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Biochemical Pharmacology 68 (2004) 1541–1548
Biochemical Pharmacology
www.elsevier.com/locate/biochempharm

$GABA_B$ receptor alterations as indicators of physiological and pharmacological function

S.J. Enna[a,*], Norman G. Bowery[b,1]

[a]*Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical School, 3901 Rainbow Boulevard, Mail Stop 1018, Kansas City, Kansas 66160-0227, USA*
[b]*Department of Pharmacology, The University of Birmingham, Edgbaston, Birmingham, UK*

Received 24 May 2004; accepted 21 June 2004

Abstract

Given the widespread distribution of $GABA_B$ receptors throughout the central nervous system, and within certain peripheral organs, it is likely their selective pharmacological manipulation could be of benefit in the treatment of a variety of disorders. Studies aimed at defining the clinical potential of $GABA_B$ receptor agonists and antagonists have included gene deletion experiments, examination of changes in receptor binding, subunit expression and function in diseased tissue, as well as after the chronic administration of drugs. The results indicate that a functional $GABA_B$ receptor requires the combination of $GABA_{B(1)}$ and $GABA_{B(2)}$ subunits, that receptor function does not always correlate with subunit expression and receptor binding, and that $GABA_B$ receptor modifications may be associated with the clinical response to antidepressants, mood stabilizers, and $GABA_B$ receptor agonists and antagonists. Moreover, changes in $GABA_B$ binding or expression suggest this receptor may be involved in mediating symptoms associated with chronic pain, epilepsy and schizophrenia. This, together with results from other types of studies, indicates the potential therapeutic value of developing drugs capable of selectively activating, inhibiting, or modulating $GABA_B$ receptor function.

Keywords: $GABA_B$ receptors; $GABA_B$ receptor subunits; $GABA_B$ receptor expression; Antidepressants; Neuropsychiatric disorders; Pain

1. Introduction

Clinical and preclinical data suggest a wide range of therapeutic possibilities for drugs that influence γ-aminobutyric acid-B ($GABA_B$) receptor function [1–4]. For example, $GABA_B$ receptor agonists display muscle relaxant and analgesic properties, reduce the craving for drugs of abuse, and may be of benefit in the treatment of gastrointestinal disorders, asthma, and overactive bladder [5–12]. As for $GABA_B$ receptor antagonists, laboratory animal studies predict neuroprotectant, anticonvulsant, cognition enhancement, and antidepressant properties [13–20]. These and other findings have spurred efforts to design new therapeutic agents that selectively interact with this site. Although it has been two decades since this receptor was first identified [21], and 30 years since a $GABA_B$ receptor agonist was first used for the treatment for spasticity, baclofen remains the only marketed drug that specifically targets this site. Major hindrances for the development of $GABA_B$ receptor-selective agonists include side effects such as sedation, asthenia, and confusion, and the tolerance that develops to their beneficial effects [22–27]. Because selective, high affinity $GABA_B$ receptor antagonists with appropriate pharmacokinetic properties were developed only recently, their clinical properties have yet to be elucidated [28]. The failure to fully exploit the apparent clinical potential of $GABA_B$ receptor agonists and antagonists is perplexing given the therapeutic successes achieved with the pharmacological manipulation of other G protein-coupled sites.

The cloning of the $GABA_B$ receptor made possible the study of this issue at a molecular level [29–34]. Thus, the discovery that a functional $GABA_B$ receptor is a heterodimer consisting of two seven-transmembrane proteins suggests it may be possible to target pharmacologically

Abbreviations: GABA, γ-aminobutyric acid; $GABA_B$, γ-aminobutyric acid-B receptors; $GABA_{B(1)}$ and $GABA_{B(2)}$, γ-aminobutyric acid-B receptor subunits

* Corresponding author. Tel.: +1 913 588 7533; fax: +1 913 588 7373.
E-mail address: senna@kumc.edu (S.J. Enna).
[1] Present address: GlaxoSmithKline S.p.A., Via A. Fleming, 4, 37135 Verona, Italy.

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doi:10.1016/j.bcp.2004.06.037

distinct receptor subtypes to minimize side effects if there is a family of $GABA_B$ receptor subunits that can mix and match to form molecularly distinct heterodimers. However, only two gene products, $GABA_{B(1)}$ and $GABA_{B(2)}$, have been identified that are capable of forming a functional receptor [30–34]. While splice variants, in particular $GABA_{B(1a)}$ and $GABA_{B(1b)}$, have been characterized, the amino acid sequence of their receptor recognition sites are identical. Moreover, heterodimeric combinations of other splice variants and related proteins are functionally inactive as $GABA_B$ receptors [3,35–38]. While this leaves in doubt the possibility of designing $GABA_B$ receptor subtype-selective receptor recognition site agonists and antagonists, it is possible that allosteric agents may be capable of discriminating among heterodimers with different splice variants [39].

The ability to study $GABA_B$ receptor subunit expression has also made possible an assessment of its involvement in mediating the symptoms of some disorders and the therapeutic response to drugs. That is, physiologically- or pharmacologically induced changes in $GABA_B$ receptor expression provide suggestive evidence that this site directly or indirectly contributes to the effects of these manipulations. Such data can be useful in determining whether $GABA_B$ receptor agonists or antagonists are of benefit in treating a particular condition, and in defining the target tissue or brain region most affected by the drug or disorder. In addition, identifying ways to manipulate $GABA_B$ receptor subunit expression enables an examination of the relationship between the production of these proteins and generation of functional $GABA_B$ receptors. Such data are crucial for understanding the mechanisms responsible for regulating receptor sensitivity and the development of tolerance.

This review focuses on studies aimed at characterizing the relationship between $GABA_B$ receptor expression and function by comparing these parameters in genetically modified animals, in disease states, and following drug administration or physiological manipulations. The results indicate that, under some circumstances, there is a lack of concordance between $GABA_B$ receptor binding, subunit expression and function. Moreover, these data reveal that modifications in $GABA_B$ receptor expression have significant behavioral consequences, that receptor expression and function are altered by chronic pain, in association with some neurological and psychiatric disorders, and by drug therapy.

2. Gene deletion studies

Gene deletion experiments are useful for assessing the influence of a particular protein on phenotype. With respect to the $GABA_B$ receptor, such studies have been conducted in mice following deletion of the $GABA_{B(1)}$ subunit gene [9,40–43]. The results indicate that $GABA_{B(1)}$ is absolutely required for a functional $GABA_B$ receptor. That is, animals and their tissues lacking this subunit are unresponsive to $GABA_B$ agonists. In addition, GABA itself does not induce a $GABA_B$ response, suggesting the absence of a residual receptor that may be insensitive to synthetic agonists. Accordingly, if there is molecular and pharmacological diversity among $GABA_B$ receptors it will have to be associated with the $GABA_{B(2)}$ subunit.

These studies also revealed that $GABA_B$ receptors exert a tonic influence on various behaviors and physiological responses (Table 1). With C57B mice, deletion of the $GABA_{B(1)}$ subunit causes the development of intractable tonic-clonic seizures that prove fatal approximately four weeks after birth [41,42]. In contrast, while $GABA_{B(1)}{}^{-/-}$ Balb/C mice also experience seizures, their life span does not appear to be affected [40,43]. Other phenotypic changes noted in the C57B mice following removal of the $GABA_{B(1)}$ subunit gene include retarded growth, an increase in sensorimotor gating, and hypothermia (Table 1). Besides seizures, $GABA_{B(1)}$ deletion Balb/C mice display memory impairments, hyperalgesia, anxiety, an increase in locomotor activity, and a decrease in immobility in the forced swim test (Table 1). The swim test behavior is similar to that observed in animals administered antidepressants. Assuming all of these responses are directly related to a deficiency in $GABA_B$ receptor function, it could be speculated that $GABA_B$ receptor agonists should have anticonvulsant properties, should decrease sensorimotor gating, anxiety and locomotor activity, and increase the pain threshold.

While these findings generally support the results of pharmacological studies in wild type animals, there are some inconsistencies. Thus, $GABA_B$ agonists cause absence-type seizures rather than being anticonvulsant, which is taken as evidence that $GABA_B$ receptor antagonists may be of benefit in the treatment of some types of epilepsy, although they reportedly can induce seizures at high doses [16,20,44]. Moreover, whereas the gene deletion studies suggest that a lack of $GABA_B$ receptor activity compromises memory (Table 1), it is reported that $GABA_B$ receptor agonists or antagonists can either impair or

Table 1
Behavioral phenotypes of $GABA_{B(1)}{}^{-/-}$ mice

Strain	Behavioral phenotype	Reference
C57B	Seizures Retarded growth Increase in sensorimotor gating	[41]
	Seizures Hypothermia	[42]
Balb/C	Seizures Hyperalgesia Hyperlocomotion Memory impairment	[40]
	Anxiety Decreased immobility in forced swim test	[43]

enhance cognitive function depending on the task and the agent [13,15–18,45–51]. Given these conflicting findings it is possible that the seizures and cognitive impairment observed in the $GABA_{B(1)}^{-/-}$ mice may be a consequence of a developmental abnormality resulting indirectly from the gene deletion rather than directly from the absence of $GABA_B$ receptors.

The finding that deletion of the $GABA_{B(1)}$ gene decreases immobility in the forced swim test coincides with reports that $GABA_B$ receptor antagonists display antidepressant properties [18,19,43]. Likewise, the hyperalgesia and hyperlocomotion noted in the $GABA_{B(1)}$ null animals (Table 1) is consistent with the fact that $GABA_B$ receptor agonists elevate the pain threshold and decrease locomotor activity [5–8,26].

Thus, gene deletion experiments provide important clues about the possible role of $GABA_B$ receptors in controlling central nervous system function. While conclusions drawn from these studies are limited by the possibility of secondary adaptations that occur in the absence of this subunit, and by variations due to differences in background strains, the results have predictive value when the phenotype corresponds to the results of pharmacological studies in wild type animals [52,53].

3. Drug-induced alterations in $GABA_B$ receptors

Soon after the identification of $GABA_B$ receptors, experiments were undertaken to determine the effect of drug administration on the number and kinetic properties of the $GABA_B$ binding sites in brain (Table 2). Early work suggested that chronic, but not acute, administration of antidepressants increases the number of $GABA_B$ binding sites in rat brain cerebral cortex [54–59]. These results suggested that increases in $GABA_B$ receptors underlie the beneficial effects of this drug class. Agents studied included desipramine, imipramine, maprotiline, pargyline, mianserin and zimelidine. Because none of these antidepressants directly interacts with the $GABA_B$ binding site, their effects on $GABA_B$ receptors is believed to be indirectly mediated by enchancement in monoaminergic activity. This conclusion is reinforced by the fact that administration of reserpine depletes monoamines and decreases $GABA_B$ receptor binding (Table 2) [54].

Functional studies tend to confirm these findings, with results indicating that chronic administration of antidepressants increase the responsiveness of the $GABA_B$ receptor system (Table 2) [55–57]. In these cases, $GABA_B$ receptor function was quantified by assessing the effect of drug administration on baclofen-induced modification in cyclic AMP formation.

Others, however, were unable to replicate these findings (Table 2) [58–62]. Although antidepressant treatment increases $GABA_B$ receptor binding in some cases, there is no change in receptor function [58]. There are also reports that $GABA_B$ receptor binding is unchanged in animals treated chronically with desipramine, impramine, zimelidine, tranylcypromine, phenelzine, paroxetine or amytryptiline (Table 2) [59–62]. The precise reason for these discrepancies remains unknown, but could include differences in animal strains, drug dose, duration of treatment, or $GABA_B$ receptor assays. More recent work appears to confirm that chronic administration of antidepressants increases $GABA_B$ receptor function in rat brain cerebral cortex and spinal cord (Table 2) [63,64]. Although $GABA_B$ receptor binding is not quantified in these studies, desipramine administration increases $GABA_{B(1a)}$ and $GABA_{B(2)}$ expression in the spinal cord at a time when receptor function is enhanced. Thus, the weight of evidence suggests that chronic administration of antidepressants is capable of modifying $GABA_B$ receptor function, which may or may not occur in conjunction with a change in receptor number or subunit expression.

While there are inconsistencies with regard to the effects of antidepressants on $GABA_B$ receptors, there appears to be general agreement with respect to the long-term effects of $GABA_B$ agonist or antagonist administration (Table 2) [23,55,59,65,66]. Thus, chronic administration of baclofen decreases $GABA_B$ receptor binding and/or function in rat brain and spinal cord tissue, although in one study no change in binding was noted in a discrete region of the frontal cortex [59]. It has also been found that chronic administration of baclofen decreases the pain threshold in rats at a time when $GABA_B$ receptor function is diminished, linking this receptor system to a complex physiological response [23]. As opposed to agonists, chronic administration of the $GABA_B$ receptor antagonists CGP 36742 and CGP 46381 increase $GABA_B$ binding in brain and spinal cord tissue, although the antagonist CGP 35348 appears to be inactive in this regard (Table 2) [59,65]. These findings indicate that the $GABA_B$ site is subject to homologous receptor up- and down-regulation, which may be responsible for tolerance.

As with receptor binding, $GABA_B$ receptor function diminishes following chronic administration of a receptor agonist (Table 2) [23,53]. However, even though receptor binding and function are compromised under this condition, no change in $GABA_B$ subunit expression is noted under this circumstance (Table 2) [23]. This suggests a dissociation between the level of $GABA_B$ subunit expression and receptor function. Thus, it appears that genomic regulation of subunit expression is not the only mechanism for inducing long-term modifications in $GABA_B$ receptor activity. Other possibilities include a change in the phosphorylation state of the $GABA_B$ receptor subunits, or the influence of the regulator of G protein signaling (RGS) protein [67,68]. If so, it may be possible to prevent or delay the development of tolerance to $GABA_B$ agonists by regulating its phosphorylation or by inhibiting RGS protein. These findings may also help explain the inconsistencies in the results of the

Table 2
Drug-induced modifications in $GABA_B$ receptor binding, function, and subunit expression in the rodent central nervous system

Treatment	Dose (mg/kg); route; duration of administration (days)	Tissue[a]	$GABA_B$ receptor						Reference
			Binding	Function[b]	Subunit expression[c]				
					1[d]	1a	1b	2	
Desipramine	5; s.c. infus.; 18	Frontal cortex	↑						[54]
	10[e]; i.p.; 14	Frontal cortex		↑					[56]
	10 bid; i.p.; 21	Cerebral cortex	↑	↔					[58]
	1.25 bid or 10 daily; i.p.; 21	Frontal cortex	↔						[60,61]
	10; s.c. infus.; 28	Frontal cortex	↔						[62]
	20; p.o.; 21	Frontal cortex	↑						[59]
	15; i.p.; 7	Lumbar spinal cord		↑		↑	↔	↑	[64]
Amitryptyline	10; s.c. infus.; 18	Frontal cortex	↑						[54]
	10[e] bid; i.p.; 14	Frontal cortex		↑					[56]
	30; p.o.; 21	Frontal cortex	↔						[59]
Imipramine	32[e]; i.p.; 14	Cerebral cortex	↑	↑					[55]
	7.5 bid; i.p.; 21	Cerebral cortex	↑	↔					[58]
	30; s.c. infus.;28	Frontal cortex	↔						[62]
Maprotiline	10; s.c. infus.;18	Frontal cortex	↑						[54]
	10 bid; i.p.; 21	Cerebral cortex	↔	↔					[58]
Tranylcypromine	1; s.c. infus.; 28	Frontal cortex	↔						[62]
	10; i.p.; 7	Cerebral cortex		↑					[63]
Pargyline	20; s.c. infus.;18	Frontal cortex	↑						[54]
Mianserin	10[e]; i.p.; 14	Frontal cortex		↑					[56]
Zimelidine	10[e]; i.p.; 14	Frontal cortex	↑						[56]
	5 bid; i.p.; 21	Frontal cortex	↔						[60,61]
Paroxetine	10; p.o.; 21	Frontal cortex	↔						[59]
Phenelzine	10; s.c. infus.; 28	Frontal cortex	↔						[62]
Lithium	1 mEq./kg; i.p.; 14	Hippocampus	↑						[69]
Carbamazepine	50; i.p.; 14	Hippocampus	↑						[69]
Reserpine	1; s.c. infus.; 18	Frontal cortex	↓						[54]
Cocaine	20; i.p.; 14	Nucleus accumbens, hippocampus, and thalamus			↑				[70]
	55; i.p.; 12	Hippocampus				↑	↑	↑	[72]
Lidocaine	65; i.p.; 12	Hippocampus				↑	↑	↑	[72]
Nicotine	3; p.o.; 28	Hippocampus			↓				[71]
Baclofen	10[e]; i.p.; 14	Cerebral cortex	↓	↓					[55]
	10; i.p.; 21	Spinal cord	↓						[65]
	10; p.o.; 21	Frontal cortex	↔						[59]
	4.3; s.c.; 14	Cerebral cortex				↔	↔	↔	[66]
	5 bid; i.p.; 7	Lumbar spinal cord		↓		↔	↔	↔	[23]
CGP 35348	100; i.p.; 21	Frontal cortex	↔						[59]
CGP 36742	100; i.p.; 21	Frontal cortex	↑						[59]
	100; i.p.; 21	Spinal cord	↑						[65]
CGP 46381	100; i.p.; 21	Spinal cord	↑						[65]

[a] The experiments were pefromed on rats unless otherwise indicated.
[b] Baclofen effects on cAMP accumulation or GTPγS binding in indicated tissue.
[c] mRNA and/or protein.
[d] Combined $GABA_{B(1a)}$ and $GABA_{B(1b)}$.
[e] Mouse.

antidepressant studies since it is possible that chronic administration of these drugs could change $GABA_B$ receptor function without necessarily modifying receptor subunit expression or receptor binding. Indeed, the most consistent finding following chronic administration of antidepressants is an increase in $GABA_B$ receptor function, with or without a change in receptor binding or subunit expession (Table 2).

Other drugs found to influence $GABA_B$ receptor binding following chronic administration include lithium and carbamazepine, both of which increase the number of $GABA_B$ binding sites in rat hippocampus (Table 2) [69]. This suggests that modifications in $GABA_B$ receptor number may contribute to the mood stabilizing effects of these agents.

Whereas chronic administration of cocaine is reported to increase the expression of $GABA_B$ subunit expression in limbic areas of the rat brain, long-term exposure to nicotine decreases its expression in the hippocampus (Table 2) [70,72]. It is speculated that these changes in subunit expression may be related to behavioral sensitization with regard to cocaine, and to the effects of nicotine on learning and memory. These conclusions must be considered tentative until it is demonstrated they are accompanied by changes in $GABA_B$ receptor function [23].

4. Physiologically- and disease-induced alterations in $GABA_B$ receptors

Alterations in $GABA_B$ receptor binding and subunit expression are associated with a variety of neurological and psychiatric disorders (Table 3) [73–77]. Thus, there is a decreased expression of $GABA_{B(1)}$ subunit expression in the hippocampus of the schizophrenic brain, and $GABA_B$ receptor binding is increased in this brain region in association with temporal lobe epilepsy. In the latter case, while the absolute amount of binding is decreased, presumably reflecting neuronal cell loss, the amount of $GABA_B$ receptor binding per remaining neuron is increased. Moreover, both $GABA_{B(1)}$ and $GABA_{B(2)}$ subunit expression is increased in various areas of the rat brain in an animal model of absence epilepsy [77] (Table 3). Although these changes in $GABA_B$ receptor binding and subunit expression could indicate an involvement of this neurotransmitter system in the pathophysiology of these conditions, it is difficult to assess their significance in the absence of functional data. Thus, the increase in the density of $GABA_B$ binding sites in the hippocampal neurons of patients with temporal lobe epilepsy does not prove an increase in the functional activity of this receptor system since nongenomic mechanisms can alter the sensitivity of these sites. Moreover, an increase in receptor binding may be indicative of a compensatory change in receptor number or affinity resulting from a deficiency in $GABA_B$ activity. Likewise, the changes in $GABA_B$ receptor subunit expression noted in the absence model of epilepsy and in schizophrenia imply, but do not prove, a commensurate change in receptor number or function at the neuronal membrane. While such studies are useful for providing evidence of a $GABA_B$ receptor involvement in a particular disorder, in the absence of functional data such findings must be considered preliminary.

Numerous studies have been undertaken to examine the effects of pain on $GABA_B$ receptor binding, subunit expression, and function (Table 3) [7,8,23,78]. Utilizing a nerve-injury model it was found that although there is a heightened sensitivity to the analgesic effects of baclofen in this condition, there is no change in $GABA_B$ receptor binding in the spinal cord dorsal horn [8]. In contrast, persistent pain associated with sciatic neurectomy or peripheral inflammation decreases $GABA_B$ receptor binding in the rat spinal cord (Table 3) [78]. This appears to be at odds with the finding that pain associated with hind paw inflammation increases $GABA_{B(1)}$ and $GABA_{B(2)}$ subunit expression in the rat spinal cord, and increases $GABA_{B(1)}$, but not $GABA_{B(2)}$, subunit expression in the dorsal root ganglia [7,23]. Apparently conflicting results between

Table 3
Physiologically- and disease-induced modifications in $GABA_B$ receptor binding, function and subunit expression in rat and human central nervous system[a]

Condition	Tissue	$GABA_B$ receptor				Reference
		Binding	Function[b]	Subunit expressions		
				1[c]	2	
Neuropathic pain	Rat spinal cord dorsal horn, lamina II	↔				[8]
Sciatic nerve neurectomy	Rat spinal cord, lamina II	↓				[78]
Peripheral inflammation (Freund's adjuvant)	Rat superficial dorsal horn	↓				
Hind paw inflammation (formalin)	Rat dorsal lumbar spinal cord			↑	↑	[7]
	Rat lumbar dorsal root ganglia			↑	↔	
Schizophrenia	Human hippocampus			↓		[73]
Temporal lobe epilepsy	Human hippocampus	↑				[74–76]
Absence epilepsy model	Rat somatosensory cerebral cortex, ventrobasal and reticular thalamic nuclei			↑	↑	[77]
Hind paw inflammation (formalin)	Rat lumbar spinal cord		↔	↑	↑	[23]

[a] mRNA or protein.
[b] Baclofen-stimulated GTPγS binding in indicated tissue.
[c] Combined $GABA_{B(1a)}$ and $GABA_{B(1b)}$.

studies may be due, in part, to differences in the nature and duration of the painful stimuli. It is notable, however, that even though hind paw inflammation increases $GABA_B$ receptor subunit expression in the spinal cord, under the same conditions there is no increase in $GABA_B$ receptor function in this tissue, as measured by the GTPγS binding assay [23]. This indicates a lack of concordance between subunit expression and receptor function, possibly providing an explanation for the increased sensitivity to baclofen in the neuropathic pain model in the absence of a change in receptor binding [8].

Given the concentration of $GABA_B$ receptors in the dorsal horn of the spinal cord, the analgesic properties of $GABA_B$ receptor agonists, the hyperalgesia associated with the deletion of the $GABA_{B(1)}$ subunit gene, and the changes in spinal cord $GABA_B$ receptor binding and subunit expression associated with persistent pain, there is little doubt this receptor system contributes to the processing of painful stimuli [5–8,23,41]. Indeed, baclofen is employed clinically as an analgesic for the treatment of certain conditions [26,79–81]. However, to fully exploit this property it is necessary to develop agents capable of selectively activating only relevant $GABA_B$ receptors to minimize side effects, and to identify ways to prevent or delay the development of tolerance.

5. Conclusions

The $GABA_B$ receptor is unusual in being a heterodimeric G protein-coupled site. As such, it may be subject to regulatory mechanisms that differ from other second messenger systems. Gene deletion, drug, and physiological studies have been useful for examining the relationship between $GABA_B$ receptor function and subunit expression. Inasmuch as studies with $GABA_{B(1)}$ null mice suggest that both $GABA_{B(1)}$ and $GABA_{B(2)}$ subunits are required for a functional receptor, it might be assumed that the expression of these two proteins would occur in tandem as the need for receptors increases. However, this does not appear to be the case, since the expression and distribution of the two subunits varies somewhat throughout development and in the adult brain, and because there is a lack of concordance between $GABA_B$ receptor function and subunit expression [23]. These findings, along with the discovery that $GABA_B$ receptor subunits are found in both neurons and glia, suggest these proteins may perform other tasks in addition to forming $GABA_B$ receptors [4,82,83]. Thus, $GABA_B$ subunit expression data, and to some extent $GABA_B$ receptor binding data, may be misleading when used alone to define $GABA_B$ receptor activity.

This principle is illustrated further by studies examining the effects of chronic drug treatments, disease, and physiological manipulations on $GABA_B$ receptor binding, expression and function. For example, the finding that chronic administration of antidepressants increases $GABA_B$ receptor binding and function could be taken as evidence that this effect is an important component of the therapeutic response, and therefore lead to the conclusion that a $GABA_B$ receptor agonist may display antidepressant properties. However, such a result could also be interpreted as indicating that the increase in $GABA_B$ receptor function is an adaptive response that limits the efficacy of antidepressants. In fact, $GABA_B$ receptor antagonists have been found in animal studies to display antidepressant properties, with $GABA_{B(1)}$ gene deletion studies tending to support this conclusion [18,19,43]. Likewise, a change in $GABA_B$ receptor binding, function or expression in disease tissue could represent an adaptive response important for maintaining homeostasis, or could contribute to symptomatology, making it difficult to conclude whether it would be best to facilitate or inhibit this modification. Thus, it is usually not possible to determine from receptor binding, expression, or even functional data, whether a drug- or disease-induced alteration in a neurotransmitter system is responsible for a beneficial or an adverse effect. It is also possible that any change in receptor expression or function is an epiphenomenon unrelated to the clinical response to the drug or the clinical manifestations of the disorder.

Even with these limitations, studies of drug- and disease-induced receptor changes, in combination with other types of clinical and preclinical studies, can provide important clues about new therapeutic approaches for the treatment of disease. Of particular importance is the information obtained on mechanisms of receptor regulation. This has been, and will continue to be, particularly true for studies involving $GABA_B$ receptors since it appears options are limited in the search for more efficacious and receptor subtype-selective agents. It is likely that data derived from studies involving modifications in $GABA_B$ receptor binding, subunit expression and function will aid in this quest.

Acknowledgements

Preparation of this manuscript was made possible, in part, by the support of the Lied Foundation. We thank Ms. Lynn LeCount for her editorial assistance and Dr. Kenneth McCarson for his helpful comments.

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