ELSEVIER

European Journal of Pharmacology 431 (2001) 339–344

ejp

www.elsevier.com/locate/ejphar

Effects of $GABA_B$ receptor antagonists on spontaneous and on GABA-induced mechanical activity of guinea-pig smooth muscle preparations

Atanas D. Kristev [a], Damianka P. Getova [b,*], Vassil A. Spassov [c], Valentin I. Turiiski [a]

[a] *Department of Physics and Biophysics, Higher Medical Institute, Plovdiv, Bulgaria*
[b] *Department of Pharmacology, Higher Medical Institute, Plovdiv, Bulgaria*
[c] *Department of Pharmacology, Medical Faculty, Thracian University, Stara Zagora, Bulgaria*

Received 14 May 2001; received in revised form 10 August 2001; accepted 14 August 2001

Abstract

The majority of $GABA_B$ receptor antagonists have been based on alterations of the acidic moiety of γ-aminobutyric acid (GABA) or baclofen, such as the first selective antagonist phaclofen. More recently, a new structural class of compounds derived by *p*-alkyl substitution in the phosphinic analog of GABA, such as CGP35348 (3-amino-propyl-(diethoxymethyl)-phosphinic acid), have been introduced as $GABA_B$ receptor antagonists. The present study examine the influence of a series of structurally related phosphinic acid analogues on mechanical activity and their effect on GABA-induced reactions in ileal smooth muscle. In our experiments, GABA exerted a biphasic contractile-relaxation effect with pronounced dose-dependent characteristics. 3-[[1-(*S*)-(3,4-Dihydrophenyl) ethyl]amino]-2-(*S*)-hydroxy-propyl]-(phenylmethyl)-phosphinic acid hydrochloride (CGP55845A) induced prolonged relaxation without changing the phasic activity of the ileum preparations. [3-[1-*R*-[[2-(*S*)-hydroxy-3-[hydroxy-4-methoxyphenyl]-methyl]-phosphinyl]-propyl]-aminoethyl]-benzoic acid (CGP62349) did not change the mechanical activity of smooth muscle preparation. *Trans* 3-[6-[[Cyclo hexylmethyl-hydroxy-phosphinyl]-methyl]-3-morpholinyl]-benzoic acid (CGP71982) itself induced smooth muscle contractions. $GABA_B$ receptor antagonists decreased concentration-dependently the relaxation phase of the action of GABA from 50% to 90%. Their effect on the contractile phase of the action of GABA was quite different—CGP55845A decreased it dose-dependently, whereas CGP62349 and CGP71982 did not change it significantly. These findings prompted us to assume that the $GABA_B$ receptor antagonists studied, being phosphinic analogues, probably act on $GABA_B$ receptors in guinea-pig ileum smooth muscles.

Keywords: $GABA_B$ receptor antagonist; GABA (γ-aminobutyric acid); Ileum; (Guinea pig)

1. Introduction

Data in the literature on the localisation and pharmacological effects of γ-aminobutyric acid (GABA) in various intestinal regions suggest its physiological significance as an autonomic neurotransmitter in the enteric nervous system (Kerr and Ong, 1984; Ong, 1987; Pencheva and Radomirov, 1993). Immuno-histochemical studies have revealed GABA-containing nerve fibres and cell bodies throughout the gastrointestinal tract with a particularly high density in the myenteric plexus (Davanger et al., 1987). Based on the anatomical localisation of these fibres intrinsic to myenteric ganglia or invading circular muscle, the suggestion was made that GABA may function in inter-neuronal communication (Hills et al., 1987). In addition, electrical stimulation of gut preparations has been shown to release GABA (Kerr and Krantis, 1983).

The guinea pig ileum has been widely used as a tool to study the effects of GABA, mediated through $GABA_A$ and $GABA_B$ receptors (Taylor et al., 1991; Ong, 1987; Bowery, 1989). It is now recognised that GABA acts on the classical bicuculline-sensitive $GABA_A$ receptor and on $GABA_B$ receptors, for which baclofen is a specific agonist and phaclofen is a specific antagonist (Kerr et al., 1990a).

* Corresponding author. Department of Pharmacology, Medical University, 155 Evlogi Georgiev str., 1504 Sofia, Bulgaria. Tel.: +359-244-7569; fax: +359-243-0156.
E-mail address: dgetova@hotmail.com (D.P. Getova).

0014-2999/01/$ - see front matter
PII: S0014-2999(01)01338-3

Generally, it is believed that $GABA_A$ is excitatory and $GABA_B$ is inhibitory, but some results are contradictory (Chaudhurl and Ganguly, 1993). The $GABA_B$ receptor antagonists *p*-alkyl-substituted GABA derivatives and phosphinic analogues CGP36742 (3-amino-propyl-*n*-butyl-phosphinic acid), CGP35348 (3-amino-propyl-(diethoxymethyl)-phosphinic acid), etc. (Kerr et al., 1990b) were studied on an ileal preparation.

The aim of our study was to examine the effects of phosphinic analogues and $GABA_B$ receptor antagonists on the spontaneous and on the GABA-induced mechanical activity of guinea pig ileum smooth muscle preparations.

2. Methods

Experiments were performed on smooth muscle preparations taken from adult male guinea pigs weighing between 370 and 480 g. The animals were kept under standard laboratory conditions: temperature, food and light/dark cycle. From 15 to 16 h before the start of the experiment the animals were not fed. The animals were decapitated under ether anaesthesia. A 10-m length of the terminal ileum was removed 13 mm above the ileo-caecal valve. Intraluminal contents were flushed out with Krebs solution.

2.1. Registration of smooth muscle mechanical activity

Mechanical activity was studied on longitudinal ileum smooth muscle preparations (11–12 mm long and 1.5–2.0 mm wide). They were fixed at one end to a plexiglas holder and at the other end to a Swema (Sweden) tensodetector. The starting mechanical tension of the ileum was 7.5 mN. The bath was perfused with a modified Krebs solution, aerated by carbogen gas (5% CO_2 and 95% O_2). The experiments started 40–45 min later. During that time preparations were washed several times with Krebs solution. The spontaneous mechanical activity and drug-induced activity were registered isometrically with a Microtechna (Cech) amplifier and recorded with a Linseis (Germany) recorder.

2.2. Drugs, solutions and chemicals

The following chemical substances and drugs were used in the experiment: acetylcholine (Pharmachim), bicuculline (Sigma), caffeine (as Coffeine Natrii benzoatis, Sopharma), dopamine (Ginlin Pharma), epinephrine (Pharmachim), GABA (Sigma), picrotoxin (Sigma), serotonin (Reanal), tetrodotoxin (Sigma). The $GABA_B$ receptor antagonists CGP55845A (3-[[1-(*S*)-(3,4-Dihydro phenyl)ethyl]amino]-2-(*S*)-hydroxy-propyl]-(phenylmethyl)-phosphinic acid hydrochloride), CGP62349 ([3-[1-*R*-[[2-(*S*)-hydroxy-3-[hydroxy-4-methoxyphenyl]-methyl]-phosphinyl]-propyl]-aminoethyl]-benzoic acid) and CGP71982 (*trans* 3-[6-[[Cyclohexylmethyl-hydroxy-phosphinyl]-methyl]-3-morpholinyl]-benzoic acid) were synthesized by Dr. W. Froestl.

All chemicals and drugs were water-soluble with the following exceptions: bicuculline (diluted in 0.1 N HCl and then adjusted by 0.1 N NaOH to pH 6.5), picrotoxin (diluted in a mixture of distilled water and alcohol 9:1). All substances used to make a solution for perfusion were from Merck. The modified Krebs used in our experiments had the following composition in mM: Na^+—139, K^+—5, Ca^{2+}—2.5, Mg^{2+}—1.1, Cl^-—144, PO_3—13, HPO_3—3 and glucose—11.5, pH 7.23–7.26. The pH of the solution was measured with a Microcomputer pH-meter 6201 (Jenco Electronics).

2.3. Statistical analysis

The mean and standard error mean (S.E.M.) of effects for each concentration used were calculated, and comparison between groups was made by using Student's *t*-test and ANOVA (analysis of variance), using the INSTAT computer program.

3. Results

3.1. Influence of CGP55845A, CGP62349 and CGP71982 on the spontaneous mechanical activity of smooth muscle preparations from guinea pig ileum

The CGP compounds influenced the mechanical activity of isolated guinea pig longitudinal ileal samples. They were applied at concentrations from 1×10^{-7} to 1×10^{-4} M.

3.1.1. CGP55845A (1×10^{-6}–1×10^{-4} M) induced concentration-dependent relaxation

After the application of 10^{-4} M of the substance, the relaxation reached a maximum value of 0.7 ± 0.2 mN ($n = 6$). The relaxation effects were sustained for more than 30 min with no significant changes.

3.1.2. The mechanical activity of smooth muscle preparations did not change in the concentration range 10^{-7}–10^{-5} M CGP62349

At a concentration of 1×10^{-4} M, CGP62349 induced a short-lasting contraction. Its maximum value was 0.4 ± 0.1 mN ($n = 7$).

3.1.3. CGP71982 (10^{-6}–10^{-4} M) induced a long-lasting smooth muscle concentration-dependent contraction

After the application of 10^{-5} and 10^{-4} M an initial peak contraction was seen that preceded the long-lasting contraction. The maximum value of the peak was 2.6 ± 0.8 mN ($n = 7$) and was several times higher than the ampli-

tude of the continuous contraction (0.7 ± 0.1 mN). Caffeine (2×10^{-4} M) completely abolished the CGP71982-induced initial peak contraction ($n = 5$). The subsequent continuous contraction was reduced by caffeine at about 75% ($P < 0.05$) too.

The effects are quantitatively presented in Fig. 1.

3.2. Effects of GABA on the mechanical activity of guinea-pig ileum

GABA (10^{-7}–2×10^{-4} M) had a biphasic contractile-relaxation effect on the mechanical activity (Fig. 2A). This effect was dose-dependent (Fig. 2B). The contraction part of the reaction was usually stronger than the relaxation part. GABA (2×10^{-4} M) caused a maximal effect: a contractile phase of 3.8 ± 0.4 mN and relaxation phase of 0.8 ± 0.1 mN ($n = 22$).

The duration of the contractile and relaxation phases of the reaction was not a function of GABA concentration. These phases lasted 22.6 ± 3.6 and 56.6 ± 4.3 s, respectively.

3.3. Influence of tetrodotoxin on GABA-induced effects

Tetrodotoxin at 1×10^{-6} M significantly influenced both phases of the GABA-induced smooth muscle reaction. The change in the contractile phase was more prominent. The results are presented in Table 1.

3.4. Effects of $GABA_A$ receptor antagonists on GABA-induced smooth muscle reaction

The $GABA_A$ receptor antagonists bicuculline (1×10^{-4} M) and picrotoxin (2×10^{-5} M) significantly minimised the contractile phase of GABA-induced ileal smooth muscle reaction. Bicuculline reduced it by more than 86%, while picrotoxin reduced it by 95% ($P < 0.05$). At the same concentrations, these $GABA_A$ receptor antagonists did not reduce the GABA-induced relaxation. The results are presented in Table 1.

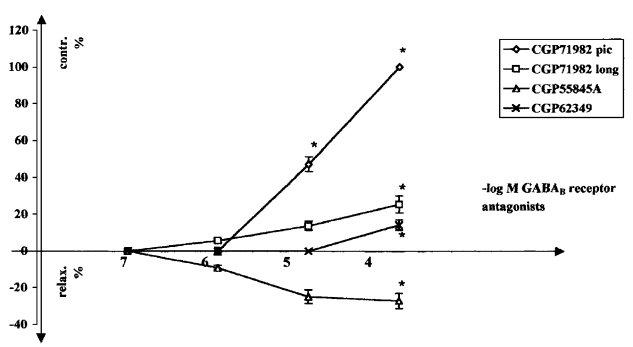

Fig. 1. Concentration–effect curves of CGP compound-induced changes in the mechanical activity of smooth muscle strips from guinea pig ileum. The mean value of the initial peak of the 10^{-4} M CGP71982-induced contraction was taken as 100%. Each point on the graph is the mean ± S.E.M. contraction expressed as a percentage of the CGP71982 contraction (100%). The contractile effects caused by increasing concentrations of CGP compounds were compared for each substance separately. [a]$P < 0.05$.

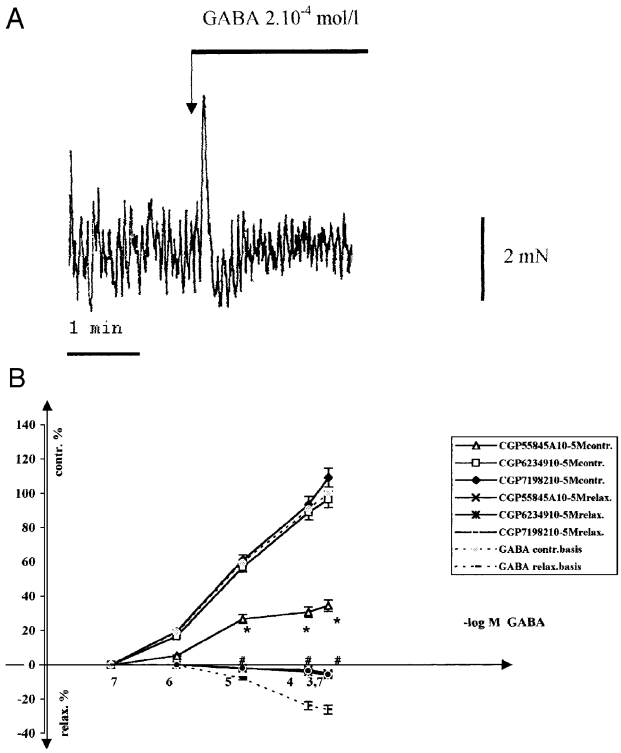

Fig. 2. (A) Record of the effect of GABA (10^{-4} M) on the mechanical activity of a guinea pig ileum longitudinal smooth muscle. (B) Concentration–effect curves of GABA-induced contractile-relaxation effects: controls ($n = 22$) and in the presence of 10^{-5} M CGP 55845A ($n = 7$), 10^{-5} M CGP 62349 ($n = 6$) and a 10^{-5} M CGP 71982 ($n = 6$). The mean value of the GABA-induced (2×10^{-4} M) contractile phase was taken as 100%. Each point on the graph is a mean ± S.E.M. expressed as a percentage of the GABA-induced contraction. The control GABA reaction and equimolar GABA reactions in the presence of CGP compounds for the contractile phase (*) and the relaxation phase (#) were compared. [a,b]$P < 0.05$.

3.5. Influence of $GABA_B$ receptor antagonists on GABA-induced smooth muscle contraction and relaxation

The $GABA_B$ receptor antagonists CGP55845A, CGP62349 and CGP71982 affected the smooth muscle reactions induced by 10^{-7}–2×10^{-4} M GABA.

3.5.1. CGP55845A (10^{-7}–10^{-4} M) reduced significantly both phases of the GABA-induced responses

The influence was dose-dependent. The effect on 10^{-5} M GABA is shown in Fig. 3.

The change in GABA dose-dependent curves in the presence of 10^{-5} M CGP55845A is shown in Fig. 2B.

Table 1
Effects of tetrodotoxin and $GABA_A$ receptor antagonists on the GABA-induced contraction and relaxation in guinea pig ileum longitudinal smooth muscle preparations
The control effects and the effects in the presence of the agents were compared.

Agents	Concentration, M	*n*	GABA 2×10^{-4} M			
			Control		After the drug	
			Contraction, mN	Relaxation, mN	Contraction, mN	Relaxation, mN
Tetrodotoxin	1×10^{-6}	4	3.63 ± 0.48	0.85 ± 0.12	$0.18 \pm 0.06^{*}$	$0.40 \pm 0.04^{*}$
Bicuculline	1×10^{-4}	4	3.60 ± 1.10	0.78 ± 0.29	$0.37 \pm 0.08^{*}$	0.67 ± 0.15
Picrotoxin	2×10^{-5}	4	3.79 ± 0.41	0.89 ± 0.17	$0.10 \pm 0.05^{*}$	0.69 ± 0.26

3.5.2. CGP62349 in a concentration ranging from 10^{-7} to 10^{-4} M decreased significantly the relaxation phase of the response to 10^{-5} M GABA

The influence was dose-dependent and was intensified with an increase in antagonist concentration. CGP62349 did not change the GABA-induced contraction. The relationships observed were valid for the whole concentration range used in our experiments (10^{-6}–2×10^{-4} M) (Fig. 2B and 3).

3.5.3. The relaxation phase of GABA smooth muscle reaction was minimized significantly by the presence of 10^{-5} M CGP71982 (Fig. 2B)

The observed effect was dose-dependent. It is demonstrated in Fig. 3. The initial contractile phase showed a tendency towards an increase.

3.6. Influence of CGP55845A, CGP62349 and CGP71982 on the effects of acetylcholine, epinephrine, 5-hydroxytryptamine and dopamine

The CGP compounds at a concentration of 10^{-5} M did not change significantly the contractile effects of 10^{-6} M acetylcholine ($n = 16$), 10^{-5} M epinephrine ($n = 8$), 10^{-6} M 5-hydroxytryptamine ($n = 6$) and 10^{-5} M dopamine ($n = 6$) on ileal smooth muscle preparations from guinea pigs.

4. Discussion

In our experiments, GABA exerted a biphasic contractile-relaxation effect on the mechanical activity of guinea pig ileum. It had pronounced dose-dependent characteristics. It is known that the biphasic character is typical of GABA-induced modulation in many intestinal organs, i.e. the circular layer of segments isolated from cat terminal ileum (Pencheva and Radomirov, 1993), the longitudinal layer from cat terminal ileum (Pencheva et al., 1991), guinea-pig duodenum, jejunum and ileum (Taylor et al., 1991; Kounenis et al., 1995). The duration of both phases was not a function of the GABA concentration. The contractile effect of GABA is a consequence of the activation of specific $GABA_A$ receptors located on cholinergic postganglionic neurons (Jessen et al., 1979). The activation of these receptors leads to the release of endogenous acetyl-

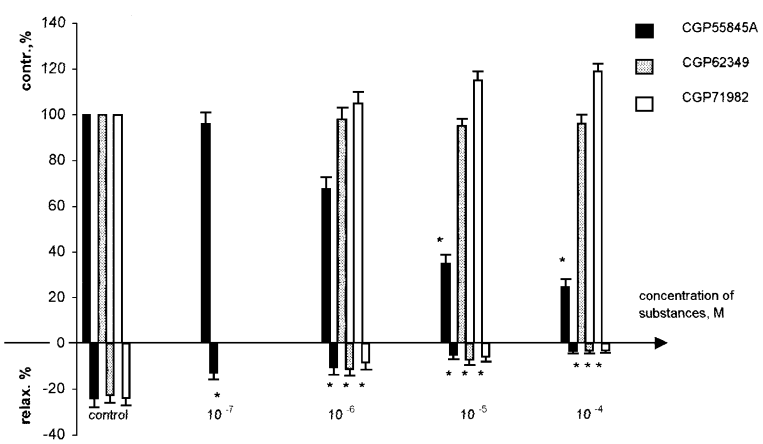

Fig. 3. Influence of $GABA_B$ antagonists (10^{-7}–10^{-4} M) on the amplitude of the contractile and relaxation phase of the 1×10^{-5} M GABA-induced smooth muscle effects. The contractile control reaction is considered to be 100%. All other results are presented as means ± S.E.M. from a relevant number of experiments (control, $n = 7$; of the background of CGP55845A, $n = 6$; CGP62349, $n = 7$ and CGP71982, $n = 6$). They are expressed as percentage of the GABA-induced contraction. The GABA control contractile (*) and relaxation ($^{\#}$) phases and the response to GABA in the presence of CGP compounds were compared for each substance separately. $^{a,b}P < 0.05$.

choline (Kaplita et al., 1982). The relaxation effect of GABA is mediated through $GABA_B$ receptors, the activation of which leads to the inhibition of acetylcholine release (Giotti et al., 1983; Kleinrok and Kilbinger, 1983; Ong and Kerr, 1983).

In our experiments, the $GABA_A$ receptor antagonists bicuculline and picrotoxin significantly reduced the contractile phase of GABA-induced mechanical activity, whilst they did not affect the GABA-induced relaxation. Similar data were reported by Ong (1987), who showed that the effects of bicuculline or picrotoxin on the ileum resulted in a rightward shift of the GABA concentration–response curve. Later, Ong et al. (1988) found that picrotoxin reduced the maximum response, whereas bicuculline did not.

We did not find many studies in the literature about the effects of $GABA_B$ receptor antagonists on the ileum. The sulphonamide analogue of GABA, 3-amino-2-hydroxy-*N*-(4-nitrophen)-propansulphonamide (AHNPS), a competitive $GABA_B$ receptor antagonist, yielded a pA_2 value of 4.0 in the guinea pig ileum (Kerr et al., 1995). β-2-thienyl-GABA (BTG), which is also a competitive $GABA_B$ receptor antagonist had an estimated pA_2 value of 4.3 (Ong et al., 1992). The $GABA_B$ receptor antagonist 4-amino-butyl-phosphonic acid (4-ABPA) (1 mM and above) occasionally elicited with a variable delay a slight transient contraction of the ileum (Kerr et al., 1990b).

Our data for the smooth muscle effects of independently applied $GABA_B$ receptor antagonists were quite interesting. CGP55845A induced a prolonged relaxation of ileum preparations. CGP62349 at concentrations up to 1×10^{-5} M did not change the mechanical activity. It induced a short-lasting contraction only at a concentration of 1×10^{-4} M. CGP71982 contracted the smooth muscle preparations. Caffeine completely abolished the CGP71982-induced initial peak and reduced the long-lasting contraction following it. An intracellular caffeine-sensitive store is probably involved in this effect (Wakui et al., 1990). Possibly the increased Ca^{2+} cytosolic level (Jiang and Stephens, 1994) participates in the increased contractile phase of the response to this $GABA_B$ receptor antagonist.

In our study, $GABA_B$ receptor antagonists did not change significantly the contractile effects of acetylcholine, epinephrine, 5-hydroxytryptamine and dopamine, which suggests their GABA-ergic mechanism of action. Bolser et al. (1995) studied the $GABA_B$ receptor antagonist SCH 50911 on guinea pig ileum and showed that it was devoid of anticholinergic activity, because SCH 50911 elicited no contractile responses and did not antagonise the contractile response to acetylcholine.

The effects of CGP compounds on the contractile phase of the response to GABA were quite different. They influenced the spontaneous mechanical activity and their effects probably are not related to $GABA_B$ receptors. Ong et al. (1988) studied alfaxalone, a typical GABA modulator, which acts on the allosteric site of $GABA_A$ receptors, activating chlorine channels. In lower concentrations it potentiated GABA-induced reactions, whilst in higher concentrations direct GABA-mimetic responses were elicited.

We observed that every $GABA_B$ receptor antagonist decreased significantly the GABA-induced relaxation phase. The influence was concentration-dependent. These observations revealed that the relaxation phase of the response of longitudinal ileal preparations to GABA is probably due to the activation of $GABA_B$ receptors. This suggestion was based on the observation that the relaxation phase was insensitive to the $GABA_A$ receptor antagonists bicuculline and picrotoxin but was blocked in a dose-dependent manner by each CGP compound.

Our experiments provided evidence for the occasional neurogenic nature of the GABA-evoked response, because it was partially blocked by tetrodotoxin. A part of the GABA-induced relaxation response was not sensitive to tetrodotoxin. This suggested the participation of non-neuronic mechanisms in the development of the smooth muscle relaxation. This direct non-neuronic effect was probably mediated by $GABA_B$ receptors directly located on smooth muscle cells. Similar direct GABA-evoked effects, with the participation of $GABA_B$ receptors, have been reported in Fallopian tubes (Erdo et al., 1984). Pencheva et al. (1991) observed similar effects in cat ileum. Thus, the analysis of the GABA-induced relaxation of the guinea pig ileum gave reason to suppose that the $GABA_B$ receptors participating in this process are located pre- and post-junctionally.

In conclusion, $GABA_B$ receptor antagonists showed different effects on spontaneous smooth muscle activity: CGP55845A-induced relaxation, CGP71982-induced contraction and CGP62349 did not change ileal mechanical activity. These effects were probably not directly connected with $GABA_B$ receptors. The specific action of CGP compounds was revealed by inhibition of the relaxation phase of the GABA effect. Our results prompted us to assume that the $GABA_B$ receptor antagonists studied, being phosphinic analogues, probably act on GABA receptors situated in intramural neurons in longitudinal preparations from guinea pig ileum and that they act directly on smooth muscle cells.

Acknowledgements

We thank the National Scientific Fund of Bulgarian Ministry of Education and Science for financial support of Project Grant L-703 and Dr. W. Froestl (Novartis, Switzerland) for supplying the CGP compounds.

References

Bolser, C.R., Blythin, D.J., Chapman, R.W., Egan, R.W., Hey, J.A., Rizzo, C., Kuo, S.-C., Kreutner, W., 1995. The pharmacology of SCH 50911: a novel, orally active $GABA_B$ receptor antagonist. J. Pharmacol. Exp. Ther. 274, 1393–1398.

Bowery, N.G., 1989. $GABA_B$ receptors and their significance in mammalian pharmacology. Trends Pharmacol. Sci. 10, 401–407.

Chaudhurl, L., Ganguly, D.K., 1993. Involvement of GABA in the stimulatory effect of meclopropamide on gastrointestinal motility. Life Sci. 54, 253–259.

Davanger, S., Ottersen, O.P., Storm-Mathisen, J., 1987. Immunocytochemical localization of GABA in cat myenteric plexus. Neurosci. Lett. 73, 27–32.

Erdo, S.L., Riesz, M., Karpati, E., Szporny, L., 1984. $GABA_B$ receptor-mediated stimulation of isolated rabbit oviduct. Eur. J. Pharmacol. 99, 333–336.

Giotti, A., Luzzi, S., Spargnesi, S., Ziletti, L., 1983. $GABA_A$ and $GABA_B$ receptor mediated effects of guinea-pig ileum. Br. J. Pharmacol. 78, 469–478.

Hills, J.M., Jessen, K.R., Mirsky, R., 1987. An immunohistochemical history of the distribution of enteric GABA containing neurones of the rat and guinea pig intestine. Neuroscience 22, 301–312.

Jessen, K.R., Mirsky, R., Dennison, M.E., Burnstock, G., 1979. GABA may be a neurotransmitter in vertebrate peripheral nerves. Nature 281, 71–74.

Jiang, H., Stephens, N.L., 1994. Calcium and smooth muscle contraction. Mol. Cell. Biochem. 135, 1–9.

Kaplita, P.V., Waters, D.H., Triggle, D.J., 1982. GABA action in guinea-pig myenteric plexus. Eur. J. Pharmacol. 79, 43–51.

Kerr, D.I.B., Krantis, A., 1983. Uptake and stimulus evoked release of ^{3}H-GABA by myenteric nerves of guinea pig intestine. Eur. J. Pharmacol. 79, 43–51.

Kerr, D.I.B., Ong, J., 1984. GABA and GABA-receptors in the enteric nervous system. Neuropharmacology 23, 835–836.

Kerr, D.I.B., Ong, J., Prager, R.H., 1990a. $GABA_B$ receptor agonist and antagonists. In: Bowery, N.G., Bittiger, H., Olpe, H.R. (Eds.), $GABA_B$ Receptors in Mammalian Function. Wiley, Chichester, pp. 29–35.

Kerr, D.I.B., Ong, J., Prager, R.H., 1990b. Antagonism of $GABA_B$ mediated responses in the guinea pig isolated ileum and vas deferens by phosphono analogues of GABA. Br. J. Pharmacol. 99, 422–426.

Kerr, D.I.B., Ong, J., Huges, R., Prager, R.H., 1995. 3-Amino-2-hydroxy-*N*-(4-nitrophenyl)-propanesulphonamide, a new class of $GABA_B$ receptor antagonist in central and peripheral preparations. Eur. J. Pharmacol. 294, 349–352.

Kleinrok, A., Kilbinger, H., 1983. GABA and cholinergic transission in the guinea-pig ileum. Naunyn-Schmiedeberg's Arch. Pharmacol. 322, 216–220.

Kounenis, G., Koutsoviti-Papadopoulou, M., Elesoglou, V., 1995. Ketamine may modify intestinal motility by acting at $GABA_A$ receptor complex, an in vitro study on the guinea-pig intestine. Pharmacol. Res. 31, 337–340.

Ong, J., 1987. Uptake inhibitors potentiate GABA-induced contractile responses in the isolated ileum of the guinea-pig. Br. J. Pharmacol. 91, 9–15.

Ong, J., Kerr, D.I.B., 1983. $GABA_A$ and $GABA_B$ receptor mediated modification of intestinal motility. Eur. J. Pharmacol. 86, 9–17.

Ong, J., Kerr, D.I.B., Johnson, G.A.R., 1988. Alfaxalone potentiates and mimics GABA-induced contractile responses in the guinea-pig ileum. Br. J. Pharmacol. 95, 33–38.

Ong, J., Kerr, D.I.B., Berthelor, P., Vaccher, C., Flouquet, N., Debaert, M., 1992. Differing actions of β-(2-thienyl)-γ-aminobutyric acid in central and peripheral preparations. Eur. J. Pharmacol. 221, 145–149.

Pencheva, N., Radomirov, R., 1993. Biphasic $GABA_A$ receptor mediated effect on the spontaneous activity of the circular layer in cat terminal ileum. Gen. Pharmacol. 24, 955–960.

Pencheva, N., Radomirov, R., Venkova, K., 1991. $GABA_A$ and $GABA_B$ receptor mediated effects on the spontaneous activity of the longitudinal layer in cat terminal ileum. Gen. Pharmacol. 22 (1), 159–163.

Taylor, D.A., Leedman, J.A., Bennett, I.E., Fleming, W.W., 1991. Effects of GABA in the morphine-tolerant longitudinal muscle, myenteric plexus preparation of the guinea pig. J. Pharmacol. Exp. Ther. 259, 1994–2001.

Wakui, M., Osipchuk, Y.V., Petersen, O.H., 1990. Receptor-activated cytoplasmic Ca^{2+} spiking mediated by inositol triphosphate is due to Ca^{2+}-induced Ca^{2+}-release. Cell 63, 1025–1032.