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Don't worry 'B' happy!: a role for $GABA_B$ receptors in anxiety and depression

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GABA, the main inhibitory neurotransmitter in the brain, regulates many physiological and psychological processes. Thus, dysfunction of the GABA system is implicated in the pathophysiology of several neuropsychiatric disorders, including anxiety and depression. However, the role of $GABA_B$ receptors in behavioural processes related to these disorders has not been resolved. $GABA_B$ receptors are G-protein-coupled receptors that function as heterodimers of $GABA_{B(1)}$ and $GABA_{B(2)}$ subunits. In addition to highly selective agonists and antagonists, novel $GABA_B$ receptor tools have been developed recently to further assist elucidation of the role of $GABA_B$ receptors in CNS function. These include mice that lack functional $GABA_B$ receptors, and novel positive modulators of the $GABA_B$ receptor. In this review, we discuss evidence that points to a role of $GABA_B$ receptors in anxiety and depression.

GABA is the main inhibitory neurotransmitter in the brain and GABA-mediated neurotransmission regulates many physiological and psychological processes. There are two major classes of GABA receptors: ionotropic $GABA_A$ (including $GABA_C$) receptors and metabotropic $GABA_B$ receptors [1–3]. In 1980, Bowery and colleagues were the first to characterize pharmacologically metabotropic $GABA_B$ receptors as receptors that are insensitive to the $GABA_A$ receptor antagonist bicuculline [3]. Baclofen is a selective agonist at $GABA_B$ receptors. Presynaptic $GABA_B$ receptors modulate neurotransmitter release by depressing Ca^{2+} influx via voltage-activated Ca^{2+} channels (Figure 1) [3]. Such presynaptic inhibition at GABAergic terminals is involved in the induction of long-term potentiation [3]. Postsynaptic $GABA_B$ receptors are coupled mainly to inwardly rectifying K^+ channels [4] and mediate slow inhibitory postsynaptic potentials (Figure 1) [3]. $GABA_B$ receptors are abundant in the brain, where they are localized in many neuronal cell types including interneuron populations and some glial cells (Figure 1). High levels of expression of $GABA_B$ receptors in the limbic system [5] indicate a role in regulating emotional behaviour. In this review, we summarize knowledge of the function of $GABA_B$ receptors in the brain. In particular, we focus on the recent development of novel pharmacological and genetic tools that have advanced knowledge on the role of $GABA_B$ receptors in emotional disorders such as anxiety and depression.

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$GABA_B$ receptors

The first $GABA_B$ receptor cDNAs were isolated in 1997 [6]. The identification of a second $GABA_B$ receptor protein soon after led to the discovery that native $GABA_B$ receptors are heterodimers of two subunits, $GABA_{B(1)}$ and $GABA_{B(2)}$ (Figure 1) (reviewed in [7,8]). In the brain, two predominant, differentially expressed isoforms are transcribed from the *Gabbr1* gene, $GABA_{B(1a)}$ and $GABA_{B(1b)}$, which are conserved in different species including humans [6,9,10]. In the rat brain $GABA_{B(1a)}$ is the prevalent isoform at birth whereas $GABA_{B(1b)}$ is more abundant in adult brain tissue [9]. Transcription of these isoforms is driven by different promoters and does not involve alternative splicing. Recently, evidence shows that $GABA_{B(1a)}$ and $GABA_{B(1b)}$ promoters are regulated differentially by cAMP-response-element-binding protein (CREB), activating transcription factor 4 (also known as CREB2) and depolarization-sensitive upstream stimulatory factor [11]. Although there is some evidence of differential association of $GABA_{B(1a)}$ and $GABA_{B(1b)}$ with presynaptic and postsynaptic structures, respectively, no conclusive picture has emerged to date [7]. It seems more likely that, depending on the brain region, $GABA_{B(1a)}$ and $GABA_{B(1b)}$ participate in the formation of both presynaptic and postsynaptic receptors through heterodimerization with $GABA_{B(2)}$.

Additional isoforms (splice variants) of *Gabbr1* have been described [termed $GABA_{B(1c–g)}$], but their physiological significance is unclear. Partial cDNAs that correspond to putative $GABA_{B(2)}$ splice variants have also been isolated [12]. However, investigation of the *Gpr51* (*Gabbr2*) gene structure provides no evidence that these cDNAs correspond to additional isoforms of $GABA_{B(2)}$ [13]. Therefore, it seems likely that two major populations of heteromeric $GABA_B$ receptors exist in the brain: one containing $GABA_{B(1a)}$ and $GABA_{B(2)}$ subunits and the other containing $GABA_{B(1b)}$ and $GABA_{B(2)}$ subunits. The behavioural phenotypes of mice with targeted deletions of either $GABA_{B(1)}$ [14,15] or $GABA_{B(2)}$ subunits [16] are similar and corroborate *in vitro* experiments that demonstrate that functional $GABA_B$-receptor-mediated

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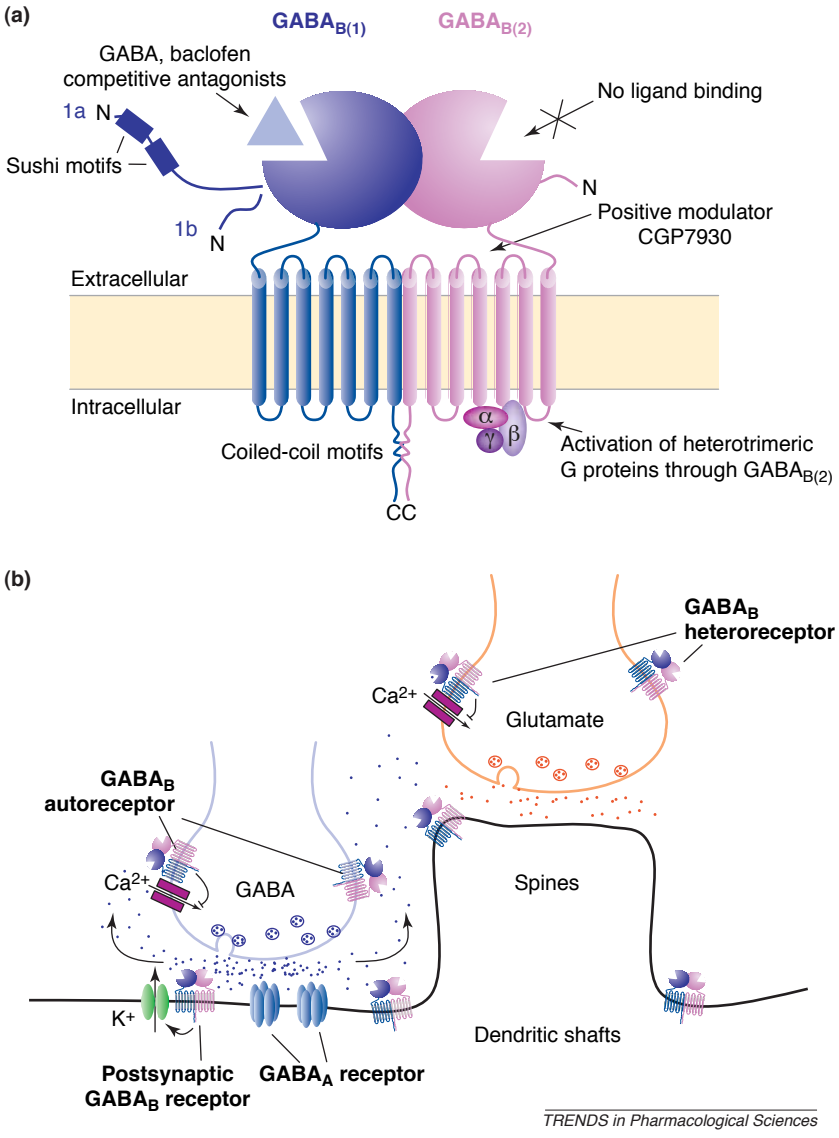

Figure 1. The GABA$_B$ receptor heterodimer and its localization in the brain. **(a)** Native GABA$_B$ receptors are heterodimers of two subunits, GABA$_{B(1)}$ and GABA$_{B(2)}$ (dark blue and violet, respectively). Heterodimerization is facilitated through coiled-coil motifs within their C-termini, and also involves interactions between the transmembrane and extracellular domains. All known GABA$_B$ receptor agonists and competitive antagonists bind to the GABA$_{B(1)}$ subunit only, whereas G-protein activation is facilitated through the GABA$_{B(2)}$ subunit. Two predominant GABA$_{B(1)}$ isoforms [GABA$_{B(1a)}$ and GABA$_{B(1b)}$], which differ at their N-termini, are expressed in the brain. GABA$_{B(1a)}$ is distinguished from GABA$_{B(1b)}$ by the presence of two 'Sushi' motifs. Mutagenesis studies and the lack of evolutionary conservation indicate that the extracellular domain of GABA$_{B(2)}$ is not the binding site of a natural ligand [72]. Recently, the binding site of the positive allosteric modulator CGP7930 has been localized to the transmembrane region of GABA$_{B(2)}$ [25]. **(b)** In the hippocampus, GABA$_B$ receptors are located presynaptically, postsynaptically and on extrasynaptic membranes. Presynaptic GABA$_B$ autoreceptors on GABA-releasing terminals inhibit the release of GABA, whereas GABA$_B$ heteroreceptors inhibit the release of several other neurotransmitters (e.g. glutamate) and bioactive peptides. Postsynaptic GABA$_B$ receptors activate K$^+$ channels and induce slow inhibitory postsynaptic potentials, the fast component of which is mediated through GABA$_A$ receptors. Extrasynaptic receptors are likely to be activated by 'spill-over' of GABA from adjacent synapses. Redrawn and modified, with permission, from [73].

responses depend on heterodimerization of GABA$_{B(1)}$ and GABA$_{B(2)}$ subunits. Furthermore, the lack of physiological GABA$_B$-receptor-mediated responses in either GABA$_{B(1)}$- or GABA$_{B(2)}$-receptor-deficient mice confirms that established functions of presynaptic and postsynaptic GABA$_B$ receptors are mediated through heterodimers of GABA$_{B(1)}$ and GABA$_{B(2)}$ [14–17], which renders the existence of additional subtypes unlikely.

Agonists

Baclofen (β-p-chlorophenyl-GABA), the prototype for GABA$_B$ receptor agonists was synthesized first in 1962 by the CIBA chemist Heinrich Keberle and shown to exert potent muscle-relaxant and analgesic properties [18]. Baclofen has been an invaluable pharmacological tool in elucidating the role of GABA$_B$ receptors in several disorders including epilepsy, cognition, pain, gastroesophageal reflux disease and addiction [3]. Furthermore, baclofen has been used clinically to treat spasticity for >30 years [19], long before the GABA$_B$ receptor was identified. A second and third generation of GABA$_B$ receptor agonists emerged in the 1980s and 1990s, including CGP27492 (see Chemical names) and CGP44532, respectively [18].

Antagonists

In the late 1980s, phaclofen, saclofen and 2-hydroxysaclofen were the first selective antagonists of the $GABA_B$ receptor to be described [20]. Despite relatively low affinities for the $GABA_B$-receptor-binding site, these antagonists have been key tools in defining the pharmacological and physiological relevance of $GABA_B$ receptors [3]. More-potent and selective $GABA_B$ receptor antagonists (phosphinic acid derivatives) such as CGP36742 (also known as SGS742), CGP55845A and CGP56433A were developed in the 1990s, mainly at Ciba–Geigy [now Novartis (http://www.nibr.novartis.com)] by Froestl, Bittiger and colleagues [18]. These second-generation $GABA_B$ receptor antagonists are used widely in research, and several have shown promising results in preclinical behavioural models [3]. Currently, the CGP36742 is in Phase II clinical trials for cognition-enhancing activity in mild cognitive impairment and mild–moderate Alzheimer's disease [Saegis Pharmaceuticals (http://www.saegispharma.com/)] [21].

Allosteric, positive modulators

Allosteric, positive modulation of metabotropic receptors is a novel way to pharmacologically manipulate G-protein-coupled receptors that act at a site that is distinct from the orthosteric binding region of the receptor protein [22]. Allosteric modulators are thought to offer several potential pharmacological improvements compared with conventional agonists, as is the case with modulators that act at ligand-gated ion channels. Modulators of $GABA_A$ receptors are used therapeutically: for example, benzodiazepines amplify the action of the endogenous neurotransmitter GABA at the $GABA_A$ receptor. More recently, novel, allosteric positive modulators of $GABA_B$ receptors, namely CGP7930 and the more efficacious compound GS39783, have been identified and characterized *in vitro* [23,24]. CGP7930 and GS39783 enhance both the potency and the maximal efficacy of GABA at $GABA_B$ receptors in both native and recombinant receptor preparations. Positive, allosteric modulators, such as GS39783, do not induce $GABA_B$-receptor-mediated responses when applied without GABA, and their effects are sensitive to competitive $GABA_B$ receptor antagonists such as CGP55845A and CGP54626A [23]. The actions of CGP7930 and GS39783 are selective insofar as no activity is observed at the related metabotropic glutamate $mGlu_2$ receptor [23,24]. The binding site of CGP7930 in the $GABA_B$ receptor heterodimer has been localized recently to the transmembrane region of $GABA_{B(2)}$ [25].

In tests of motor ability (rotarod and locomotor activity) GS39783 is devoid of sedative activity and cognitive impairment compared with baclofen and the anxiolytic agent chlordiazepoxide [26]. Therefore, for therapeutic use, positive modulators of the $GABA_B$ receptor might have advantages over full agonists in treating disorders in which sedation and muscle relaxation are undesired. GS39783 also differs from baclofen because it has no intrinsic influence on body temperature whereas baclofen induces a marked hypothermia [26].

$GABA_B$ receptor knockout mice

The availability of mice that lack subunits of the $GABA_B$ receptor adds new tools to investigate $GABA_B$ receptor function. Three groups of investigators have generated $GABA_{B(1)}{}^{-/-}$ mice [14,15,17]. Interestingly, mice generated on a C57BL/6 genetic background do not survive into adulthood whereas those on a BALB/c background do survive into adulthood [14]. The phenotype of these mice provides further evidence for a role of $GABA_B$ receptors in epilepsy, sensorimotor gating, nociception and temperature regulation, in addition to psychiatric disorders. Recently, mice that lack the $GABA_{B(2)}$ subunit have been generated [16] that have essentially the same overt, behavioural phenotype as $GABA_{B(1)}{}^{-/-}$ mice. These data demonstrate that the absence of heteromeric $GABA_{B(1)}$–$GABA_{B(2)}$ receptors underlies these phenotypes.

In contrast to $GABA_{B(1)}{}^{-/-}$ mice, atypical electrophysiological $GABA_B$-receptor-mediated responses have been recorded from hippocampal slices in $GABA_{B(2)}{}^{-/-}$ mice [16]. The spatial and temporal expression of $GABA_{B(1)}$ and $GABA_{B(2)}$ subunits does not always match precisely [7]. Therefore, it is possible that functional $GABA_B$ receptors that incorporate $GABA_{B(1)}$ are formed in neurons that lack $GABA_{B(2)}$ subunits. Further studies are needed to support this hypothesis.

$GABA_B$ receptors and anxiety

Anxiety can be viewed as an appropriate, adaptive response to impending danger that is integral to an organism's preparations to either cope with or avoid a potential environmental threat [27]. Anxiety disorders, the pathological manifestation of anxiety, are prevalent, chronic and disabling, and include generalized anxiety disorder, obsessive–compulsive disorder, panic disorder, post-traumatic stress disorder and social and specific phobias [28]. The neurobiological mechanisms that underlie anxiety disorders are not fully understood, but recent advances in human imaging show that dysfunction in brain areas such as the amygdala, anterior cingulate cortex, hippocampus and medial prefrontal cortex might be responsible [29]. Pharmacological treatment for anxiety disorders involves targeting either the GABA using benzodiazepines or 5-HT systems using $5\text{-}HT_{1A}$ receptor agonists and selective 5-HT reuptake inhibitors (SSRIs) [30]. These approaches have drawbacks because benzodiazepines have many unwanted side-effects, including tolerance, sedation, cognitive impairments and ethanol interactions, and, generally, the onset of action of 5-HT receptor ligands is slow [30].

Although GABA-mediated neurotransmission has long been known to have a crucial role in anxiety, data on the specific role of $GABA_B$ receptors are limited and variable [31]. Largely, this is because investigators have relied on baclofen for such analysis, which has a narrow window of efficacy before confounding side-effects are manifested in anxiety paradigms [32]. Renewed interest in the role of $GABA_B$ receptors in anxiety has emerged recently because $GABA_{B(1)}$-deficient mice are more anxious than their wild-type counterparts in several anxiety-related tests such as the light–dark box and staircase test (Table 1) [33]. Furthermore, $GABA_{B(1)}$-deficient mice have a panic-like

response on an elevated zero maze and quickly jump off [33]. Interestingly, the anxiolytic-like effects of benzodiazepines are markedly diminished in $GABA_{B(1)}$-deficient mice [34].

These data indicate that activation of $GABA_B$ receptors might reduce anxiety. In accordance with this, and despite its weakness as a behavioural tool, baclofen has anxiolytic-like effects in several preclinical tests. It reduces separation-induced calling by mouse pups [35], enhances punished drinking in rats [36,37] and has an anxiolytic-like response to novelty in a T-maze [38]. Furthermore, baclofen also reverses the anxiogenic response induced by withdrawal from chronic diazepam and alcohol treatment [39–41]. Clinically, baclofen reverses the anxiety associated with alcohol withdrawal [42], post-traumatic stress [43], panic disorder [44] and traumatic spinal-cord lesions [45].

More recently, the positive modulator GS39783 has been shown to be active in several animal models of anxiety, including ethological tests such as the elevated zero maze in mice and rats, the elevated plus maze and the light–dark box [26,33]. Furthermore, GS39783 reverses stress-induced hyperthermia in mice [26]. This latter paradigm gives an objective analysis of the physiological response to anxiety (in this case the anticipatory anxiety caused by an acute stressor) and has been validated extensively as a preclinical paradigm that is useful in detecting conventional and putative anxiolytics [46]. The anxiolytic effects of chronic administration of GS39783 persist over 21 days [33], which indicates that there is no obvious tolerance, and no interaction with ethanol was observed [26]. Both of these side-effects are associated with benzodiazepines [47]. However, chronic treatment with the $GABA_B$ receptor antagonist CGP56433A does not induce an anxiogenic response [33]. This indicates that although mice deficient in $GABA_B$ receptor subunits are useful in providing clues to the role of $GABA_B$ receptors in some behaviours, the responses observed do not necessarily recapitulate the effects of antagonists in wild-type animals. Thus, data from genetically modified animals must be interpreted cautiously [48]. Further studies are needed to characterize the anxiolytic potential of other positive modulators of $GABA_B$ receptors but current data indicate that they might represent a novel class of anxiolytic with a superior side-effect profile than benzodiazepines. The mechanisms responsible for the influence of $GABA_B$ receptors on anxiety behaviour are not well understood. Therefore, future studies should focus on behavioural and electrophysiological responses of $GABA_B$ receptor activation in key brain regions that are associated with anxiety.

$GABA_B$ receptors and depression

Although depression is seen largely as a dysfunction in monoamine neurotransmission and all antidepressant strategies focus largely on monoamines [49], strong clinical and preclinical evidence implicates dysfunction of the GABA system in depression [50,51]. GABA concentrations in cerebrospinal fluid and plasma are lower in unipolar depressed patients compared with controls [51]. Recently, Sanacorra and colleagues have used *in vivo* proton magnetic resonance spectroscopy to show decreased GABA concentrations in the occipital cortex of depressed patients and a corresponding increase in patients treated with either SSRIs or electroconvulsive-shock therapy [52,53]. However, evidence for a specific role of $GABA_B$ receptors is unclear. Although $GABA_B$ receptors were proposed to have a role in depression and antidepressant action >20 years ago [54], progress has been hampered by the lack of appropriate tools. Furthermore, data are largely controversial, with rival hypotheses suggesting that both positive and negative modulation of this receptor might be a useful antidepressant therapy [55,56]. More recently, there has been more emphasis on antagonism of $GABA_B$ receptors as a potential therapeutic strategy for depression [3]. In support of this, we recently demonstrated that $GABA_{B(1)}$ subunit knockout mice display antidepressant-like activity in the forced swim test (FST) model of antidepressant action (Table 1) [33]. These effects are recapitulated in pharmacological studies of the $GABA_B$ receptor antagonist CGP56433A in the mouse FST [33]. Supporting the use of $GABA_B$ receptor antagonists as antidepressants, Nakagawa and colleagues [57] demonstrated that baclofen attenuates the decrease in immobility caused by antidepressants in the traditional FST. These effects were caused by a sedative effect of baclofen because the drug has no effect on immobility behaviour at the doses tested. Furthermore, in the learned helplessness model, another animal model of antidepressant action, chronic treatment with the $GABA_B$ receptor antagonist CGP36742 has an antidepressant-like response [55] but baclofen increases susceptibility to helplessness and attenuates the effects of antidepressants [58,59]. Of note, $GABA_B$ receptor antagonists (including CGP56433A) increase the concentration of brain-derived neurotrophic factor (BDNF) in the hippocampus and cortex [21,60], which might contribute to their antidepressant-like effects [61].

In further support of antidepressant potential for $GABA_B$ receptor antagonists, it has been demonstrated recently that $GABA_B$ antagonists CGP56433A and CGP55845A selectively increase swimming time in a modified rat FST model of depression [62]. Qualitatively, this pattern of behaviour is similar to that following administration of SSRIs and 5-HT receptor agonists [63]. Interestingly, depleting 5-HT concentrations in the brain blocks the antidepressant-like effects of CGP56433A, which demonstrates that this neurotransmitter is essential for the antidepressant response. Several studies provide evidence of an interaction between $GABA_B$ receptors and 5-HT-mediated neurotransmission. Recently, it has been demonstrated that >95% of 5-HT-immunoreactive cell bodies in the raphé complex are also positive for $GABA_B$ receptors [64]. Furthermore, $GABA_B$ receptors and 5-HT receptors are coupled to the same K^+ channel (GirK) in 5-HT-containing neurons [65]. It is also noteworthy that GABA released from dorsal raphé interneurons and afferents from the amygdala, periaqueductal grey and habenula inhibits the firing of 5-HT-containing cells in the dorsal raphé nucleus (DRN), whereas injecting GABA directly into the DRN decreases the firing of 5-HT-containing cells by >50%. Inhibition of 5-HT firing is controlled by $GABA_B$ receptors [66]. Furthermore,

Table 1. Pharmacological and genetic evidence for a role of $GABA_B$ receptors in animal models of anxiety and antidepressant-like behaviour[a]

Test	Description	$GABA_B$ receptor agonist[b]	$GABA_B$ receptor positive modulator[c]	$GABA_B$ receptor antagonist[d]	$GABA_{B(1)}$-receptor-deficient mice	Refs
Anxiety						
Light–dark box	Animals avoid a bright, open space in preference to a dark enclosed area	–	Anxiolytic	No effect (chronic)	Increased anxiety; reduced sensitivity to anxiolytics	[33]
Elevated plus maze	Animals are placed on a cross-shaped apparatus; they avoid the open arms in preference to dark, enclosed arms	No effect	Anxiolytic	No effect	–	[26,32]
Elevated zero maze	Animals are placed on an 'O'-shaped apparatus; they avoid the open arms in preference to dark, enclosed arms	–	Anxiolytic	–	Increased anxiety; mice have panic-like response and jump off the maze	[26,33]
Stress-induced hyperthermia	Mild stress or anticipation of mild stress elevates body temperature, which is reversed by anxiolytic pretreatment	Hypothermia precludes interpretation	Anxiolytic	–	Difficult to test because of altered baseline temperature	[26,46,74]
Staircase test	Animals are placed on an enclosed staircase; anxiolytics promote the ratio of steps:rearing	–	–	–	Increased anxiety	[33]
Vogel conflict test	Mild electrical shocks suppress water intake in thirsty animals; anxiolytics increase the number of shocks accepted	Anxiolytic	–	–	–	[36,37]
Drug-withdrawal-induced anxiety	Withdrawal from either long-term alcohol or benzodiazepines increases anxiety levels	Anxiolytic	–	–	–	[40,41]
Depression						
Forced swim test	Rodents develop an immobile posture when placed in an inescapable cylinder of water; antidepressant pretreatment reverses the immobility	No effect in test but blocked effects of anti-depressant	No effect	Antidepressant-like	Antidepressant-like	[33,57,75]
Modified rat forced swim test	Rats develop an immobile posture when placed in an inescapable cylinder of water; antidepressant pretreatment reverses the immobility; anti-depressants that act through 5-HT systems increase swimming and those that act on catecholamine mechanisms increase climbing	–	No effect	Antidepressant-like	–	[62]
Tail-suspension test	Mice develop an immobile posture when hung inescapably by their tails; antidepressant pre-treatment reverses the immobility	Increased immobility	–	No effect	No effect	[26,33,76]
Learned helplessness	Rodents demonstrate escape deficits following repeated uncontrollable shocks; anti-depressants reverse this helpless behaviour	Worsened helpless behaviour; blocked effects of antidepressants	–	Antidepressant-like	–	[59,77]
Chronic mild stress	Chronic exposure to mild stressors reduces sucrose preference in rodents; chronic (but not acute) antidepressant treatment reinstates the preference	–	–	Antidepressant-like	–	[78]

[a]'–' indicates no data available.
[b]For example, baclofen.
[c]For example, GS39783 (see Chemical names).
[d]For example, CGP35348, CGP36742, CGP55845A and CGP56433A (see Chemical names).

Chemical names

CGP27492: 3-aminopropylphosphinic acid
CGP35348: 3-aminopropyl(diethoxymethyl)phosphinic acid
CGP36742: 3-aminopropyl-*n*-butyl-phosphinic acid
CGP44532: ((S)-3-amino-2-hydroxy-propyl)-methyl-phosphinic acid
CGP55845A: benzyl-{(S)-3-[(S)-1-(3,4-dichloro-phenyl)-ethylamino]-2-hydroxy-propyl}-phosphinic acid hydrochloride
CGP56433A: 3-{(S)-1-[(S)-3-(cyclohexylmethyl-hydroxy-phosphinoyl)-2-hydroxy-propylamino]-ethyl}-benzoic acid lithium salt
CGP7930: N,N′-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine
CGP54626A: cyclohexylmethyl-{(S)-3-[(S)-1-(3,4-dichloro-phenyl)-ethylamino]-2-hydroxy-propyl}-phosphinic acid hydrochloride
GS39783: N,N′-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine

blunted $GABA_B$-receptor-induced effects (including electrophysiological and signalling responses) have been demonstrated in the DRN of mice lacking the 5-HT transporter that is the molecular substrate for SSRI antidepressants [67]. However, responses are normal in animals that lack $5\text{-}HT_{1A}$ autoreceptors, which indicates that the altered $GABA_B$-receptor-mediated effects in the 5-HT transporter knockout animals are independent of downregulation of $5\text{-}HT_{1A}$ autoreceptors [67]. Further studies are required to elucidate the exact molecular interactions between the 5-HT and $GABA_B$ receptor systems at the level of the DRN and shed more light on the antidepressant-like behavioural effects of $GABA_B$ receptor antagonists.

It might seem counterintuitive that modulation of one type of receptor can induce different effects on anxiety and depression-like behaviours, given the extensive comorbidity of such disorders clinically [68]. However, $GABA_B$ receptors are localized presynaptically and postsynaptically, and elucidating the relative contribution of these individual receptor populations to behavioural phenotypes is not possible currently. Interestingly, acute enhancement of the 5-HT system with SSRIs can also have opposite effects on anxiety and depression-like behaviour [69,70]. Therefore, it is possible that differential effects of $GABA_B$ receptors on the firing of 5-HT-containing neurons, particularly in the DRN might partly account for the behavioural effects of genetic and pharmacological manipulation of $GABA_B$ receptors. Future studies are needed to understand the functional interactions of $GABA_B$ receptors with 5-HT and other neurotransmitter systems, and how these might contribute to the differential anxiolytic and antidepressant-like effects of positive, allosteric modulators and antagonists of $GABA_B$ receptors, respectively. Conventional proton spectroscopy imaging reveals no distinct differences in the global concentration of GABA in depression and panic disorder: both have reduced concentrations compared with control subjects [53,71]. The development of imaging tools to investigate $GABA_B$ receptor function in clinical populations is needed to reveal potential differences in regional alterations in $GABA_B$ receptors in depression and various anxiety disorders.

Concluding remarks

During the past decade the development of novel pharmacological and genetic tools has helped elucidate a discrete role for $GABA_B$ receptors in regulating emotional behaviour. These advances have identified $GABA_B$ receptors as a target for the pharmacotherapy of anxiety and depression. However, the molecular mechanisms by which modulation of the $GABA_B$ receptor system regulates behaviour and role of this system in other disorders, such as drug dependence and cognitive dysfunction, are elusive. The relative contributions of presynaptic and postsynaptic receptors to the behavioural effects of $GABA_B$ receptor ligands and the functions of $GABA_{B(1a)}$ and $GABA_{B(1b)}$ isoforms needs to be resolved. Selective targeting of $GABA_B$ receptors might lead to more-effective psychotherapeutics for mood disorders in which there is a high, unmet medical need.

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