A gut feeling about GABA: focus on GABA$_B$ receptors

Niall P Hyland* and John F. Cryan*

Alimentary Pharmabiotic Centre and Department of Pharmacology and Therapeutics, University College Cork, Cork, Ireland

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*Correspondence:
Niall P Hyland and John F Cryan,
Alimentary Pharmabiotic Centre and Department of Pharmacology and Therapeutics, University College Cork, Cork, Ireland
E-mail: n.hyland@ucc.ie; j.cryan@ucc.ie

INTRODUCTION

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the body and hence GABA-mediated neurotransmission regulates many physiological functions, including those in the gastrointestinal (GI) tract. GABA is located throughout the GI tract and is found in enteric nerves as well as in endocrine-like cells, implicating GABA as both a neurotransmitter and an endocrine mediator influencing GI function. GABA mediates its effects via GABA receptors which are either ionotropic GABA$_A$ or metabotropic GABA$_B$. The latter which respond to the agonist baclofen have been least characterized, however accumulating data suggest that they play a key role in GI function in health and disease. Like GABA, GABA$_B$ receptors have been detected throughout the gut of several species in the enteric nervous system, muscle, epithelial layers as well as on endocrine-like cells. Such widespread distribution of this metabotropic GABA receptor is consistent with its significant modulatory role over intestinal motility, gastric emptying, gastric acid secretion, transient lower esophageal sphincter relaxation and visceral sensation of painful colonic stimuli. More intriguing findings, the mechanisms underlying which have yet to be determined, suggest GABA$_B$ receptors inhibit GI carcinogenesis and tumor growth. Therefore, the diversity of GI functions regulated by GABA$_B$ receptors makes it a potentially useful target in the treatment of several GI disorders. In light of the development of novel compounds such as peripherally acting GABA$_B$ receptor agonists, positive allosteric modulators of the GABA$_B$ receptor and GABA producing enteric bacteria, we review and summarize current knowledge on the function of GABA$_B$ receptors within the GI tract.

Keywords: GABA$_B$, motility, visceral hypersensitivity, secretion, baclofen, allosteric modulator, agonist

GABA$_B$ receptor proteins

The first GABA$_B$ receptor cDNAs were isolated only in 1997 (Kaupmann et al., 1997). The identification of a second GABA$_B$ receptor protein soon after led to the discovery that native GABA$_B$ receptors are heterodimers composed of two subunits, GABA$_B_1$ and GABA$_B_2$ (reviewed in Calver et al., 2002; Betller et al., 2004). In the brain two predominant, differentially expressed splice variants are transcribed from the Gabbr1 gene, GABA$_B_{1a}$ and GABA$_B_{1b}$, which are conserved in different species including humans (Kaupmann et al., 1997; Bischoff et al., 1999; Fritschy et al., 1999). The human GABA$_B_1$ gene encodes a third isoform, GABA$_B_{1c}$, a functional role for which has yet to be determined, although it may play a role in the developing human brain (Calver et al., 2002). In the human GI tract there appears to be a similar expression pattern for both GABA$_B_{1a}$ and GABA$_B_{1b}$ splice variants, with little or no expression of GABA$_B_{1c}$ (Calver et al., 2000). The GABA$_B_{1a}$ and GABA$_B_{1b}$ isoforms differ by the insertion of a pair of tandem “Sushi” domains, which are potentially involved in protein–protein interactions, in the N-terminus of GABA$_B_{1a}$ and differentiate this isoform from GABA$_B_{1b}$ (Calver et al., 2002). In the GABA$_B_{1b}$ subtype, the N-terminal extracellular domain is the ligand binding domain and differs from the GABA$_B_{1a}$ splice variant at the N-terminus by the presence of a tandem pair of CP modules, while the GABA$_B_{1b}$ splice variant differs in the fifth transmembrane region and the second extracellular loop by an additional 31 amino acids (Blein et al., 2000). Human GABA$_B_{1b}$ is similar to GABA$_B_{1a}$ yet lacks one “Sushi” repeat because the splice machinery skips exon 4 and its expression pattern parallels that of GABA$_B_{1a}$ (Bettler et al., 2003). It appears at least in some brain regions that GABA$_B_{1a}$ and GABA$_B_{1b}$ can participate, through heterodimerization with GABA$_B_{1b}$, in the formation of both pre- and post-synaptic receptors. Similar heterodimerization has also been postulated to occur in the GI tract between GABA$_B_{1a}$ and GABA$_B_{2b}$ (Kawakami et al., 2004) and is further supported by recent immunohistochemical data obtained for both subunits in the upper GI tract (Torashima et al., 2009).
Partial cDNAs corresponding to putative GABA<sub>B</sub> subunit splice variants have also been isolated (Clark et al., 2000). However, investigation of the <i>Gpr51</i> (Gabbr2) gene structure did not provide evidence that these cDNAs correspond to additional GABA<sub>B</sub> subunit splice variants (Martin et al., 2001). Furthermore, the absence of an expression profile for GABA<sub>B1a</sub>, GABA<sub>B2a</sub>, and GABA<sub>B2b</sub> in the human GI tract would suggest such splice variants do not play a significant role in GI function (Calver et al., 2000). Therefore, it seems likely that in the brain two major populations of heteromeric GABA<sub>B</sub> receptors exist, GABA<sub>B1a</sub>B<sub>2a</sub> and GABA<sub>B1a</sub>B<sub>2b</sub>. The behavioral phenotypes of mice with targeted deletions of either the GABA<sub>B1a</sub> (Prosser et al., 2001; Schuler et al., 2001; Mombereau et al., 2004) or the GABA<sub>B2b</sub> subunits (Gassmann et al., 2004; Mombereau et al., 2005) are similar and corroborate the in vivo experiments demonstrating that functional GABA<sub>B1a</sub> receptor responses are dependent on the heterodimerization of GABA<sub>B1a</sub> and GABA<sub>B2b</sub> subunits. Additionally, GABA-mediated inhibition of GI motility appears to be dependent on the GABA<sub>B1a</sub> receptor subunit (Sanger et al., 2002). The more recent development of mice lacking both the GABA<sub>B1a</sub> and GABA<sub>B1b</sub> receptor splice variants have been generated (Vigot et al., 2006) and are proving to be very useful in understanding the role of these receptor isoforms in physiological processes (Jacobson et al., 2006, 2007; Vigot et al., 2006), however, such studies have yet to be extended into the GI tract.

**LOCALIZATION OF GABA AND GABA<sub>B</sub> RECEPTORS IN THE GASTROINTESTINAL TRACT**

γ-aminobutyric acid is located throughout the GI tract and has been localized in enteric nerves as well as in endocrine-like cells implicating GABA as both a neurotransmitter and an endocrine mediator in the GI tract. The primary synthesis pathway for enteric GABA is catalyzed by L-glutamate decarboxylase (GAD; Figure 1) using the substrate glutamate, and has been localized in both Dogiel type I and Dogiel type II enteric neurons (for a review see Krantis, 2000). High affinity plasma membrane GABA transporters (GAT) are also present in the rat GI tract and have been localized to both enteric glia (GAT2) and myenteric neurons (GAT3) of the duodenum, ileum, and colon (Fletcher et al., 2002). In the enteric nervous system (ENS) approximately 5–8% of myenteric neurons, which largely regulate GI motility, contain GABA, and in the colon it predominantly co-localizes with the inhibitory neurotransmitter somatostatin, but also to a lesser extent with enkephalins and nitric oxide (Krantis, 2000). GABA has also been implicated in the regulation of intestinal fluid and electrolyte transport by virtue of its presence in submucosal nerve cell bodies and mucosal nerve fibers (Krantis, 2000). Therefore, it is not surprising that GABA plays a multifunctional role in the regulation of GI activity. In addition to the ENS and endocrine-like sources of GABA, newer endeavors have adapted <i>Bifidobacteria</i>, found in the intestines of breast-fed children and healthy adults, to increase GABA production by genetically increasing GAD activity (Park et al., 2005), and GABA-producing bacteria have been exploited in the production of GABA-containing functional foods such as fermented goats milk (Minervini et al., 2009). Genetically exploiting commensal bacteria to elevate intestinal GABA production allows for local delivery of GABA to the GI tract and may therefore be of some therapeutic use in regulating epithelial proliferation (see GABA<sub>B</sub> Receptors and Gastrointestinal Carcinogenesis) or may directly alter intestinal secretory activity. Although the current literature would suggest that GABA would need to access the enteric plexi to exert an effect on the later (see GABA<sub>B</sub> Receptor Modulation of Intestinal Electrolyte Transport).

Nakajima et al. (1996) demonstrated using an antibody generated against amino-terminal blocked baclofen, GABA<sub>B</sub> receptor immunoreactivity in the rat ENS, muscle and epithelial layers. The 80-kDa antigen against which the antibody was raised was subsequently demonstrated to bind GABA and baclofen, but not the GABA<sub>B</sub> antagonist, bicuculline (Nakayasu et al., 1993). Our own studies in mouse intestine, using a different GABA<sub>B</sub> receptor antibody (Ab25; Engle et al., 2006) corroborated the findings of Nakajima et al. (1996) with respect to localization of GABA<sub>B</sub> receptors on both submucosal and myenteric neurons in the ENS, however we did not detect any mucosal staining in this species (Casanova et al., 2009).

In the rat mucosal epithelium, GABA<sub>B</sub> receptor positive cells were observed along the length of the GI tract from the gastric body to the colon, decreasing in number in the oral to anal direction, on cells that were morphologically similar to enteroendocrine cells. Both gastric and intestinal regions displayed mucosal GABA<sub>B</sub> immunoreactivity, however gastric GABA<sub>B</sub>-positive cells tended to contain...
somatostatin, in contrast to duodenal GABA\textsubscript{B} positive cells which stained positively for serotonin (Nakajima et al., 1996). Therefore, the functional effects of GABA\textsubscript{B} receptors are likely to differ along the GI tract, and are likely to be dependant on its colocalization with prominent enteroendocrine cell mediators such as somatostatin and serotonin. Neural GABA\textsubscript{B1}-positive fibers were observed in the muscle layers of the rat GI tract, and both plexi of the ENS (Nakajima et al., 1996). In the myenteric plexus at least 50% of GABA\textsubscript{B} positive neurons display NADPH-diaphorase activity (Nakajima et al., 1996) suggesting that GABA\textsubscript{B} receptors may directly modulate inhibitory, nitric oxide-driven neurotransmission. By taking advantage of newly developed transgenic mice expressing GABA\textsubscript{B1a} and GABA\textsubscript{B1b} subunits fused to the enhanced green fluorescence protein (eGFP) we also immunohistochemically localized the GABA\textsubscript{B1} receptor subunit to both myenteric and submucosal neurons in mouse colon and ileum (Figure 2). Similar to our studies with an anti-GABA\textsubscript{B1} antibody, we did not detect any enteroendocrine-like staining for the GABA\textsubscript{B1} receptor subtype in this species (Casanova et al., 2009). Analysis of GABA\textsubscript{B1} receptor subunit expression has been examined in human small intestine and stomach (Calver et al., 2000), rat small and large intestine (Castelli et al., 1999) as well as dog intestine (Kawakami et al., 2004). In the human GI tract GABA\textsubscript{B1a} and GABA\textsubscript{B1b} subunits are differentially expressed (Calver et al., 2000) with the GABA\textsubscript{B1a} receptor subunit, and its splice variants GABA\textsubscript{B1a1} and GABA\textsubscript{B1a2}, predominating. GABA\textsubscript{B1b} on the other hand, irrespective of the splice variant examined, was undetectable in either region of the human GI tract (Calver et al., 2000). Despite the initial findings of Calver et al. (2000) subsequent studies have identified GABA\textsubscript{B1b} message in the human lower esophageal sphincter (LES), cardia and corpus (Torashima et al., 2009) as well as in dog intestine (Kawakami et al., 2004). Furthermore, immunohistochemical analysis identified GABA\textsubscript{B1b} protein on myenteric neurons in human LES and gastric corpus (Torashima et al., 2009).

**GABA\textsubscript{B1} RECEPTORS AND GASTROINTESTINAL FUNCTION**

**GABA\textsubscript{B1} INDUCED SYNTHESIS AND RELEASE OF ENTERIC NEUROTRANSMITTERS AND ENTOCROMAFFIN CELL-DERIVED SEROTONIN**

Microdialysis sampling of myenteric plexus neurotransmitter release demonstrated a significant inhibitory effect of the GABA\textsubscript{B1} receptor agonist, baclofen on canine intestinal acetylcholine (ACh) release and this was sensitive to GABA\textsubscript{B1} receptor antagonism (Kawakami et al., 2004). Of particular note, in this species at least, was the sensitivity of ACh release (and motility) to the GABA\textsubscript{B1} receptor antagonist alone (Kawakami et al., 2004). Therefore, in the canine ileum it would appear that GABA\textsubscript{B1} receptor activation is inhibitory and that GABA via GABA\textsubscript{B1} receptors tonically inhibits excitatory ACh release. In contrast, release of the inhibitory neurotransmitter, vasoactive intestinal polypeptide from rat colon was insensitive to inhibition by the GABA\textsubscript{B2} receptor antagonist, phaclofen (Grider and Makhlouf, 1992). Similarly, in guinea-pig ileum the production of electrically induced citrulline, as a marker for nitric oxide synthase activity, was insensitive to GABA\textsubscript{B1} receptor modulation with baclofen, but was reduced by the GABA\textsubscript{B1} agonist, muscimol (Hebeiss and Kilbinger, 1999). Therefore, with the caveat of species differences, it would appear that GABA\textsubscript{B1} receptors exert an inhibitory effect on release of ACh, without any significant effect on inhibitory neurotransmitter release or synthesis.

Both GABA\textsubscript{B1} and GABA\textsubscript{B2} receptors have also been shown to regulate the release of enterochromaffin cell-derived serotonin from guinea-pig small intestine, although they appear to have opposing effects (Schworer et al., 1989). Baclofen-induced, GABA\textsubscript{B1}-driven, inhibition of serotonin release occurs via a tetrodotoxin (TTX) insensitive, non-neural pathway while GABA\textsubscript{B2} receptor activation causes a predominant TTX-sensitive, muscarinic receptor-driven release of serotonin (Schworer et al., 1989). Therefore, the potential exists for GABA\textsubscript{B1} receptors to indirectly regulate ENS activity via release of enteroendocrine-cell derived mediators such as serotonin.

**GABA\textsubscript{B1} RECEPTOR MODULATION OF INTESTINAL MOTILITY**

\(\gamma\)-Aminobutyric acid, and as such GABA receptor-mediated effects on GI motility are dependant on an intact ENS as isolated rat smooth muscle cells are unresponsive to addition of GABA (Grider and Makhlouf, 1992). Both electrically induced ileal twitch responses and spontaneous colonic smooth muscle contraction (cholinergic in nature) are sensitive to inhibition by baclofen in the guinea-pig (Ong and Kerr, 1982; Allan and Dickenson, 1986; Minocha and Galligan, 1993; Table 1). In vitro data suggest that this GABA\textsubscript{B1} mediated inhibitory effect is countered by GABA\textsubscript{B2} receptors, as GABA\textsubscript{B2} receptor activation caused a rightward shift in the ED\textsubscript{50} for baclofen on the ileal twitch response, and this was recovered to some extent in the presence of the GABA\textsubscript{B2} receptor antagonist, biccuculline (Allan and Dickenson, 1986). In addition to which complex GABA\textsubscript{B1}...
Table 1 | Summary of GABA<sub>B</sub> receptor-induced effects on gastrointestinal motility.

| Region       | Species     | Baclofen induced-effect                                                                 | Reference                          |
|--------------|-------------|----------------------------------------------------------------------------------------|------------------------------------|
| Duodenum/jejunum Human | TTX sensitive inhibition of spontaneous and DMPP-induced contraction                       | Gentilini et al. (1992) |
| Rat          | Reduction in electrically evoked cholinergic contraction                                   | Krantis and Harding (1987)         |
|              | Disruption of migrating motor complex activity *(i.v. administration)*                   | Fargeas et al. (1988)              |
|              | Atropine-sensitive increase in migrating motor complex activity *(i.v. administration)* |                                     |
| Ileum Guinea-pig | Decrease in electrically evoked (cholinergic) twitch response                              | Ong and Kerr (1982) and            |
|              | Relaxation (all levels of the intestine)                                                  | Marcoli et al. (2000)              |
|              | Inhibition of somatostatin inhibitory activity on cholecystokinin-induced contraction (cholinergic) | Roberts et al. (1993) |
|              | TTX- and hyoscine-sensitive relaxation (basal) and hyoscine-sensitive relaxation following histamine and prostaglandin F<sub>20</sub> stimulation | Giotti et al. (1983) |
|              | Inhibition of electrically stimulated NO-mediated relaxation                              | Kilbinger et al. (1999)            |
| Mouse        | Inhibition of electrically evoked contraction *(GABA<sub>B</sub>,+)*                      | Sanger et al. (2002)               |
|              | Loss of baclofen-induced relaxation *(GABA<sub>B</sub>,−*)                                 |                                     |
| Cat          | Contraction of longitudinal muscle (distal and terminal ileum; modest if any sensitivity to atropine and TTX) and no effect on circular muscle activity | Pencheva et al. (1999) |
| Intestine Dog | Reduction of circular muscle motor activity coupled with a decrease in ACh release *(intra arterial administration)* | Kawakami et al. (2004) |
| Colon        | Human                                                |                                      |
| Guinea-pig   | No effect                                            | Gentilini et al. (1992)             |
|              | Decrease in fecal pellet expulsion and TTX-sensitive relaxation                            | Ong and Kerr (1982)               |
|              | Decrease in basal and physostigmine-induced tone *(i.v. administration)*                 | Giotti et al. (1985)               |
|              | TTX and scopolamine-sensitive relaxation            | Giotti et al. (1985) and           |
|              |                                                     | Minocha and Galligan (1993)        |
| Rat          | Increase in electrically evoked cholinergic and non-cholinergic circular muscle contraction that is sensitive to nicotinic receptor blockade | Bayer et al. (2003)               |
| Rabbit       | Modest decrease in resting tone and inhibition of electrically-induced (cholinergic) contraction. Inhibition of NANC neurotransmission and decreased transit | Tonini et al. (1989)               |

ACh, acetylcholine; DMPP, dimethylphenylpiperazinium; i.v. intravenous; i.c.v. intracerebroventricular; NANC, non-adrenergic non-cholinergic; NO, nitric oxide; TTX, tetrodotoxin. Unless otherwise noted in italicize, all drug additions were to in vitro preparations.

receptor-dependant signaling pathways, in the guinea-pig ileum at least, have been identified and involve GABA<sub>B</sub> receptor-mediated inhibition of somatostatin-sensitive cholecystokinin-induced contraction (Roberts et al., 1993; Table 1).

In the human GI tract spontaneous activity of jejunal longitudinal muscle is sensitive to inhibition by both GABA and baclofen. However, spontaneous colonic activity was insensitive to GABAergic modulation (Gentilini et al., 1992) suggesting that GABA<sub>B</sub> receptor-mediated inhibition predominates in the small intestine of humans. However, in other species GABA<sub>B</sub> receptors have been demonstrated to alter colonic motor activity. For example, desensitization of GABA<sub>B</sub> receptors with baclofen, thereby relieving GABA<sub>B</sub>-induced effects on motility, resulted in decreased colonic fecal pellet output in the guinea pig (Ong and Kerr, 1982; Table 1), potentially due to dysregulation of cholinergic activity and peristalsis as suggested by the authors, or a disinhibition of inhibitory activity. In contrast to the guinea-pig colon, the propulsive velocity of a distended balloon along rabbit colonic preparations was significantly reduced by GABA<sub>B</sub> receptor activation with baclofen, consistent with an inhibitory effect of this receptor on excitatory neurotransmission (Tonini et al., 1989; Table 1). In the same species, baclofen had a minor inhibitory effect on colonic longitudinal muscle tone but a more significant inhibitory effect on TTX- and hyoscine-sensitive electrically stimulated responses, suggesting that the inhibitory effects of the GABA<sub>B</sub> agonist on colonic activity in the rabbit is dependant on cholinergic neurotransmission (Tonini et al., 1989; Table 1). Consistent with modulation of cholinergic enteric nerves, baclofen decreases both GABA<sub>B</sub> receptor-induced relaxation of guinea-pig ileal (Giotti et al., 1983) and colonic (Giotti et al., 1985) longitudinal muscle via a TTX-sensitive, cholinergic pathway and in vivo inhibited physostigmine-induced colonic tone (Giotti et al., 1985; Table 1). GABA receptor-induced relaxation appears to be mediated predominantly via GABA<sub>B</sub> receptors in guinea-pig colon, as less than 10% of the GABA-induced relaxant effect is sensitive
to GABA<sub>B</sub> receptor blockade (Giotti et al., 1985). However, there is also evidence for GABA<sub>B</sub> receptor-mediated activation of inhibitory pathways in guinea-pig colon (Minocha and Galligan, 1993) which one would expect to potentiate GABA<sub>B</sub>-mediated relaxation. Non-adrenergic non-cholinergic inhibitory responses also display sensitivity to GABA<sub>B</sub> receptor activation in the rabbit (Tonini et al., 1989; Table 1), indicative of a co-ordinated regulatory role for GABA<sub>B</sub> receptors in the modulation of peristalsis in this species.

The availability of GABA<sub>B</sub> subunit receptor deficient mice has led to further characterization of GABA<sub>B</sub> receptor-mediated effects in the GI tract (Sanger et al., 2002). Baclofen-induced inhibitory responses were observed in wildtype mouse intestine following electrical stimulation, but were absent in GABA<sub>B</sub> subunit deficient animals (Sanger et al., 2002). This unresponsiveness to baclofen does not appear to be due to an overt dysregulation of ileal function in GABA<sub>B</sub> mutant mice as these animals respond in a similar manner as wildtype animals to both electrical and cholinergic stimulation (Sanger et al., 2002; Table 1). Therefore, the functional dependence of GABA<sub>B</sub> receptors in the mouse is dependant on the GABA<sub>B</sub> subunit, and this finding is consistent with the preferential expression of this subunit in the GI tract of several species, including humans (Castelli et al., 1999; Calver et al., 2000; Kawakami et al., 2004).

As well as having a peripheral site of action, GABA can exert effects on GI motility via central mechanisms (Fargeas et al., 1988). In unanesthetized rats intracerebroventricular administration of baclofen had a stimulatory effect on GABA<sub>B</sub> receptor- and atropine-sensitive migrating myoelectric complexes (MMC) (Fargeas et al., 1988; Table 1). While seemingly in disagreement with in vitro data, or data from anesthetized animals, which point toward a peripheral inhibitory effect for GABA<sub>B</sub> receptors in the GI tract, the authors suggest that this enhancement of MMC activity may represent baclofen-induced adaptation of vagal afferent activity.

**GABA<sub>B</sub> RECEPTOR MODULATION OF INTESTINAL ELECTROLYTE TRANSPORT**

Despite localization of GABA<sub>B</sub> receptors in the submucosal plexus of rat (Nakajima et al., 1996) and mouse (GABA<sub>B<sub>1</sub>; Casanova et al., 2009) intestine, they do not appear to be involved in the regulation of electrolyte transport. In guinea-pig intestine, only GABA<sub>B</sub> receptor activation, but not baclofen, mimicked GABA<sub>B</sub>-induced elevations in short-circuit current (MacNaughton et al., 1996). A similar bias toward GABA<sub>B</sub> receptor-mediated modulation of chloride ion-dependant secretion was also observed in rat small intestine (Hardcastle et al., 1991). However, in this species the GABA-induced effect was dependent on the presence of intact myenteric neurons, suggesting a myenteric reflex is involved in initiating the GABA-induced secretory response (Hardcastle et al., 1991). However, given the paucity of data in this area it is difficult to draw a firm conclusion on the role of GABA<sub>B</sub> receptor modulation of intestinal ion transport which may vary among intestinal regions and across species.

**GABA<sub>B</sub> RECEPTORS AND GASTROINTESTINALafferent SIGNALING AND NOCICEPTION**

Vagal afferent fibers display sensitivity to baclofen and this response is, as expected, sensitive to GABA<sub>B</sub> receptor antagonism (Page and Blackshaw, 1999). Further investigation of this vagal afferent pathway elucidated GABA<sub>B</sub> receptor-mediated opening of K<sup>+</sup> and closing of Ca<sup>2+</sup> channels as contributing to the inhibitory effect of GABA on afferent activity, although this inhibitory effect varied dependent on the sensitivity of the fibers to mucosal, tension or tension-mucosal stimulation, in addition to which Ca<sup>2+</sup>- and K<sup>+</sup>-independent pathways were also identified (Page et al., 2006). In addition to vagal afferents, GABA<sub>B</sub> receptors also regulate spinal afferent signaling (Hara et al., 1990, 1999; Sengupta et al., 2002). Intrathecal injection of baclofen significantly reduced the threshold response to colorectal distension (CRD) in a dose-dependant manner (Hara et al., 1999). Furthermore, when co-administered with morphine, the antinociceptive effect of the later was potentiated, indicative of a GABA<sub>B</sub>/μ-opiod receptor interaction, which the authors suggest may involve synergistic activation of cAMP and potentiation of the anti-nociceptive effects of both GABA and morphine (Hara et al., 1999). A similar potentiation of the baclofen-induced effect on visceral pain was also observed with the Ca<sup>2+</sup> channel blocker, diltiazem (Hara et al., 2004). In addition to acting synergistically with morphine and diltiazem, both studies also demonstrated that intrathecal administration of baclofen alone was sufficient to reduce the visceral pain response to CRD (Hara et al., 1999, 2004). These functional data are consistent with subsequent findings describing baclofen-sensitive electrical activity of S<sub>D</sub> dorsal roots following pelvic nerve stimulation during CRD (Sengupta et al., 2002).

Moreover, systemic intravenous (i.v.) administration of baclofen to rats also significantly reduced the visceral pain response, suggesting the GABA<sub>B</sub> agonist can potentially exert its anti-nociceptive effects at sites outside the central nervous system, including in the GI tract (Brusberg et al., 2009). The same authors also demonstrated that the positive allosteric modulator of the GABA<sub>B</sub> receptor, CGP7930 also displayed efficacy in reducing CRD-induced effects on the visceromotor response, blood pressure, and heart rate following i.v. administration (Brusberg et al., 2009). However, the efficacy of CGP7930 was less than that of baclofen (Brusberg et al., 2009), potentially as its mechanism of action as an allosteric modulator is dependant on the levels of endogenous GABA or GABA tone. In a similar manner to baclofen, CGP7930 does not appear to alter colonic compliance (Brusberg et al., 2009), suggesting the anti-nociceptive effect of CGP7930 is not due to increased accommodation, as a result of muscle relaxation, of the distension stimulus.

In addition to decreasing CRD-induced pain responses, baclofen also alters gut to brain signaling following peripheral colonic inflammation (Lu and Westlund, 2001). Mustard oil-induced colonic inflammation significantly enhanced spinal cord expression of the early gene product Fos, and this response was sensitive to inhibition by baclofen (Lu and Westlund, 2001), suggesting a dampening of afferent signaling from the periphery to the central nervous system. Additionally, baclofen pretreatment per se, as well as in the presence of mustard oil, concomitantly increased activity in the rostral nucleus tractus solitarius suggesting that activation of descending anti-nociceptive autonomic pathways or an inhibition of inhibitory activity may also occur, resulting in an enhancement of Fos activity (Lu and Westlund, 2001). Therefore, GABA<sub>B</sub> receptor agonists have the potential to exert a dual effect in the GI tract in response to noxious physical or chemical stimuli by decreasing afferent signaling and enhancing anti-nociceptive outflow.
**GABA<sub>B</sub> Receptor-Mediated Regulation of Gastric Motility, Emptying, and Acid Secretion**

Baclofen exerts a vagus nerve-dependent dual effect on gastric motility that involves an increase in gastric pressure as a result of an inhibition of non-adrenergic non-cholinergic inhibitory neurons in the gastric corpus, as well as an atropine-sensitive stimulation of rhythmic contractions in both the corpus and antrum (Andrews et al., 1987). Moreover, independent of innervation by the central nervous system, peripheral GABA<sub>B</sub> receptor activation induces TTX- and atropine-sensitive gastric contractility in vitro (Rotondo et al., 2010), suggesting that baclofen locally increases gastric tone through activation of intrinsic cholinergic neurons. Not unexpectedly then, GABA<sub>B</sub> receptors have been shown to regulate gastric emptying (in mouse; Symonds et al., 2003). However, this was dependant on the consistency of the diet consumed and on the dose of baclofen administered (Symonds et al., 2003). Lower doses significantly increased gastric emptying of a solid meal, but decreased emptying of a liquid meal at a higher dose (Symonds et al., 2003). This divergent effect of baclofen reflects the different mechanisms that underlie gastric emptying of solid and liquid meals. In a model of delayed gastric emptying, induced by central and peripheral administration of diprypyrone, intracerebroventricular baclofen dose-dependently reversed diprypyrone-induced gastric retention (Collares and Vinagre, 2005).

Given the evidence for central and peripheral regulation of gastric cholinergic neurons by GABA<sub>B</sub> receptors, it is perhaps not surprising that GABA and GABA<sub>B</sub> receptors might also influence cholinergic-induced gastric acid secretion. In keeping with such a hypothesis baclofen, or the GABA mimetic PCP-GABA, induce an increase in gastric acid secretion beyond that induced by histamine and cholinergic agonism alone (Goto and Debas, 1983). This effect occurs independently of GABA<sub>A</sub> receptors (Hara et al., 1990; Yamasaki et al., 1991) and is accompanied by an increase in vagal cholinergic outflow (Yamasaki et al., 1991). Consistent with such a vagal-cholinergic pathway, systemic baclofen-induced acid secretion (and gastric motility) was inhibited by both atropine and vagotomy (Andrews and Wood, 1986). Similar effects have also been observed in mice, and are mimicked by the GABA<sub>B</sub> receptor agonist, SKF-97541 (Piqueras and Martinez, 2004). As predicted by earlier studies Piqueras and Martinez (2004), demonstrated a vagally mediated atropine-sensitive regulation of acid secretion in mouse stomach, however they also demonstrated that GABA<sub>B</sub> receptor-activated acid secretion was sensitive to neutralization of gastrin and enhanced in the presence of a somatostatin neutralizing antibody; the former suggesting that GABAergic induced gastric acid secretion occurs via a neurohumoral route which is sensitive to feedback inhibition by the later. Other studies have identified baclofen-induced acid secretion as also being partially dependant on histamine H<sub>1</sub> receptors, and identified extravagal effects of baclofen on gastric acid secretion in vagotomized rats (Blandizzi et al., 1992).

**GABA<sub>B</sub> Receptors as a Therapeutic Target in the Gastrointestinal Tract**

GABA<sub>B</sub> receptors and transient lower esophageal relaxation (TLESR) and the application of GABA<sub>B</sub> agonists in the treatment of gastroesophageal reflux disease (GERD) is of particular translational relevance, being the only case of the use of GABA<sub>B</sub> receptors as a clinical target (as recently reviewed by Lehmann, 2009; Lehmann et al., 2010). In pre-clinical studies, intravenous and intragastric administration of baclofen displayed almost equal potencies with respect to inhibition of TLESRs in the dog, despite a concomitant increase in gastric pressure, and these effects were sensitive (to some extent) to GABA<sub>B</sub> receptor antagonism and absent when the S enantiomer of baclofen was used (Lehmann et al., 1999). Similar inhibition of TLESRs by baclofen was observed in ferrets (Blackshaw et al., 1999), and the site of action for the GABA<sub>B</sub>-mediated effect on TLESR in this species was later demonstrated to involve inhibition of vagal motor output, via GABA<sub>B</sub> (GBA<sub>B</sub>) receptors (McDermott et al., 2001), and thought to involve subsequent inhibition of non-adrenergic non-cholinergic activity. However, inhibition of mechano-sensitive gastric vagal afferents and their central synaptic connections with brain stem neurons must also be considered as a site of action for GABA<sub>B</sub> receptor agonists in the treatment of GERD. In parallel clinical trials, conducted in and around the same period as pre-clinical studies, data demonstrated that baclofen increased lower esophageal pressure and decreased TLESRs and the number of reflux episodes in healthy human subjects (Lidums et al., 2000). A later study conducted in patients suffering from GERD, similarly demonstrated a significant effect of orally administered baclofen on esophageal pH and on the incidence of reflux episodes and TLESRs, however in this particular study patients did not report any improvement in reflux symptoms (van Herwaarden et al., 2002). Nonetheless, a subsequent study indicated that 4 week treatment with baclofen significantly decreased the intensity of a number of symptoms associated with reflux, including fasting and post prandial epigastric pain, day- and night-time heartburn and regurgitation (Cicciogione and Marzio, 2003). Despite its efficacy in relieving GERD symptoms, one of the common features associated with baclofen administration in GERD patients is the development of centrally mediated side-effects, with over 80% of baclofen-treated patients reporting neurological events such as dizziness (van Herwaarden et al., 2002). In order to overcome such central side-effects a number of GABA<sub>B</sub> receptor agonists have been developed and tested for efficacy in reducing TLESRs, these include the GABA<sub>B</sub> agonists AZD9343 (Beaumont et al., 2009), AZD3355 (lesogaberan; Boeckxstaens et al., 2010a,b) and a prodrug of the R enantiomer of baclofen, XP19986 (arbaclofen placabil; Gerson et al., 2010). The pre-clinical data for AZD9343 favored a decreased side-effect profile as its pharmacology suggested the GABA<sub>B</sub> agonist did not readily cross the blood brain barrier and was sequestered intracellularly via a GABA-carrier independent mechanism (Lehmann et al., 2008). Although AZD9343 reduced the number of TLESRs in healthy volunteers, significant side-effects unfortunately remained and included drowsiness and paresthesia (Beaumont et al., 2009). However, other side effects such as the incidence of dizziness in AZD9343-treated subjects were less than those reported in the baclofen-treated group (Beaumont et al., 2009). Of most promise currently in terms of efficacy in treating the symptoms of GERD and having a reduced side-effect profile is lesogaberan. Its pharmacology differs from that of AZD9343 in that lesogaberan displays affinity for GABA<sub>B</sub> carriers, thereby reducing GABA<sub>B</sub>-mediated central side effects (Lehmann et al., 2009). Initial trials with lesogaberan in healthy male subjects were positive, with
lesogaberan and baclofen decreasing the number of TLESRs and reflux episodes to a similar extent (Boeckxstaens et al., 2010a). As predicted by pre-clinical studies, subjects treated with lesogaberan had a similar side-effect profile to that observed in those treated with placebo (Boeckxstaens et al., 2010a). Lesogaberan similarly reduced TLESRs in patients with GERD and no significant differences in the side-effect profile between placebo and lesogaberan were observed (Boeckxstaens et al., 2010b). Therefore therapeutically exploiting affinity for GABA-carriers may be to beneficial in reducing the central side effects associated with baclofen.

**GABA<sub>B</sub> RECEPTORS AND GASTROINTESTINAL CARCINOGENESIS**

The GABA<sub>B</sub>-induced effects on gastric pH may potentially inhibit chemically-induced gastric carcinogenesis observed as a decrease in the incidence and number of gastric tumors (Tatsuta et al., 1990). However, this remains unproven, and the exact mechanism underlying the baclofen-induced decrease in proliferation of antral mucosa has yet to be determined (Tatsuta et al., 1992). In the rat lower GI tract, the same group also observed a GABA<sub>B</sub>-induced inhibitory effect on colon tumor growth, but not incidence (Tatsuta et al., 1992).

**SUMMARY AND CONCLUSIONS**

The diversity of GI functions regulated by GABA<sub>B</sub> receptors make it a potentially useful target in the treatment of several GI disorders, but may also limit its therapeutic application due to off target side effects, both in the GI tract and centrally. For example GERD patients and healthy volunteers treated with baclofen reported adverse effects of a neurological nature that included drowsiness and dizziness (Lidums et al., 2000; van Herwaarden et al., 2002; Ciccaglione and Marzio, 2003). However, the development of peripherally acting compounds such as lesogaberan, which by virtue of its affinity for GABA carrières (Lehmann et al., 2009) limits its effects at central GABA<sub>B</sub> receptors, may well overcome the disadvantages associated with traditional GABA<sub>B</sub> agonists. Lesogaberan, like baclofen, displays efficacy in the treatment of GERD (Boeckxstaens et al., 2010a,b), but has yet to be tested in other GI disorders where targeting peripheral GABA<sub>B</sub> receptors could also be therapeutically useful, i.e., in motility disorders. Furthermore, over the last several years a number of positive allosteric modulators of the GABA<sub>B</sub> receptor have been developed (Urwyler et al., 2001, 2003; Malherbe et al., 2008). One of which, CGP79390, reduces the visceral pain response induced by CRD (Brusberg et al., 2009) and may therefore be therapeutically useful in the treatment of functional bowel disorders such as irritable bowel syndrome where visceral pain is a predominant and debilitating symptom. These modulators offer advantages over traditional GABA<sub>B</sub> agonists, such as baclofen, as their actions occur following enhancement of endogenous GABA release or transmission, thereby limiting the side-effects that are normally associated with traditional agonist treatment. More novel strategies for delivering GABA to the GI tract in the form of engineered bacteria, such as GAD transfected *Bifidobacterium longum* (Park et al., 2005), or the development of GABA containing functional foods (Minervini et al., 2009) are in their infancy, but may offer potential in treating GI conditions that are GABA or GABA<sub>B</sub> receptor-sensitive.

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