

Title	GABAB receptors, anxiety and mood disorders
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Publication date	2020-08-30
Original Citation	Felice, D., Cryan, J. F. and O'Leary, O. F. (2020) 'GABAB receptors, anxiety and mood disorders', in Vlachou S. and Wickman K. (eds.) Behavioral Neurobiology of GABAB Receptor Function. Current Topics in Behavioral Neurosciences, vol. 52, pp. 241-265, Springer, Cham. doi: 10.1007/7854_2020_171
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1007/7854_2020_171
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Download date	2025-04-28 04:02:04
Item downloaded from	https://hdl.handle.net/10468/12431



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1 Abstract

Gamma-Aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, acts at 2 the ionotropic GABA_A and GABA_C receptors, and the metabotropic GABA_B receptor. This 3 4 chapter summarizes the studies that have investigated the role of the GABA_B receptor in stressrelated psychiatric disorders including anxiety and mood disorders. Overall, clinical and 5 6 preclinical evidence strongly suggests that the GABA_B receptor is a therapeutic candidate for 7 depression and anxiety disorders. However, the clinical development of GABAB receptor-based drugs to treat these disorders has been hampered by their potential side-effects, particularly 8 9 those of agonists. Nevertheless, the discovery of novel GABA_B receptor allosteric modulators, 10 and increasing understanding of the influence of specific intracellular GABAB receptor-11 associated proteins on GABA_B receptor activity, may now pave the way towards GABA_B receptor therapeutics in the treatment of mood and anxiety disorders. 12

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Keywords: GABA_B receptor, anxiety, depression, stress, mood, stress resilience, hippocampal
 neurogenesis

1 1. Introduction

2 The inhibitory action of GABA is mediated by the ionotropic GABAA and GABAC receptors, and the metabotropic GABA_B receptor. The GABA_A receptor is bicuculline-sensitive and the 3 4 subsequent opening of its transmembrane channel which is permeable to chloride mediates rapid neuronal inhibition in the adult brain. In 1979, Norman Bowery and colleagues published 5 the discovery of a novel type of GABA receptor that was described as being "atypical" and 6 7 insensitive to the GABA_A receptor antagonist bicuculline (Bowery et al., 1979). Baclofen was identified to be a potent and selective agonist of this novel receptor, and in 1980 it was 8 demonstrated that baclofen acting on this novel receptor decreased neurotransmitter release in 9 10 the central nervous system (Bowery et al., 1980). This atypical receptor described by Bowery and colleagues would later be referred to as the GABA_B receptor (Hill and Bowery, 1981). The 11 GABA_B receptor is a G-protein-coupled receptor that inhibits adenylate cyclase activity and 12 mediates the slow and prolonged component of synaptic inhibition (Bowery et al., 2004). 13 GABA_B receptors are localized in most brain regions and GABA_{B(1)} receptor mRNA is 14 15 detectable in almost all neuronal cell populations and is highly expressed in the limbic system (Bettler et al., 2004, McDonald et al., 2004). The receptor consists of two subunits, GABA_{B(1)} 16 and GABA_{B(2)}, which heterodimerise to form the functional GABA_B receptor (Bettler et al., 17 2004). The GABA_{B(1)} subunit contains the orthosteric ligand binding site, while the GABA_{B(2)} 18 subunit is responsible for G-protein activation and contains binding sites for positive allosteric 19 modulators (Galvez et al., 2001, Bettler et al., 2004, Binet et al., 2004, Gassmann and Bettler, 20 2012). Isoforms of the GABA_{B(1)} receptor subunit have been identified (Lee et al., 2010) and 21 22 the two main isoforms expressed in the brain are $GABA_{B(1a)}$ and $GABA_{B(1b)}$ which form 23 GABA_{B(1a,2)} and GABA_{B(1b,2)} receptors, respectively (Lee et al., 2010). Structurally, GABA_{B(1)} isoforms differ only by the presence of a sushi domain in the N-terminal ectodomain of the 24 $GABA_{B(1a)}$ receptor subunit isoform (see Figure 1). 25

Since its discovery, there has been a long-standing interest in the therapeutic potential of the 1 2 GABA_B receptor. In this review, we will summarize studies assessing the role of the GABA_B receptor in mood disorders, specifically in depression, and in anxiety disorders. Clinical and 3 preclinical evidence supporting a role for GABA_B receptors in the pathophysiology of 4 depression and anxiety disorders will be summarized in addition to the preclinical evidence of 5 the antidepressant and anxiolytic effects of pharmacological and genetic modulation of GABA_B 6 7 receptor activity. Unless otherwise stated, most of the preclinical studies discussed in this chapter have been conducted in male rodents. Since most of this evidence is from preclinical 8 studies, readers outside this research field are advised to first read Table 1, which summarizes 9 the behavioural tests used to assess depression-, antidepressant- and anxiety-like behavior in 10 rodents (Cryan and Slattery, 2007), prior to reading the review. 11

12

13 2. The Role of the GABA_B receptor in the modulation of anxiety

14 2.1 Effects of GABA_B receptor agonists and positive allosteric modulators on anxiety-

15 like behaviour

Baclofen is the first described GABA_B receptor agonist (Bowery et al., 1980). It was 16 17 synthetized in 1962 by Heinrich Keberle in CIBA (Basel, Switzerland). Baclofen was formulated as an antiepileptic drug and marketed in 1972 as Lioresal. Currently, baclofen is 18 indicated primarily to treat spasticity but it also has beneficial effects in treating pain, is used 19 off-label in the treatment of alcohol use disorder, and has been shown to inhibit the re-enforcing 20 effects of many other addictive drugs (Bowery et al., 2002). However, there is also much 21 preclinical evidence suggesting that GABA_B receptor agonists such as baclofen may be 22 potential therapeutic approaches to treat anxiety disorders (Cryan et al., 2005, Cryan and 23 Slattery, 2010, Felice et al., 2016) (summarized in Table 2). 24

2 Acute baclofen administration has been shown to reduce anxiety-like behavior in several rat and mouse models (Ketelaars et al., 1988, File et al., 1991, Nastiti et al., 1991, File et al., 1992, 3 Shephard et al., 1992, Andrews and File, 1993, Amikishieva and Semendyaeva, 2007, Lu et al., 4 5 2016), although some conflicting findings have also been reported. For instance, while one study reported that baclofen was effective in the Vogel conflict test (Ketelaars et al., 1988), another 6 7 study reported no such effect (Agmo et al., 1991). However, the latter study also reported that higher doses of baclofen induced motor deficits in rats which may have reduced the number of 8 licks thus resulting in a potentially false negative finding in this test (Agmo et al., 1991). 9 10 Similarly, Li and colleagues have reported that baclofen had sedative but not anxiolytic effects in rats in several behavioural tests (Li et al., 2015). Conflicting findings have also been reported 11 in mice whereby baclofen was anxiolytic in some studies (Nastiti et al., 1991, Amikishieva and 12 Semendyaeva, 2007) but not in others (Dalvi and Rodgers, 1996, Varani and Balerio, 2012, Li 13 et al., 2013). In one such study, baclofen increased punished drinking in the Vogel conflict test 14 15 which would be indicative of an anxiolytic effect, but the authors suggest that this finding may also be due to analgesic effects of baclofen (Li et al., 2013). Motor impairing and hypothermic 16 effects are characteristic side effects of GABA_B receptor agonists and this likely confounds the 17 interpretation of anxiety-related behavioural tests that are dependent on motor activity (e.g. 18 elevated plus maze, Vogel conflict test, etc.) or body temperature (e.g. stress-induced 19 hyperthermia) (Cryan et al., 2004). In addition, the effects of baclofen on anxiety may depend 20 upon the developmental stage of the brain. For example, we have found that chronic treatment 21 22 with R-baclofen during early postnatal life (Postnatal day (PND) 14- PND 28) in mice induced 23 anxiety-like behaviour in adulthood in the elevated plus maze (EPM) but not in the stressinduced hyperthermia (SIH) and marble burying (MB) tests (Sweeney et al., 2014). This 24 suggests that during early life GABA_B receptor signaling might play a functional role in 25

programming anxiety behaviour in adulthood (Sweeney et al., 2014), although this effect might
 also be test-specific.

3

Importantly, baclofen has several side effects including sedation or somnolence, hypothermia, 4 vertigo and muscle relaxation (Agabio et al., 2013). Moreover, repeated administration of 5 GABAB agonists such as baclofen can induce receptor tolerance/desensitization resulting in a 6 7 reduced therapeutic response following chronic administration (Lehmann et al., 2003). Thus, there has been great interest in developing drugs that target the GABA_B receptor but with a 8 9 reduced side effect profile and that would not result in tolerance. As such, positive allosteric modulators (PAMs) offer several advantages over receptor agonists such as baclofen 10 (Christopoulos, 2002): (1) PAMs target more diverse sites that are distinct from the highly 11 12 evolutionary conserved orthosteric site thus potentially contributing to greater selectivity; (2) PAM binding leads to potentiation of GABA-mediated effects on the receptor rather than direct 13 14 activation of the receptor; (3) saturation of allosteric binding sites does not induce 15 downregulation or overstimulation of the target receptor; (4) PAMs are active only in tissues where the endogenous agonist is present giving a more specific drug activity. Essentially, PAMs 16 of GABA_B receptors offer the advantage of reduced risk for receptor desensitization/tolerance 17 when compared with classical GABA_B receptor agonists such as baclofen (Gjoni and Urwyler, 18 2008, 2009). 19

The first GABA_B receptor PAMs that were identified and characterized were CGP7930
(Urwyler et al., 2001, Adams and Lawrence, 2007) and GS39783 (Urwyler et al., 2003), shortly
followed by rac-BHFF (Malherbe et al., 2008), BHF177 (compound # 27 (Guery et al., 2007)),
CMPPE (Perdona et al., 2011), COR627 and COR628 (Castelli et al., 2012).

Several preclinical studies have interrogated the effects of some of these GABA_B receptor 1 2 PAMs on anxiety-like behaviour (summarized in Table 2). Chronic and acute administration of GS39783 has been shown to induce anxiolytic-like effects with no effects on locomotion, 3 cognition, temperature, or narcosis (Cryan et al., 2004, Mombereau et al., 2004). A recent study 4 identified the brain structures that are modulated by GS39783 under either basal, or mild stress 5 (anxiogenic) conditions which were induced by exposing mice to the open arm of an EPM 6 (Pizzo et al., 2018). Under basal conditions, GS39783 increased c-Fos expression in the 7 amygdala nuclei, cortical areas and periaqueductal gray (PAG) subregions, while it inhibited c-8 Fos expression in the dorsal raphe nucleus (DRN) (Pizzo et al., 2018). Under stress conditions 9 10 (open arm exposure), GS39783 reversed stress-induced c-Fos expression in the granular cell layer of the dentate gyrus of the hippocampus, no longer increased c-Fos expression in the 11 amygdala nor did it reduce c-Fos expression in the DRN (Pizzo et al., 2018). Together, this 12 13 suggests that GS39783 modulation of anxiety may involve neural circuits involving the dentate gyrus of the hippocampus, the amygdala and the DRN. 14

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CGP7930 has only modest anxiolytic-like effects in mice but a superior side-effect profile than
GABA_B receptor agonists (Frankowska et al., 2007, Jacobson and Cryan, 2008). Specifically,
CGP7930 was effective in the elevated zero maze (EZM) in rats (Frankowska et al., 2007) and
exhibited modest anxiolytic effects in the SIH, staircase test and EZM in mice (Jacobson and
Cryan, 2008). However, CGP7930 had no anxiolytic effects in the EPM in mice (Jacobson and
Cryan, 2008).

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Both Rac-BHFF and BHF177 induce anxiolytic effects in some tests but not others.
Specifically, Rac-BHFF and BHF177 induced anxiolytic like effects in the SIH test in mice and

rats, a test of the physiological anxiety response (Malherbe et al., 2008, Vinkers et al., 2010, Li 1 2 et al., 2015). BHF177 induced anxiolytic-like effects on light-enhanced startle (LES; a test 3 based on the innate aversion of rodents for bright light) in high-, but not low-LES responding rats in the staircase test (Li et al., 2015) but was inactive in the EPM and light dark box test in 4 mice (Li et al., 2013). Importantly, BHF177, at doses over 40mg/kg caused hypothermia in 5 6 contrast to other GABA_B receptor PAMs including CGP7930 and Rac- BHFF (Vinkers et al., 7 2010) which may have confounded findings in SIH test. On the other hand, Rac- BHFF at the same dose that induced anxiolytic-like effects in the SIH (100 mg/kg) did not enhance baclofen-8 and γ -Hydroxybutyric acid (GHB)-induced hypothermia (Koek et al., 2010), suggesting that its 9 10 effects in the SIH test are not confounded by effects of GABA_B receptor modulation of body temperature. A novel GABAB receptor PAM ADX71441 has also been shown to be effective 11 in the MB test in mice and in the EPM in mice and rats (Kalinichev et al., 2017). Recently, 12 13 Rondard and colleagues (Lecat-Guillet et al., 2017) developed time-resolved fluorescence resonance energy transfer (trFRET) sensors which represent an innovative tool to screen and 14 15 identify new GABA_B receptors PAMs with lower side-effect profiles. Interestingly, trFRET revealed that GS39783 exhibits low intrinsic agonist activity (as expected by a PAM), whereas 16 CGP7930 and rac-BHFF display agonist-PAMs characteristics (Lecat-Guillet et al., 2017). This 17 finding is in agreement with behavioural studies outlined above demonstrating that GS39783-18 induced anxiolytic-like behavioural effects without affecting locomotion, cognition, 19 temperature, or narcosis, and suggests that this drug may be a good target for clinical 20 development. Effects of PAMs on conditioned anxiety have also been examined. BHF177 did 21 not affect conditioned fear responses in the fear-potentiated startle (FPS) test in rats (Li et al., 22 2015) and was ineffective in the Vogel conflict test (Li et al., 2013). Similarly, treatment with 23 GS39783 did not affect conditioned fear responses in mice (Sweeney et al., 2013). 24

Taken together, preclinical evidence suggests that activation of the GABA_B receptor may
induce anxiolytic-like effects particularly in tests of innate anxiety whereby PAMs decrease
innate anxiety in some tests but not others, and thus perhaps do so is a test-specific manner.
Importantly, these findings may also be confounded by motor impairing and hypothermic
effects.

6

7 2.2 The effects of GABA_B receptor loss of function and GABA_B receptor antagonists on 8 anxiety-like behaviour

9 Given the evidence that agonists and PAMs of the GABA_B receptor can exert anxiolytic effects,
10 several studies have also interrogated the impact of genetically induced GABA_B receptor loss
11 of function and GABA_B receptor antagonists on anxiety-like behaviour (summarized in Table
12 3).

Mice lacking either the $GABA_{B(1)}$ or $GABA_{B(2)}$ receptor subunits exhibit an anxious phenotype. 13 Specifically, $GABA_{B(1)}^{-/-}$ mice, were more anxious in the light dark box (LDB) test and the 14 staircase test (Mombereau et al., 2004). In addition, these mice exhibited anxiety/panic-like 15 behavior in the EZM actively jumping off the maze (Mombereau et al., 2004). Similarly, mice 16 17 lacking the GABA_{B(2)} receptor subunit also exhibit anxiety-like behaviour in the LDB (Mombereau et al., 2005). Anxiety behaviour has also been assessed in mice lacking specific 18 isoforms of the GABA_{B(1)} receptor subunit. GABA_{B(1a)}^{-/-} and GABA_{B(1b)}^{-/-} mice did not exhibit 19 altered behaviour in innate tests of anxiety including in the EPM, SIH and MB tests (Jacobson 20 et al., 2007, O'Leary et al., 2014). Similarly, GABA_{B(1a)}-/- and GABA_{B(1b)}-/- mice that underwent 21 early life stress (via maternal separation) or chronic stress in adulthood (via social defeat stress) 22 did not exhibit differences in innate anxiety behaviour when compared to wild type mice 23 (O'Leary et al., 2014). On the other hand, $GABA_{B(1a)}^{-/-}$ mice were unable to acquire conditioned 24

taste aversion (CTA), whereas GABA_{B(1b)}^{-/-} mice were unable to extinguish aversive taste 1 2 memories in this test (Jacobson et al., 2006). Taken together this suggests that loss of function of either the GABA_{B(1)} or GABA_{B(2)} receptor subunit increases innate anxiety while loss of 3 function of just one GABA_{B(1)} receptor subunit isoform is not sufficient to affect innate 4 anxiety-like behaviour. However; changes in locomotor activity can be a confounding factor of 5 the behavioural tests, for instance $GABA_{B(1)}^{-/-}$ and $GABA_{B(1b)}^{-/-}$ (but not $GABA_{B(1a)}^{-/-}$) mice 6 7 display hyperlocomotor activity in a new environment (Mombereau et al., 2004, O'Leary et al., 2014). 8

9

In contrast to the findings in genetically altered mice, the effects of GABAB receptor 10 antagonists on anxiety behaviour are less clear (Table 3). Overall however, the findings suggest 11 that GABA_B receptor antagonists can induce anxiolytic-like effects in rats (Zarrindast et al., 12 2001, Frankowska et al., 2007, Partyka et al., 2007) but less so in mice (Dalvi and Rodgers, 13 14 1996, Mombereau et al., 2004, Sweeney et al., 2014). When given systemically to rats, GABAB 15 receptor antagonists were effective in the EPM, EZM, Vogel conflict test and four-plate test (Zarrindast et al., 2001, Frankowska et al., 2007, Partyka et al., 2007) but were ineffective when 16 locally administered into the basolateral amygdala or the shell of the nucleus accumbens 17 (Sanders and Shekhar, 1995, Lopes et al., 2012). In mice, chronic treatment with the GABAB 18 receptor antagonist CGP56433A had no effect in the LDB test (Mombereau et al., 2004). 19 Similarly, acute treatment with the GABA_B receptor antagonist CGP 52432 did not have 20 anxiolytic effects in the EPM, MB and SIH tests (Dalvi and Rodgers, 1996, Sweeney et al., 21 2014) or in cued auditory fear conditioning (Sweeney et al., 2013). However, the GABA_B 22 receptor antagonist CGP36742 induced anxiolytic-like effects in the four-plate test in mice 23 (Partyka et al., 2007) and the GABA_B receptor antagonist 2OH-Saclofen reversed the effects of 24 nicotine treatment on anxiety-like behaviours in mice (Varani and Balerio, 2012). In addition, 25

the GABA_B receptor antagonist CGP 36216 when administered intracerebroventricularly (ICV)
or in the dorsal hippocampus, or ventral hippocampus induced fear generalization in mice
treated after fear memory consolidation (Lynch et al., 2017). Importantly, the clinical use of
GABA_B receptor antagonists has been limited mainly by their potential side effects including
pain, gastroesophageal reflux disease, drug additcion and proconvulsive action (Vergnes et al.,
1997, Ghose et al., 2011).

7

In summary, GABAB receptor agonists and PAMs exert anxiolytic-like effects while loss of 8 function of the GABA_B receptor (GABA_{B(1)}^{-/-} and GABA_{B(2)}^{-/-} mice) induced anxiogenic-like 9 effects. However, loss of function of either the GABA_{B(1a)} or GABA_{B(1b)} receptor subunit 10 isoform alone did not affect anxiety-like behaviour, likely because these mice still express 11 12 functional GABA_B receptors (GABA_{B(1b, 2)} or GABA_{B(1a,2)}, respectively). The impact of GABA_B receptor antagonists on anxiety are at present somewhat less clear but sometimes 13 14 similarly to agonists/PAMs appear to be anxiolytic. The precise mechanisms underlying the 15 anxiolytic effects of both GABA_B receptor antagonists, and agonists/PAMS which would be expected to have opposing pharmacological effects is not yet fully understood but may be a 16 function of the fact that GABA_B receptors are found both pre-synaptically and post-synaptically 17 and that drugs might differ in their efficacy at these different receptor sites and at different 18 subunits of the receptor (Cryan and Kaupmann, 2005, Sun et al., 2016, Freyd et al., 2017). 19 Nevertheless, the evidence overwhelmingly supports the GABA_B receptor as a valid drug 20 21 development target for the treatment of anxiety disorders.

22

3. The role of the GABA_B receptor in depression and antidepressant action

One of the first indications that the GABA_B receptor may play a role in depression came from 1 2 preclinical studies reporting that chronic treatment with antidepressant drugs or repeated electroconvulsive shock upregulated GABAB receptor binding and function in the mouse and 3 rat frontal cortex (Pilc and Lloyd, 1984, Lloyd et al., 1985, Suzdak and Gianutsos, 1986, Gray 4 and Green, 1987, Szekely et al., 1987, Pratt and Bowery, 1993). More recently, it has been 5 reported that chronic treatment with antidepressants (fluoxetine, phenelzine, desipramine and 6 7 tranylcypromine) increased the expression of the GABA_{B(1a)} receptor subunit isoform in the rat hippocampus (Sands et al., 2004). As outlined below, it has since been shown that 8 pharmacological or genetic blockade of GABA_B receptor activity exerts antidepressant-like 9 10 effects. While these effects of GABA_B-receptor antagonist induction of antidepressant-like 11 behaviour seem to be opposing to antidepressant-induced upregulation of the GABA_B receptor they might be due to drug selective effects on either or both presynaptic and postsynaptic 12 GABA_B receptors (Cryan and Kaupmann, 2005, Sun et al., 2016, Freyd et al., 2017) 13

14

15 **3.1** The effects of GABA_B receptor agonists on depression-like behaviour

The effects of GABA_B receptor agonists on depression-related behaviours in rodents are 16 17 summarized in Table 4. Several studies have reported that baclofen induced antidepressantlike behaviour in the forced swimming test (FST) in both mice and rats (Aley and Kulkarni, 18 1989, 1990, Car and Wisniewska, 2006, Frankowska et al., 2007, Khan et al., 2016). In 19 agreement, it has also been reported that acute treatment with the GABAB receptor agonist SKF 20 97541, or the GABA_B receptor PAM, CGP 7930, induced antidepressant-like effects in the rat 21 22 FST (Frankowska et al., 2007). However, negative findings have also been reported. Indeed, the GABA_B receptor agonists Phaclofen and CGP 44532, and the PAM, GS39783, did not 23 exhibit antidepressant-like activity in the FST in mice or rats (Mombereau et al., 2004, Slattery 24 et al., 2005, Nowak et al., 2006, Araki et al., 2016, Pesarico et al., 2016). Moreover, it was 25

reported that chronic administration of baclofen exacerbated learned helplessness in rats
(Nakagawa et al., 1996b) and that baclofen attenuated the effects of several antidepressants in
the rat FST and in the learned helplessness model (Nakagawa et al., 1996a, b). More recently,
a study showed the baclofen inhibited the antidepressant-like effects of ketamine (which has
rapid antidepressant effects) in the mouse tail suspension test (TST) (Rosa et al., 2016). Taken
together, it is not yet entirely clear whether pharmacological activation of the GABA_B receptor
has antidepressant-like effects.

8

9 3.2 The effects of GABA_B receptor blockade or loss of function on depression-like

10 behaviour

In contrast to the data on GABA_B receptor agonists and PAMs, we have much stronger evidence 11 that GABA_B receptor blockade (either pharmacologically or genetically) induces 12 antidepressant-like behaviour (see Table 5). Most studies report that chronic or acute treatment 13 with GABA_B receptor antagonists have antidepressant-like effects in both mice and rats. For 14 instance, the GABA_B receptor antagonist, CGP36742, exhibits antidepressant-like activity in 15 mice in several behavioural tests including the FST, chronic mild stress paradigm, olfactory 16 bulbectomy model, and the learned helplessness paradigm (Nakagawa et al., 1999, Nowak et 17 al., 2006). Similarly, the GABA_B receptor antagonists CGP51176, CGP51176A, CGP56433A, 18 SCH50911 and CGP52432 also induced antidepressant-like effects in both the mouse and rat 19 20 FST (Mombereau et al., 2004, Slattery et al., 2005, Frankowska et al., 2007, Felice et al., 2012). In addition CGP51176A has also been shown to reduce stress-induced anhedonia as measured 21 by increased sucrose consumption in the chronic mild stress rat model (Nowak et al., 2006). 22

Studies in genetically modified GABA_B receptor mice have revealed findings similar to that 1 observed with receptor antagonists. $GABA_{B(1)}^{-/-}$ and $GABA_{B(2)}^{-/-}$ mice exhibit an 2 antidepressant-like phenotype in the FST (Mombereau et al., 2004, Mombereau et al., 2005). 3 In the TST, male but not female $GABA_{B(1b)}^{-/-}$ mice displayed decreased immobility suggesting 4 antidepressant-like phenotype whereas male and female $GABA_{B(1a)}^{-/-}$ mice exhibited increased 5 immobility, suggesting a depression-like phenotype. In the FST, both GABA_{B(1a)}- /- and 6 $GABA_{B(1b)}^{-/-}$ mice exhibited an antidepressant-like phenotype (O'Leary et al., 2014). However, 7 male but not female $GABA_{B(1b)}^{-/-}$ mice are hyperactive in the open field test which may have 8 contributed to the reduced immobility of males in the FST and TST (O'Leary et al., 2014). 9 Interestingly, $GABA_{B(1a)}^{-/-}$ mice are more susceptible whereas $GABA_{B(1b)}^{-/-}$ mice are more 10 resilient to early life stress (via maternal separation) and social defeat stress in adulthood 11 (O'Leary et al., 2014). Specifically, $GABA_{B(1a)}^{-/-}$ mice are more susceptible to stress (maternal 12 separation or social defeat stress) -induced anhedonia as measured in the saccharin preference 13 and female urine sniffing tests, and were also more susceptible to social defeat stress-induced 14 social avoidance (O'Leary et al., 2014). On the other hand, $GABA_{B(1b)}$ --- mice were resilient to 15 stress-induced anhedonia and psychosocial stress-induced social withdrawal (O'Leary et al., 16 2014). In addition, $GABA_{B(1a)}^{-/-}$ but not $GABA_{B(1b)}^{-/-}$ mice exhibited a blunted 8-OH-DPAT-17 18 induced corticosterone and adrenocorticotropic hormone (ACTH) release thus suggesting disrupted regulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis which is the 19 neuroendocrine stress response system (Jacobson et al., 2017). 20

21

Taken together, preclinical pharmacological studies and studies using genetically altered GABA_B receptor mice strongly suggest that inhibition of GABA_B receptors has therapeutic potential in the treatment of depression (Alexander, 2017, Jacobson et al., 2018). As described earlier, sometimes, the GABA_B receptor agonist baclofen has also been shown to have

antidepressant-like effects in the forced swim test (FST). The precise mechanisms underlying 1 2 how opposing pharmacological manipulations (agonist vs. antagonist) could exert similar antidepressant-like effects is unknown. However, it may be a function of the fact that GABAB 3 receptors are found both pre-synaptically and post-synaptically, and that drugs might differ in 4 their selectivity for these differentially located GABA_B receptors. The subunit composition of 5 affected receptors might also influence behavioural responses to pharmacological agents. For 6 7 example, it has been shown that mice lacking lacking $GABA_{B(1b)}$ receptor subunit isoform exhibit a stress-resilient phenotype while mice lacking the GABA_{B(1b)} subunit are more stress-8 susceptible (O'Leary et al., 2014). 9

10

4. Clinical evidence of a role for the GABA_B receptor in mood disorders

The preclinical evidence of the therapeutic potential of GABA_B receptor modulation in the 12 treatment of depression is also supported by clinical evidence. One of the first clinical 13 14 indications of a role for the GABA_B receptor in depression comes from a small study reporting that baclofen may worsen depressive like-symptoms (Post et al., 1991). In that study, patients 15 with primary affective disorder were chronically treated with baclofen (10-55) mg/day. Out of 16 17 5 patients, 3 patients exhibited increased depression during baclofen treatment and these depressive symptoms improved during baclofen withdrawal (Post et al., 1991). This baclofen-18 induced worsening of depressive symptoms seems counterintuitive to its antidepressant-like 19 effects in preclinical studies. The reasons underlying this discrepancy are unclear but may 20 relate to the fact that preclinical assessments of baclofen were not done in animal models of 21 22 depression per se e.g. stress-induced anhedonia, but were conducted using "normal" animals in the FST which is a behavioural test of antidepressant-drug-like activity and not a model of 23 depression. Nevertheless, several studies also reported that depressed patients displayed blunted 24 baclofen-induced growth hormone release (Marchesi et al., 1991, O'Flynn and Dinan, 1993), 25

further suggesting a role for the GABA_B receptor in depression. The effects of baclofen on
 depression and anxiety-related clinical measures are contradictory however as summarized in
 a recent review on its off-label use to treat alcohol use disorder (Agabio and Leggio, 2018).

4

Postmortem studies have reported regional alterations in GABA_B receptor subunit expression 5 in brains from depressed suicide victims (Ghose et al., 2011) and depressed individuals 6 7 (Klempan et al., 2009). Specifically, it was reported that depressed suicide victims exhibited upregulation of the $GABA_{B(2)}$ receptor subunit in cortical and subcortical brain regions 8 9 compared with non-depressed suicide victims (Klempan et al., 2009). More recently, it was reported that GABA_{B(1)} and GABA_{B(2)} receptor subunit expression was reduced in the superior 10 frontal cortex of subjects with bipolar disorder (Fatemi et al., 2017). In the hippocampus of 11 depressed patients, GABA_{B(2)} gene expression was reported to be increased by 50% (Ghose et 12 al., 2011). In addition, in the dentate gyrus of the hippocampus of these depressed patients, 13 14 there was a 30% decrease in the expression of the $GABA_{B(1a)}$ receptor subunit isoform when 15 compared with controls (Ghose et al., 2011). Interestingly, the dentate gyrus is one of just a few brain areas where neurogenesis, the birth of new neurons occurs throughout life (Altman, 16 1962b, a, Spalding et al., 2013, Boldrini et al., 2018, Moreno-Jimenez et al., 2019). 17 Hippocampal neurogenesis has been implicated in the mechanism of antidepressant action 18 (Santarelli et al., 2003, David et al., 2009, O'Leary and Cryan, 2014, Miller and Hen, 2015) and 19 recently we and others reported that GABA_B receptor antagonists that have antidepressant-like 20 behavioural effects increase hippocampal neurogenesis (Felice et al., 2012, Giachino et al., 21 2014). We have also found that the stress-resilient behavioural phenotype of $GABAB_{(1b)}^{-/-}$ mice 22 23 is accompanied by resilience to stress-induced decreases in adult hippocampal neurogenesis (O'Leary et al., 2014). 24

There is also evidence from human transcranial magnetic stimulation (TMS) studies that there 1 2 are alterations in GABA_B receptor activity in depression. The first such study suggested that GABA_B neurophysiological deficits are closely related to the pathophysiology of major 3 depressive disorder (Levinson et al., 2010). In that study, patients with major depressive 4 disorder (MDD) exhibited decreased cortical silence, a measure of intracortical inhibition 5 thought to be a marker of $GABA_B$ receptor neurotransmission. Other more recent studies have 6 7 confirmed that depressed patients exhibit a decreased cortical silent period (a TMS measure of GABA_B receptor activity) (Veronezi et al., 2016). Accordingly, adolescents with depression 8 and a lifetime history of suicidal behaviors exhibited impaired long-interval intracortical 9 10 inhibition (LICI; which is a TMS measure of GABA_B receptor-mediated inhibition) when 11 compared to healthy adolescents and to depressed adolescents without a history of suicidal behavior (Lewis et al., 2018). A follow-up small study by the same group reported an 12 association between increases in GABA_B-mediated cortical inhibition and a reduction in 13 suicidal ideation over time in adolescents treated for depression (Lewis et al., 2019). A paired-14 15 pulse TMS (ppTMS) study revealed that patients with treatment resistant depression (TRD) exhibit more reduced GABAA and GABAB receptor-mediated cortical inhibition compared to 16 17 non-TRD patients and healthy subjects (Jeng et al., 2019) thus suggesting a potential role for 18 GABA_B receptor function in TRD. In addition selective serotonin reuptake inhibitor (SSRI) 19 antidepressants were shown to modulate GABA_B receptor-mediated long-interval intracortical inhibition, in non-TRD patients (Jeng et al., 2019) thus providing clinical evidence for a role 20 21 of GABA_B receptors in antidepressant action.

22

In contrast to depression, clinical studies interrogating a role for the GABA_B receptor in anxiety disorders are sparse and the evidence is largely indirect. Nevertheless, there is strong evidence that GABAergic neurotransmission plays a role in the treatment and pathophysiology of anxiety disorders as benzodiazepines (which act on the GABA_A receptor) are used to treat anxiety
disorders (Nemeroff, 2003). In terms of a potential role for GABA_B receptors, baclofen has
been shown to attenuate the anxiety that is associated with alcohol withdrawal, post-traumatic
stress, panic disorder and traumatic spinal-cord lesions (Cryan et al., 2005).

5

6 In summary, both clinical and preclinical evidence strongly support a role for the GABAB 7 receptor in depression and anxiety disorders. However, the involvement of the GABA_B receptor in the pathophysiology of anxiety disorders is less explored in clinical studies when compared 8 9 with depression. Indeed, the majority of clinical studies on the role of the GABAergic system in anxiety disorders are focused on the GABA_A receptor. However, it is worth noting that the 10 GABA_B receptor can contribute to inhibition by also modulating GABA_A receptor activity at 11 12 presynaptic and postsynaptic sites (Cryan et al., 2005, Tao et al., 2013), thus suggesting a potential upstream modulating role for the GABA_B receptor in anxiety disorders. Moreover, 13 14 preclinical studies suggest that agonists and PAMs of the GABA_B receptor have anxiolytic 15 effects.

16 6. Conclusions and perspectives

17 Although both preclinical and clinical studies suggest the GABA_B receptor as a potential target for the development of new therapeutic approaches for mood and anxiety disorders, only one 18 19 GABA_B receptor-based compound, SGS272 (CGP36742, a GABA_B receptor antagonist), progressed to Phase II clinical trials and was investigated as a potential treatment for cognitive 20 deficits (Ghose et al., 2011). To date however, no clinical trials assessing the effects of GABAB 21 22 receptor antagonists in depressed patients has been ever conducted. The development of such antagonists of the GABA_B receptor for the treatment of mood disorders is mainly hampered by 23 its potential side effects, particularly the potential risk of proconvulsive action. However, the 24

abundance of preclinical evidence of the antidepressant-like effects of GABAB receptor 1 2 antagonists cannot be ignored and thus novel and more selective GABA_B receptor antagonists 3 with a better side effects profile could lead to new therapeutic approaches in the clinic. In 2014, the first negative allosteric modulator (NAM) of the GABA_B receptor was generated. This was 4 a CGP7930 analogue, called CLH304a (also named Compound 14) (Chen et al., 2014). In 2016, 5 6 two additional novel NAMs, CLH391 and CLH393, were synthetized based on the structure of 7 CLH304a (Sun et al., 2016). It would be expected that NAMS would have a better side effect profile than antagonists and as such, the discovery of these NAMs are very promising for the 8 development of innovative drugs that negatively modulate GABA_B receptor action and thus, 9 10 might have antidepressant potential with a reduced side effect profile.

11

The GABA_B receptor plays a key role in anxiety disorders as demonstrated by a plethora of preclinical evidence. PAMs represent promising drugs to treat anxiety-like disorders with safer side effect profiles than GABA_B receptor agonists. ADX 71441 is the first GABA_B receptor PAM approved for phase I clinical trial (Kalinichev et al., 2017) indicated for alcohol use disorder, Charcot-Marie-Tooth disease and nicotine dependence. However, future clinical trials are required to evaluate the effects of PAMs in anxiety disorders.

18

Overall, the GABA_B receptor represents a promising target to develop new therapeutic treatments for depression and anxiety disorders. Since Bowery and colleagues' discovery of the GABA_B receptor in 1979, thousands of studies investigating its role in mammals and nonmammals such as the drosophila model (Manev and Dzitoyeva, 2010) have been published. The introduction of genetic tools has allowed the further study of the role of GABA_B receptor subunits and their isoforms in mice. Despite the drive of scientists to study the GABA_B receptor,

there is still a lot unknown. In particular, side effects associated with GABAB receptor 1 2 modulation hamper its path to become a relevant drug target. However, the introduction of novel tools to study GABAB receptor (e.g. FRET-Based Sensors) and the discovery of novel 3 GABA_B receptor PAMs & NAMs will pave the way towards GABA_B receptor therapeutics in 4 human disorders such as depression and anxiety disorders. However, NAMs have yet to be 5 tested in vivo Intracellular GABAB receptor-associated proteins may also be important targets 6 7 to modulate GABA_B receptor activity because protein-protein interaction may allow more precise and temporal GABA_B receptor activity modulation. Particularly, the K+ channel 8 tetramerization domain (KCTD) that is associated with the GABA_{B2} receptor C-terminus is 9 10 envisaged to be a promising target (Sereikaite et al., 2019).

11

Figure 1. Schematic representation of the GABA_B receptor. GABA_B receptors are composed of GABA_{B(1)} and GABA_{B(2)} receptor subunits, that form an active heterodimer. The GABA_{B(1)} receptor subunit is essential for the binding of GABA and GABA_B receptor agonists and antagonists. GABA_{B(1)} receptor subunit presents as two main isoforms, namely GABA_{B(1a)} and GABA_{B(1b)} that differ by the presence of a sushi domain in the N-terminal of the GABAB(1a) isoform. Adapted from (Cryan and Kaupmann, 2005).

18

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