number and severity of muscle spasms caused by

multiple sclerosis or spinal cord diseases. It also improves muscle movement and is an efficient treatment for neuropathic pain, epilepsy or migraine [19, 21, 61]. Moreover, clinical trials of baclofen efficacy in bronchospasm (e.g., asthmatic dyspnea, [48]), gastrointestinal disturbances (e.g., gastroesophageal reflux or gastric hypersecretion, [40]) and urinary tract disorders (e.g., urination disturbances, [7]) are under way. Phase II clinical trials are also in progress to evaluate the use of $GABA_B$ receptor antagonists SGS742 (CGP 36742) as a memory-improving agent in patients diagnosed with Alzheimer's disease [cf. 57].

$GABA_B$ receptors and drugs of abuse

Preclinical studies

Preclinical studies of addiction are carried out on experimental animal models based either on the symptoms of abuse and addiction (psychomotor stimulation, subjective effects, rewarding/reinforcing properties, relapses), on the diagnostic criteria of addiction (compulsive drug use, drug craving) or on the analysis of different reinforcers (drug of abuse, cue-related conditioned stimuli, stress). It is important to note that there is no single animal model that can wholly reflect the complex symptomatology of addiction.

The most frequently used model in addiction studies is the self-administration paradigm. It allows researchers to investigate the principal components of addiction, i.e., spontaneous initiation, persistence and relapse to drug abuse; thus, it is the best simulation of drug abuse in humans. In this model, based on the positive reinforcement of instrumental reactions, the reaction of an animal (e.g., lever pressing) is rewarded by a dose of the drug (e.g., *via* intravenous route). Addiction intensity is easily quantifiable by measuring the number of drug injections and response rate to the drug-associated lever [142].

Another instrumental model used to study the rewarding properties of drugs of abuse in laboratory animals is the self-stimulation model. In this model, animals lever-press for trains of impulses delivered by a stimulator to an electrode implanted in a specific brain structure (e.g., medial forebrain bundle). The persistent drug-appropriate lever responding indicates that the animal has experienced pleasure. Drugs of abuse enhance the self-stimulation reaction, more precisely speaking, they lower the self-stimulation threshold. The rewarding properties of drugs of abuse can also be investigated by the conditioned place preference test. In this test, an animal is trained for several sessions to associate the injection of a drug of abuse and its vehicle with the environmental cues, as the test chambers differ in color, odor and/or surface structure. Thereafter, one can investigate to what degree the animal prefers to spend more time in the chamber paired with the reinforcing drug [142].

Some addictive substances increase locomotor activity in rodents, and a repeated intermittent drug administration induces sensitization to this effect, while constant exposure to the drug produces tolerance. Neuroadaptations underlying sensitization are thought to resemble those that are responsible for addictive behaviors. An increased understanding of the molecular mechanisms of sensitization could lead to improved treatments for addiction [142].

Extinguishing of an instrumental reaction and induction of reinstatement (by the unconditioned stimulus, i.e., the drug of abuse or a conditioned stimulus associated with the intravenous drug injections during the acquisition stage in trained animals), along with expression of sensitization or expression of conditioned place preference to drugs of abuse, are also used to investigate drug craving and relapses after repeated exposure to the drug of abuse [142].

Apart from the above-described behavioral effects, drugs of abuse produce an interoceptive stimulus that allows animals to distinguish the psychoactive drug from its vehicle in the drug discriminations test. In this model, an animal is trained to perform a certain instrumental reaction (e.g., lever pressing) in response to a conditioned stimulus, signaling availability of the reinforcer (e.g., water in water-deprived animals). After a long training, animals discriminate between the training substance and its vehicle. The drug discrimination model can be used to study the behavioral and pharmacological effects of different drugs, and the discriminative properties of drugs of abuse in animals seem to be closely related to the self-reported effects in humans. What is more, the use of different drugs of abuse in this model (several times a week, intermittently) can resemble, to some extent, the addiction cycle with the alternating phases of maintenance and reinstatement of drug abuse. In the drug discrimination model, examination of another drug than the training substance aims to determine whether it is able

to elicit the same reaction as the training drug (in the substitution tests – when drugs substituted for the training substance "mimic" its effects) or whether it can change the discriminating effects of the training drug during combined treatment in the augmentation or antagonism tests [142].

Laboratory animals that are repeatedly treated with drugs of abuse and then withdrawn from this treatment exhibit behavioral symptoms of withdrawal (anxiety, depression, anhedonia, dysphoria, sleep disturbances, hyperphagia, decreased locomotor activity), which correlates well with the deficits observed in humans during an abstinence period. Dysphoric symptoms have been detected in the conditioned place preference model during cocaine withdrawal [52]. The anhedonic symptoms have been identified in the intracranial self-stimulation model, in which cocaine-, amphetamine- and nicotine-withdrawn rats exhibited an increased rewarding stimulus threshold (electrical stimulation) [73, 103]. In the modified forced swim test in rats [45], withdrawal from chronic continuous infusion of amphetamine (*via* minipump) [43] or withdrawal from cocaine self-administration [60] resulted in a prolonged immobility time indicative of an increase in "depressive-like" behavior. In the mouse tail suspension test, withdrawal from chronic continuous infusion of amphetamine (*via* minipump) induced increases in immobility scores, indicative of "depressive-like" behavior [43].

$GABA_B$ receptors and rewarding effects of drugs of abuse

Recently published data have provided a premise for a modulatory role of GABA and its B type receptors in the mechanism of the rewarding action of different drugs of abuse. Numerous observations indicate that a tonic activation of the $GABA_B$ receptors is irrelevant to the rewarding effects of morphine and cocaine, since selective antagonists of these receptors (CGP 56433A, SCH 50911) changed neither the dose of intravenously self-administered cocaine [28, 56] nor the expression of morphine-induced conditioned place preference [153]. On the other hand, pharmacological stimulation of these receptors by agonists did modify the rewarding effects of cocaine. For examples, peripherally administered baclofen prevented the acquisition of cocaine self-administration, peripheral or local (into the ventral tegmental area or nucleus accumbens septi) administration of $GABA_B$ receptor agonists (baclofen, CGP 44532, SKF 97541) or positive allosteric modulators of these receptors (CGP 7930, GS 39783) suppressed the rewarding effects of cocaine in different self-administration models in rats and baboons (see Tab. 2; [146]) and reversed the effects of cocaine in the intracranial self-stimulation model, and repeated administration (three days) of baclofen to rats had an inhibitory effect on the rewarding effects of cocaine [143]. The inhibitory effects of baclofen, SKF 97541 and CGP 7930 did not develop in animals that had previously received the $GABA_B$ receptor antagonist, SCH 50911, which indicates that the $GABA_B$ receptors are implicated in the above-mentioned effects of agonists and positive modulators.

Stimulation of the $GABA_B$ receptor with agonists and positive modulators also prevented or weakened the rewarding effects of many other drugs of abuse, including methamphetamine in the self-administration model and the conditioned place preference paradigm, nicotine in the self-administration and conditioned place preference model, heroin or morphine in the self-administration model, and morphine in the condition place preference procedure, and suppressed ethanol self-administration (see Tab. 2; [94, 97, 122, 128]).

Summarizing the obtained data, the tonic activation of the $GABA_B$ receptors is not a prerequisite for the rewarding properties of cocaine and morphine, but their pharmacological stimulation weakens the reinforcing properties of cocaine and other drugs of abuse. It is worth emphasizing that $GABA_B$ receptor agonists are characterized by low selectivity (only threefold) for the motivational behaviors (cocaine *vs.* food) [10, 27, 56, 114], which indicates that these compounds provoke a general motivational decline. Unlike the $GABA_B$ receptor agonists, administration of the positive allosteric modulator of $GABA_B$ receptors, CGP 7930, at doses that are able to inhibit the rewarding effects of cocaine did not modify food self-administration [56].

$GABA_B$ receptors and reinstatement of drug-seeking behavior

Studies addressing the implication of the $GABA_B$ receptor in the reinstatement of drug-seeking behavior have revealed that tonic activation of the $GABA_B$ receptors was essential for the expression of drug-seeking after cocaine withdrawal, since the antagonist of these receptors, SCH 50911, reduced cocaine-

appropriate lever responding reinstated by the cocaine challenge (10 mg/kg, *ip*) or by a conditioned stimulus [55]. Considering the significant similarities between the conditioned stimulus-induced reinstatement of drug-seeking behavior in animals and the relapses of drug abuse in humans [33, 77], it appears that the stronger inhibitory effect of SCH 50911 on the conditioned stimulus-induced reinstatement than on the cocaine challenge-induced relapse corroborates the use of this antagonist in relapse prevention strategies.

The alleviation of cocaine-seeking behavior by SCH 50911 seems to rely on its influence on the reinstatement induced by cocaine self-administration rather than on other processes, e.g., locomotor activity or discriminating stimulus [56], which could nonspecifically change the animals' reactions. It appears that the contribution of the amnestic properties of SCH 50911 can also be excluded, since other $GABA_B$ receptor antagonists (CGP 35742, CGP 56433, CGP 61334) quicken learning and enhance the acquisition phase in animals [69, 109]. Additionally, SCH 50911 did not alter the number of active lever-pressing responses during the food-induced reinstatement of seeking behavior, which provides further evidence for the specificity of this compound for the reinstatement in animals with an extinguished cocaine self-administration reaction.

Furthermore, the ability of $GABA_B$ receptor stimulation to both weaken or block the cocaine challenge- or conditioned stimulus-induced reinstatement of drug-seeking in rats and baboons in the extinguishing phase of cocaine self-administration, and abate the locomotor stimulation in rats exposed to the environmental cues associated with repeated cocaine exposure (Tab. 2) provides additional support for the involvement of the $GABA_B$ receptor in the reinstatement of drug-seeking behavior. Baclofen also inhibits the heroin challenge- and conditioned incentive-induced reinstatement of drug-seeking behavior in animals trained to self-administer heroin, the alcohol-induced relapse in rats self-administering alcohol and the reinstatement elicited by nicotine self-administration-associated cues (Tab. 2).

It is interesting to note that $GABA_B$ receptor agonists (baclofen, SKF 97541) have been shown to pre-

Tab. 2. Preclinical evaluation of the $GABA_B$ receptor agonists in the behavioral responses to drugs of abuse

Model	Drug of abuse				
	Cocaine	Amphetamines	Nicotine	Opiates	Alcohol
Self-administration:					
– acquisition	↓ [31]	↓ [25, 135]	↓ [54, 104, 127]	↓ [26, 168, 169]	↓ [8, 36, 38, 39, 78, 98, 110, 151, 161]
– maintenance	↓ [29, 56, 137, 143]				
Reinstatement of drug-seeking:					
– drug-induced	↓ [31, 55]		↓ [126]	↓ [46, 149]	↓ [36, 39]
– cue-induced	↓ [46, 55, 162]				↓ [39, 96]
Self-stimulation	↓ [145]				
Conditioned place preference:					
– acquisition		↓ [92]	↓ [80]	↓ [46, 153]	
– expression		↓ [92]	↓ [108]		
Conditional locomotion	↓ [74]				
Behavioral sensitization:					
– acquisition	↓ [124]	↓ [11]		↓ [166]	
– expression	↓ [124]	↓ [12]		↓ [13, 91]	
Drug discrimination	∅ [10, 55, 114]			∅ [148]	

↓ – attenuation; ∅ – lack of effect

vent the cocaine challenge-induced relapse at doses that are two to three times lower than the doses needed to block the effect of the conditioned stimulus [55]. The opposite effect was observed with the positive allosteric modulator of $GABA_B$ receptors, CGP 7930, which was more efficient in preventing the effects of the cue than cocaine [55].

The $GABA_B$ receptor agonists, baclofen and SKF 97541, both suppressed the reinstatement of drug-seeking behavior induced by food presentation, but those inhibitory effects were observed only after administering four or ten times higher doses than those required to alleviate drug seeking after cocaine withdrawal [55]. The observation that baclofen induces a lowering of basal locomotor activity provides additional evidence that indicates that the influence of this compound on the expression of drug-seeking behavior after cocaine withdrawal is nonspecific [55]. Taken together, the results from all of these studies suggest that the antagonist, agonists and positive allosteric modulators of the $GABA_B$ receptors temper the cocaine-seeking behavior. Pharmacological stimulation of $GABA_B$ receptors by baclofen and SKF 97541 (but not CGP 7930) also suppressed the reinstatement of food intake [55], indicating that the intensification of GABAergic neurotransmission *via* these receptors deteriorates general motivation. The above results substantiate the use of $GABA_B$ receptor antagonists to alleviate drug cravings and relapses in cocaine abusers, whereas the inhibitory effects of the agonists and positive allosteric modulators of these receptors are due either to a nonspecific action by baclofen and SKF 97541 or to the blockade of the rewarding effect of cocaine by CGP 7930 [55, 56].

The $GABA_B$ receptor agonist, baclofen, results in the complete suppression of the extra-amount of alcohol consumed during the re-access to alcohol seven days after deprivation [37] or attenuates the cue-induced reinstatement of alcohol-seeking behavior [96] in selectively-bred Sardinian alcohol-preferring rats.

$GABA_B$ receptors and locomotor effects of drugs of abuse

Baclofen inhibits the acquisition and expression of amphetamine, cocaine and opiate sensitization in rats (Tab. 2).

$GABA_B$ receptors and discriminative effects of drugs of abuse

A multitude of literature data indicates that the discriminative effects of cocaine in rats were not changed by the $GABA_B$ receptor antagonist (SCH 50911), agonists (baclofen and SKF 97541) or the positive allosteric modulator (CGP 7930) (Tab. 2, [56]). Additionally, baclofen also did not alter the discriminative effects of heroin in rats (Tab. 2). These data, along with the inabilities of SCH 50911, SKF 97541 or CGP 7930 to substitute for cocaine [56] and of baclofen to substitute for cocaine [56] or heroin [148] in the substitution test (maximum 15% of drug-appropriate lever responding), seem to exclude the possibility of a $GABA_B$ receptor-cocaine and a $GABA_B$ receptor-heroin interaction.

$GABA_B$ receptors and withdrawal symptoms

Baclofen inhibited the naloxone-induced withdrawal syndrome in mice that were chronically treated with morphine [47, 83] and counteracted the withdrawal-induced anxiety in rats that were chronically exposed to ethanol [86]. Baclofen, SKF 97541, CGP 7930 and SCH 50911 diminished the withdrawal-related prolongation of the immobility time in the forced swim test in rats exhibiting depressive behavior during withdrawal from cocaine self-administration [58]. The $GABA_B$ receptor antagonist, SCH 50911, was the most efficient in the latter paradigm. These results suggest that both of the $GABA_B$ receptor ligands possess therapeutic efficacy in inhibiting the withdrawal symptoms in drug abusers.

$GABA_B$ receptor ligands and neurochemical effects of drugs of abuse

It is commonly accepted that the behavioral responses (i.e., reinforcing and locomotor effects) of several abused substances are strongly related to increases in dopamine concentrations in the nucleus accumbens [cf. 88, 165]. Microdialysis experiments have demonstrated that baclofen attenuates the non-contingent cocaine-, nicotine- and morphine-induced increases in accumbal dopamine levels [53, 111]. Furthermore, following systemic administration of baclofen, a significant decrease in accumbal dopamine efflux was observed in rats trained to self-administer amphetamine [25]. A suggested mechanism by which baclofen

may inhibit activity in the dopamine system could involve stimulation of the $GABA_B$ receptors located on the cell bodies of dopamine neurons in the ventral tegmental area [23, 95, 164] that project into the nucleus accumbens. Baclofen-induced hyperpolarization of these dopamine cell bodies could potentially inhibit dopamine release in the nucleus accumbens. To confirm such a hypothesis, it was reported that local infusion of baclofen into the ventral tegmental area reduced dopamine efflux in the nucleus accumbens in cocaine [29] or heroin [163, 168, 170] self-administered rats. To summarize, the data from neurochemical studies suggest that baclofen may inhibit the increases in mesolimbic dopamine transmission caused by drugs of abuse.

Apart from effects of baclofen on dopamine neurotransmission, its effects on other neurotransmitters in other brain regions implicated in drug reinforcement should be also taken into account. Thus, baclofen attenuates the extracellular glutamate levels in the nucleus accumbens in rats during conditioned locomotion to cues associated with cocaine administration [74]. Steninger and Kretschmer [150] reported that baclofen infused into the pedunculopontine tegmental nucleus – an area receiving glutamatergic and GABAergic input – decreases local dopamine release. Both dopaminergic and glutaminergic systems have been suggested to have a significant role in drug-seeking behavior (for review see [79, 90, 102, 136, 138, 140]). $GABA_B$ receptors are widely distributed in several brain areas related to drug seeking where they modulate both the excitatory and the inhibitory components of pre- and postsynaptic mechanisms [152]. In the ventral tegmental area, $GABA_B$ receptors act as heteroreceptors present on dopamine and glutamatergic neurons [23, 95, 164] as well as presynaptic autoreceptors on GABA interneurons [134]. Activation of these receptors by local injection of baclofen suppresses extracellular dopamine levels in the nucleus accumbens [53] and prefrontal cortex [163, 168, 170]. In the prefrontal cortex, $GABA_B$ receptors are localized on the presynaptic terminals of the glutamatergic nerve endings and/or cell bodies [101] and on GABA neurons where they act as autoreceptors [30].

Clinical trials

Preliminary clinical trials have revealed that baclofen, a $GABA_B$ receptor agonist, reduces cocaine use in cocaine addicts [144], cocaine self-administration in non-opioid dependent cocaine smokers [72] and limbic (amygdala) system activation during presentation of the cocaine use-associated cues [26, 159]. On the other hand, baclofen did not change the subjective effects of cocaine (the "high" feeling) [72], while data on its effects toward withdrawal-induced cocaine cravings are inconsistent [26, 144]. Baclofen was effective in reducing the subjective effects of nicotine in smokers and promoting abstinence from nicotine [cf. 41] as well as attenuating opiate withdrawal in dependent subjects [9].

In the preliminary, double-blind studies, baclofen was found to decrease the obsessive and compulsive components of craving [3] as well as alcohol intake [1–3] in subjects totally abstinent from alcohol. Additionally, some recent limited clinical trials show that baclofen was able to suppress alcohol withdrawal symptoms, including state anxiety (but not depressive symptoms) [3] and delirium tremens [5]. Baclofen is currently finding use in treating addiction as an effective medication in inducing abstinence from alcohol and reducing alcohol craving and consumption in alcoholics [3] and seems to be generally well-tolerated [cf. 3]. Further clinical investigations are needed to determine if long-term treatment with baclofen results in off-target effects and tolerance.

Conclusions

The currently-available knowledge of $GABA_B$ receptors supports the opinion that pharmacological manipulation of this receptor heterodimer can efficiently counteract the effects of drugs of abuse-induced withdrawal and prevent reinstatement of the abuse. Baclofen, the $GABA_B$ agonist, is currently finding use in treating addiction, but its off-target effects and the development of tolerance to it may limit its utility. Further intensive studies are needed to precisely define both the effects of antagonists and positive allosteric modulators of the $GABA_B$ receptor and the modes of implication for the mechanism of drugs of abuse.

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Received:
June 10, 2008; in revised form: November 11, 2008.