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$GABA_B$ receptors, anxiety and mood disorders

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Abstract

Gamma-Aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, acts at the ionotropic $GABA_A$ and $GABA_C$ receptors, and the metabotropic $GABA_B$ receptor. This chapter summarizes the studies that have investigated the role of the $GABA_B$ receptor in stress-related psychiatric disorders including anxiety and mood disorders. Overall, clinical and preclinical evidence strongly suggests that the $GABA_B$ receptor is a therapeutic candidate for depression and anxiety disorders. However, the clinical development of $GABA_B$ receptor-based drugs to treat these disorders has been hampered by their potential side-effects, particularly those of agonists. Nevertheless, the discovery of novel $GABA_B$ receptor allosteric modulators, and increasing understanding of the influence of specific intracellular $GABA_B$ receptor-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.

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

1. Introduction

The inhibitory action of GABA is mediated by the ionotropic $GABA_A$ and $GABA_C$ receptors, and the metabotropic $GABA_B$ receptor. The $GABA_A$ receptor is bicuculline-sensitive and the 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 the discovery of a novel type of GABA receptor that was described as being "atypical" and 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 demonstrated that baclofen acting on this novel receptor decreased neurotransmitter release in 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 $GABA_B$ receptor is a G-protein-coupled receptor that inhibits adenylate cyclase activity and mediates the slow and prolonged component of synaptic inhibition (Bowery et al., 2004). $GABA_B$ receptors are localized in most brain regions and $GABA_{B(1)}$ receptor mRNA is 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, $GABA_{B(1)}$ and $GABA_{B(2)}$, which heterodimerise to form the functional $GABA_B$ receptor (Bettler et al., 2004). The $GABA_{B(1)}$ subunit contains the orthosteric ligand binding site, while the $GABA_{B(2)}$ subunit is responsible for G-protein activation and contains binding sites for positive allosteric modulators (Galvez et al., 2001, Bettler et al., 2004, Binet et al., 2004, Gassmann and Bettler, 2012). Isoforms of the $GABA_{B(1)}$ receptor subunit have been identified (Lee et al., 2010) and the two main isoforms expressed in the brain are $GABA_{B(1a)}$ and $GABA_{B(1b)}$ which form $GABA_{B(1a,2)}$ 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 $GABA_{B(1a)}$ receptor subunit isoform (see **Figure 1**).

Since its discovery, there has been a long-standing interest in the therapeutic potential of the $GABA_B$ 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 preclinical evidence supporting a role for $GABA_B$ receptors in the pathophysiology of depression and anxiety disorders will be summarized in addition to the preclinical evidence of the antidepressant and anxiolytic effects of pharmacological and genetic modulation of $GABA_B$ 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 studies, readers outside this research field are advised to first read **Table 1**, which summarizes the behavioural tests used to assess depression-, antidepressant- and anxiety-like behavior in rodents (Cryan and Slattery, 2007), prior to reading the review.

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

2.1 Effects of $GABA_B$ receptor agonists and positive allosteric modulators on anxiety-like behaviour

Baclofen is the first described $GABA_B$ receptor agonist (Bowery et al., 1980). It was 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 indicated primarily to treat spasticity but it also has beneficial effects in treating pain, is used off-label in the treatment of alcohol use disorder, and has been shown to inhibit the re-enforcing effects of many other addictive drugs (Bowery et al., 2002). However, there is also much preclinical evidence suggesting that $GABA_B$ receptor agonists such as baclofen may be potential therapeutic approaches to treat anxiety disorders (Cryan et al., 2005, Cryan and Slattery, 2010, Felice et al., 2016) (summarized in **Table 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, Shephard et al., 1992, Andrews and File, 1993, Amikishieva and Semendyaeva, 2007, Lu et al., 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 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 licks thus resulting in a potentially false negative finding in this test (Agmo et al., 1991). 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 in mice whereby baclofen was anxiolytic in some studies (Nastiti et al., 1991, Amikishieva and Semendyaeva, 2007) but not in others (Dalvi and Rodgers, 1996, Varani and Balerio, 2012, Li et al., 2013). In one such study, baclofen increased punished drinking in the Vogel conflict test 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 effects are characteristic side effects of $GABA_B$ receptor agonists and this likely confounds the interpretation of anxiety-related behavioural tests that are dependent on motor activity (e.g. elevated plus maze, Vogel conflict test, etc.) or body temperature (e.g. stress-induced hyperthermia) (Cryan et al., 2004). In addition, the effects of baclofen on anxiety may depend upon the developmental stage of the brain. For example, we have found that chronic treatment with R-baclofen during early postnatal life (Postnatal day (PND) 14- PND 28) in mice induced anxiety-like behaviour in adulthood in the elevated plus maze (EPM) but not in the stress-induced hyperthermia (SIH) and marble burying (MB) tests (Sweeney et al., 2014). This suggests that during early life $GABA_B$ receptor signaling might play a functional role in

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

Importantly, baclofen has several side effects including sedation or somnolence, hypothermia, vertigo and muscle relaxation (Agabio et al., 2013). Moreover, repeated administration of GABAB agonists such as baclofen can induce receptor tolerance/desensitization resulting in a 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 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 (Christopoulos, 2002): (1) PAMs target more diverse sites that are distinct from the highly 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 activation of the receptor; (3) saturation of allosteric binding sites does not induce 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 of $GABA_B$ receptors offer the advantage of reduced risk for receptor desensitization/tolerance when compared with classical $GABA_B$ receptor agonists such as baclofen (Gjoni and Urwyler, 2008, 2009).

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 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, cognition, temperature, or narcosis (Cryan et al., 2004, Mombereau et al., 2004). A recent study identified the brain structures that are modulated by GS39783 under either basal, or mild stress (anxiogenic) conditions which were induced by exposing mice to the open arm of an EPM (Pizzo et al., 2018). Under basal conditions, GS39783 increased c-Fos expression in the amygdala nuclei, cortical areas and periaqueductal gray (PAG) subregions, while it inhibited c-Fos expression in the dorsal raphe nucleus (DRN) (Pizzo et al., 2018). Under stress conditions (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 amygdala nor did it reduce c-Fos expression in the DRN (Pizzo et al., 2018). Together, this suggests that GS39783 modulation of anxiety may involve neural circuits involving the dentate gyrus of the hippocampus, the amygdala and the DRN.

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).

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 et al., 2015). BHF177 induced anxiolytic-like effects on light-enhanced startle (LES; a test 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 mice (Li et al., 2013). Importantly, BHF177, at doses over 40mg/kg caused hypothermia in contrast to other $GABA_B$ receptor PAMs including CGP7930 and Rac- BHFF (Vinkers et al., 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- and γ-Hydroxybutyric acid (GHB)-induced hypothermia (Koek et al., 2010), suggesting that its effects in the SIH test are not confounded by effects of $GABA_B$ receptor modulation of body temperature. A novel $GABA_B$ receptor PAM ADX71441 has also been shown to be effective in the MB test in mice and in the EPM in mice and rats (Kalinichev et al., 2017). Recently, 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 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 CGP7930 and rac-BHFF display agonist-PAMs characteristics (Lecat-Guillet et al., 2017). This finding is in agreement with behavioural studies outlined above demonstrating that GS39783-induced anxiolytic-like behavioural effects without affecting locomotion, cognition, temperature, or narcosis, and suggests that this drug may be a good target for clinical development. Effects of PAMs on conditioned anxiety have also been examined. BHF177 did not affect conditioned fear responses in the fear-potentiated startle (FPS) test in rats (Li et al., 2015) and was ineffective in the Vogel conflict test (Li et al., 2013). Similarly, treatment with GS39783 did not affect conditioned fear responses in mice (Sweeney et al., 2013).

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.

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

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

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

taste aversion (CTA), whereas $GABA_{B(1b)}^{-/-}$ mice were unable to extinguish aversive taste 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 function of just one $GABA_{B(1)}$ receptor subunit isoform is not sufficient to affect innate anxiety-like behaviour. However; changes in locomotor activity can be a confounding factor of the behavioural tests, for instance $GABA_{B(1)}^{-/-}$ and $GABA_{B(1b)}^{-/-}$ (but not $GABA_{B(1a)}^{-/-}$) mice display hyperlocomotor activity in a new environment (Mombereau et al., 2004, O'Leary et al., 2014).

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

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).

In summary, $GABA_B$ receptor agonists and PAMs exert anxiolytic-like effects while loss of function of the $GABA_B$ receptor ($GABA_{B(1)}^{-/-}$ and $GABA_{B(2)}^{-/-}$ mice) induced anxiogenic-like effects. However, loss of function of either the $GABA_{B(1a)}$ or $GABA_{B(1b)}$ receptor subunit isoform alone did not affect anxiety-like behaviour, likely because these mice still express 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 similarly to agonists/PAMs appear to be anxiolytic. The precise mechanisms underlying the 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 function of the fact that $GABA_B$ receptors are found both pre-synaptically and post-synaptically and that drugs might differ in their efficacy at these different receptor sites and at different subunits of the receptor (Cryan and Kaupmann, 2005, Sun et al., 2016, Freyd et al., 2017) . Nevertheless, the evidence overwhelmingly supports the $GABA_B$ receptor as a valid drug development target for the treatment of anxiety disorders.

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 preclinical studies reporting that chronic treatment with antidepressant drugs or repeated electroconvulsive shock upregulated $GABA_B$ receptor binding and function in the mouse and rat frontal cortex (Pilc and Lloyd, 1984, Lloyd et al., 1985, Suzdak and Gianutsos, 1986, Gray and Green, 1987, Szekely et al., 1987, Pratt and Bowery, 1993). More recently, it has been reported that chronic treatment with antidepressants (fluoxetine, phenelzine, desipramine and 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 pharmacological or genetic blockade of $GABA_B$ receptor activity exerts antidepressant-like effects. While these effects of $GABA_B$-receptor antagonist induction of antidepressant-like 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 $GABA_B$ receptors (Cryan and Kaupmann, 2005, Sun et al., 2016, Freyd et al., 2017)

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 summarized in **Table 4**. Several studies have reported that baclofen induced antidepressant-like behaviour in the forced swimming test (FST) in both mice and rats (Aley and Kulkarni, 1989, 1990, Car and Wisniewska, 2006, Frankowska et al., 2007, Khan et al., 2016). In agreement, it has also been reported that acute treatment with the $GABA_B$ receptor agonist SKF 97541, or the $GABA_B$ receptor PAM, CGP 7930, induced antidepressant-like effects in the rat 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 exhibit antidepressant-like activity in the FST in mice or rats (Mombereau et al., 2004, Slattery et al., 2005, Nowak et al., 2006, Araki et al., 2016, Pesarico et al., 2016). Moreover, it was

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.

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

In contrast to the data on $GABA_B$ receptor agonists and PAMs, we have much stronger evidence that $GABA_B$ receptor blockade (either pharmacologically or genetically) induces antidepressant-like behaviour (see **Table 5**). Most studies report that chronic or acute treatment with $GABA_B$ receptor antagonists have antidepressant-like effects in both mice and rats. For instance, the $GABA_B$ receptor antagonist, CGP36742, exhibits antidepressant-like activity in mice in several behavioural tests including the FST, chronic mild stress paradigm, olfactory bulbectomy model, and the learned helplessness paradigm (Nakagawa et al., 1999, Nowak et al., 2006). Similarly, the $GABA_B$ receptor antagonists CGP51176, CGP51176A, CGP56433A, SCH50911 and CGP52432 also induced antidepressant-like effects in both the mouse and rat 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 by increased sucrose consumption in the chronic mild stress rat model (Nowak et al., 2006).

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

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 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 $GABA_B$ receptors are found both pre-synaptically and post-synaptically, and that drugs might differ in their selectivity for these differentially located $GABA_B$ receptors. The subunit composition of affected receptors might also influence behavioural responses to pharmacological agents. For 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-susceptible (O'Leary et al., 2014).

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 treatment of depression is also supported by clinical evidence. One of the first clinical 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 with primary affective disorder were chronically treated with baclofen (10-55) mg/day. Out of 5 patients, 3 patients exhibited increased depression during baclofen treatment and these depressive symptoms improved during baclofen withdrawal (Post et al., 1991). This baclofen-induced worsening of depressive symptoms seems counterintuitive to its antidepressant-like effects in preclinical studies. The reasons underlying this discrepancy are unclear but may relate to the fact that preclinical assessments of baclofen were not done in animal models of 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 depression. Nevertheless, several studies also reported that depressed patients displayed blunted baclofen-induced growth hormone release (Marchesi et al., 1991, O'Flynn and Dinan, 1993),

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).

Postmortem studies have reported regional alterations in $GABA_B$ receptor subunit expression in brains from depressed suicide victims (Ghose et al., 2011) and depressed individuals (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 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 frontal cortex of subjects with bipolar disorder (Fatemi et al., 2017). In the hippocampus of depressed patients, $GABA_{B(2)}$ gene expression was reported to be increased by 50% (Ghose et al., 2011). In addition, in the dentate gyrus of the hippocampus of these depressed patients, there was a 30% decrease in the expression of the $GABA_{B(1a)}$ receptor subunit isoform when 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, 1962b, a, Spalding et al., 2013, Boldrini et al., 2018, Moreno-Jimenez et al., 2019). Hippocampal neurogenesis has been implicated in the mechanism of antidepressant action (Santarelli et al., 2003, David et al., 2009, O'Leary and Cryan, 2014, Miller and Hen, 2015) and recently we and others reported that $GABA_B$ receptor antagonists that have antidepressant-like behavioural effects increase hippocampal neurogenesis (Felice et al., 2012, Giachino et al., 2014). We have also found that the stress-resilient behavioural phenotype of $GABAB_{(1b)}^{-/-}$ mice is accompanied by resilience to stress-induced decreases in adult hippocampal neurogenesis (O'Leary et al., 2014).

There is also evidence from human transcranial magnetic stimulation (TMS) studies that there 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 depressive disorder (Levinson et al., 2010). In that study, patients with major depressive disorder (MDD) exhibited decreased cortical silence, a measure of intracortical inhibition thought to be a marker of $GABA_B$ receptor neurotransmission. Other more recent studies have 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 and a lifetime history of suicidal behaviors exhibited impaired long-interval intracortical inhibition (LICI; which is a TMS measure of $GABA_B$ receptor-mediated inhibition) when 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 association between increases in $GABA_B$-mediated cortical inhibition and a reduction in suicidal ideation over time in adolescents treated for depression (Lewis et al., 2019). A paired-pulse TMS (ppTMS) study revealed that patients with treatment resistant depression (TRD) exhibit more reduced $GABA_A$ and $GABA_B$ receptor-mediated cortical inhibition compared to non-TRD patients and healthy subjects (Jeng et al., 2019) thus suggesting a potential role for $GABA_B$ receptor function in TRD. In addition selective serotonin reuptake inhibitor (SSRI) 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 of $GABA_B$ receptors in antidepressant action.

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).

In summary, both clinical and preclinical evidence strongly support a role for the $GABA_B$ 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 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 $GABA_B$ receptor can contribute to inhibition by also modulating $GABA_A$ receptor activity at 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, preclinical studies suggest that agonists and PAMs of the $GABA_B$ receptor have anxiolytic effects.

6. Conclusions and perspectives

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 $GABA_B$ 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 deficits (Ghose et al., 2011). To date however, no clinical trials assessing the effects of $GABA_B$ 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 its potential side effects, particularly the potential risk of proconvulsive action. However, the

abundance of preclinical evidence of the antidepressant-like effects of $GABA_B$ receptor antagonists cannot be ignored and thus novel and more selective $GABA_B$ receptor antagonists 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 a CGP7930 analogue, called CLH304a (also named Compound 14) (Chen et al., 2014). In 2016, two additional novel NAMs, CLH391 and CLH393, were synthetized based on the structure of 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 development of innovative drugs that negatively modulate $GABA_B$ receptor action and thus, might have antidepressant potential with a reduced side effect profile.

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.

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 non-mammals 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 $GABA_B$ receptor modulation hamper its path to become a relevant drug target. However, the introduction of novel tools to study $GABA_B$ receptor (e.g. FRET-Based Sensors) and the discovery of novel $GABA_B$ receptor PAMs & NAMs will pave the way towards $GABA_B$ receptor therapeutics in human disorders such as depression and anxiety disorders. However, NAMs have yet to be tested *in vivo* Intracellular $GABA_B$ receptor-associated proteins may also be important targets 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 tetramerization domain (KCTD) that is associated with the $GABA_{B2}$ receptor C-terminus is envisaged to be a promising target (Sereikaite et al., 2019).

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).

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