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Actions of Daiichi DQ-2511 on electrical and synaptic behavior of enteric neurons in the guinea-pig small intestine

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Abstract

Intracellular recording of electrical and synaptic behavior of neurons in the enteric nervous system of guinea-pig small intestine was used to evaluate actions of DQ-2511 (3-[[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]amino-*N*-methylbenzamide). DQ-2511 is a new drug with gastrointestinal prokinetic action. DQ-2511 was most effective in the nanomolar range. The drug depolarized some of the neurons and this was accompanied by increased input resistance and augmented excitability. DQ-2511 in nanomolar concentrations increased the amplitude of fast excitatory postsynaptic potentials at nicotinic synapses. Slow inhibitory postsynaptic potentials, produced by release of norepinephrine from sympathetic postganglionic fibers, were suppressed by DQ-2511. This appeared to reflect presynaptic suppression of release of norepinephrine because postsynaptic responses to exogenously applied norepinephrine were unaffected. The results suggest that the prokinetic action of DQ-2511 on gastrointestinal transit might emerge from actions that augment excitatory synaptic transmission in the microcircuits of the enteric nervous system while suppressing inhibitory sympathetic neurotransmission.

Keywords: Gastrointestinal tract; Intestine; Ganglion; Enteric nervous system; Myenteric plexus; Submucous plexus; Gastrointestinal motility; Intestinal prokinetic drug; Benzamide, substituted

1. Introduction

DQ-2511 (ecabapide) is a substituted benzamide (3-[[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]amino-*N*-methylbenzamide) originally developed as an anti-ulcer drug (Asano et al., 1990; Hosokami et al., 1992; Hirohashi et al., 1993a; Hirohashi et al., 1993b). Later studies found that DQ-2511 significantly enhanced gastric emptying in rodent models and nonhuman primates, suggesting that the drug has gastrointestinal prokinetic properties (Hatanaka et al., 1995; Kawarabayashi et al., 1995).

The present study was done to explore the actions of DQ-2511 on electrical and synaptic behavior of neurons in the myenteric and submucous plexuses of the guinea-pig small intestine. The rationale for the project was to test the hypothesis that the drug may have gastrointestinal prokinetic actions that emerge from effects on excitability of individual neurons and/or on chemical neurotransmission at synapses that form the integrative microcircuits of the enteric nervous system. This was based on results of previous studies showing that gastrointestinal motility enhancing drugs, such as cisapride and analogs of macrolide antibiotics, act to facilitate neurotransmission and excitability in the enteric nervous system (Nemeth et al., 1985; Tonini et al., 1989; Tack et al., 1991; Tack and Wood, 1991; Wood, 1992).

2. Materials and methods

Male guinea-pigs (400–600 g) were stunned by a blow to the head and exsanguinated from the cervical vessels according to protocols approved by The Ohio State University Laboratory Animal Care and Use Committee. 5–10 cm of small intestine were removed 10–20 cm proximal to the ileocecal junction. Preparations of the myenteric or submucous plexus were dissected, as described in detail elsewhere (Wood and Mayer, 1978; Frieling et al., 1991). The preparations were mounted in a 1.5-ml glass-bottomed recording chamber that was perfused at a rate of 10–15

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ml/min with Krebs solution warmed to 37°C and gassed with 95% O_2-5% CO_2 to buffer at pH 7.3–7.4. The composition of the Krebs solution was (in mM) NaCl, 120.9; KCl, 5.9; MgCl, 1.2; NaH_2PO_4, 1.2; $NaHCO_3$, 14.4; CaCl, 2.5; and glucose, 11.5.

The ganglionated plexuses were visualized with differential interference contrast optics and epilumination. Ganglia selected for study were immobilized with 100-μm diameter stainless steel wires on either side of the ganglion. Recording electrodes were glass micropipettes filled with 3 M KCl. Resistances of the electrodes were 40–120 MΩ. A WPI M-707 amplifier (World Precision Instruments, Saratoga, FL, USA) was used in the bridge circuit mode to record transmembrane potentials and to inject electrical current into the ganglion cell somas. Constant current, rectangular pulses were driven by a Grass SD9 stimulator (Grass Instruments, Quincy, MA, USA), Electrometer output was amplified and observed on an oscilloscope (Tektronics 5113; Tektronics, Beaverton, OR, USA) and recorded on videotape (A.R. Vetter, Rebersburg, PA, USA) for later analysis.

Synaptic potentials were evoked by focal electrical stimulation (200-μs pulses) of interganglionic fiber tracts with electrodes made of 20 μm diameter Teflon-coated platinum wire and connected through a stimulus-isolation unit (Grass SIN5) to a Grass S48 stimulator. Chart records were made on an Astro-Med thermal recorder (Astro-Med, Cleveland, OH, USA). The amplitude of the spikes, in some of the figures, were blunted by the low frequency response of the recorder.

Actions of DQ-2511 and other pharmacological agents were studied by micropressure ejection or by application in the superfusion solution. Micropressure ejection involved micropipettes (10 μm diameter) manipulated with the tip close to the impaled neurons. Pressure pulses of nitrogen with predetermined force and duration were applied to the micropipettes through electronically controlled solenoid valves.

Agents used and sources were: acetylcholine and noradrenaline HCl from Sigma (St. Louis, MO, USA). DQ-2511 (Lot 2016) was synthesized by Daiichi Pharmaceutical (Tokyo, Japan). It was dissolved in distilled H_2O as a 1 mM stock solution and kept refrigerated at 5°C. Dilutions were made in Krebs solution and applied in the superfusion solution. Norepinephrine and acetylcholine (0.1–1 mM) in Krebs solution were applied by pressure microejection. Data on amplitudes of synaptic potentials and neuronal input resistance are expressed as means ± S.E.

3. Results

DQ-2511 was tested on 43 submucous neurons consisting of 36 S/type-1 neurons, 3 AH/type-2 neurons and 4 neurons with intermediate behavior (for details of classification of enteric neurons, see Wood, 1987, 1989, 1994a,b). Neurons selected for study had resting membrane potentials greater than −50 mV and action potentials with greater than 5 mV 'overshoot' from zero potential. Mean input resistance for 30 neurons within a 30-min period after impalement was 242 ± 25 MΩ. All neurons were current clamped at the resting potential prior to application of test substances and stimulation of synaptic potentials. The drug was tested on fast excitatory postsynaptic potentials (fast EPSPs) in 4 myenteric neurons. Submucous neurons became the focus of the study after discovery of significant effects of DQ-2511 on noradrenergic inhibitory postsynaptic potentials (IPSPs) that are found only in neurons of the submucous plexus (Surprenant, 1989).

DQ-2511 was tested in concentrations ranging from 1 nM to 100 μM. The effects of the drug described below were concentration-dependent and can be grouped roughly into actions of the drug in the relative high micromolar range and in the nanomolar range.

3.1. DQ-2511 in micromolar concentrations

Application of DQ-2511 in concentrations of 1–100 μM in 19 neurons produced variable and inconsistent effects on electrical behavior and synaptic transmission. In 4 of the neurons, concentrations greater than 1 μM evoked membrane depolarization ranging from 5 to 10 mV, an increase in input resistance and enhancement of excitability manifest as increased numbers of action potentials evoked by intraneuronal injection of constant current depolarizing pulses. Enhanced excitability was seen occasionally as appearance of spontaneous discharge of action potentials. In the remainder of the neurons, no changes in the electrical behavior were found for the high range of concentrations.

Both EPSPs and IPSPs were affected by high concentrations of the drug. Nevertheless, these effects were variable and inconsistent. In 6 of the neurons, the amplitude of fast EPSPs was increased whereas, in 6 other cells, the fast EPSPs were suppressed. DQ-2511, in the micromolar range of concentrations, suppressed IPSPs in all of 6 submucous neurons. This action was the same as observed in the nanomolar range of concentrations (see below).

3.2. DQ-2511 in nanomolar concentrations

3.2.1. Effects on electrical behavior

DQ-2511 in the nanomolar range (10–100 nM) evoked membrane depolarization in 10 of 15 neurons tested. The depolarization averaged 6.5 mV. Enhanced excitability was associated with the membrane depolarization. This was evident as an increase in the number of action potentials evoked by intraneuronal injection of constant-current depolarizing pulses that was reversed by washout of the drug (Fig. 1). In AH/type-2 neurons, enhanced excitability was evident as the appearance of anodal-break excita-

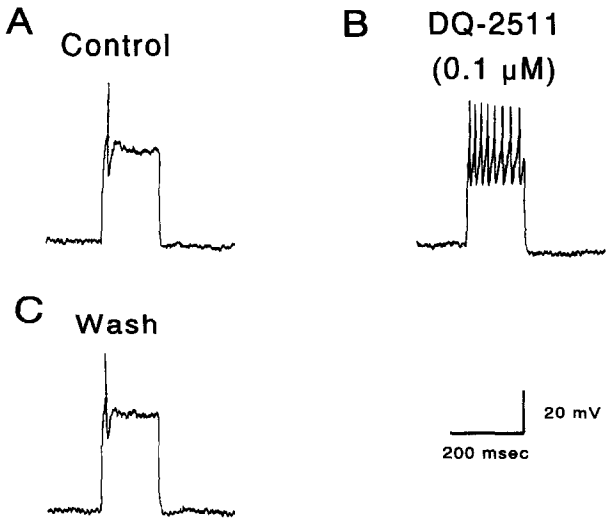

Fig. 1. DQ-2511 enhanced the excitability of enteric neurons. (A) Control response consisted of a single action potential at the onset of a depolarizing current pulse injected from the recording microelectrode. (B) Injection of a current pulse of the same strength, as in A, evoked multiple action potentials after 10 min in the presence of DQ-2511. (C) Washout of the drug reversed the excitatory action.

tion at the offset of intraneuronal injection of hyperpolarizing current pulses.

Increases in input resistance, indicative of decreased resting ionic conductance of the neuronal membranes, were observed in the same neurons in which enhanced membrane depolarization and enhanced excitability were observed. The increase in input resistance was dose-dependent and amounted to $12 \pm 6\%$ at 10 nM and $19 \pm 8\%$ at 100 nM for 10 and 8 neurons, respectively.

3.2.2. *Effects on fast EPSPs*

DQ-2511 in the nanomolar range (10–100 nM) increased the amplitude of fast EPSPs in all of 18 neurons tested (Fig. 2). The increases ranged from 15 to 40% of the amplitude prior to application (Fig. 2d) and were reversed by washing the drug from the preparation (Fig. 2c).

3.2.3. *Effects on slow EPSPs*

DQ-2511 in the nanomolar concentration range also enhanced slow excitatory synaptic transmission in the submucous plexus (Fig. 3). This was observed in 7 of 9 S/type-1 neurons of the submucous plexus. Enhancement consisted of prolongation of the depolarizing response by 0.7–1.4 s and multiple spike discharge indicative of augmented excitability during the depolarization. The enhancing action of the drug on the slow EPSPs was reversed by washout.

3.2.4. *Effects on slow IPSPs in submucous plexus*

DQ-2511 (10–100 nM) suppressed or abolished stimulus-evoked slow IPSPs in 13 of 15 submucous ganglion cells (Fig. 4). This effect was reversible upon washout of the drug.

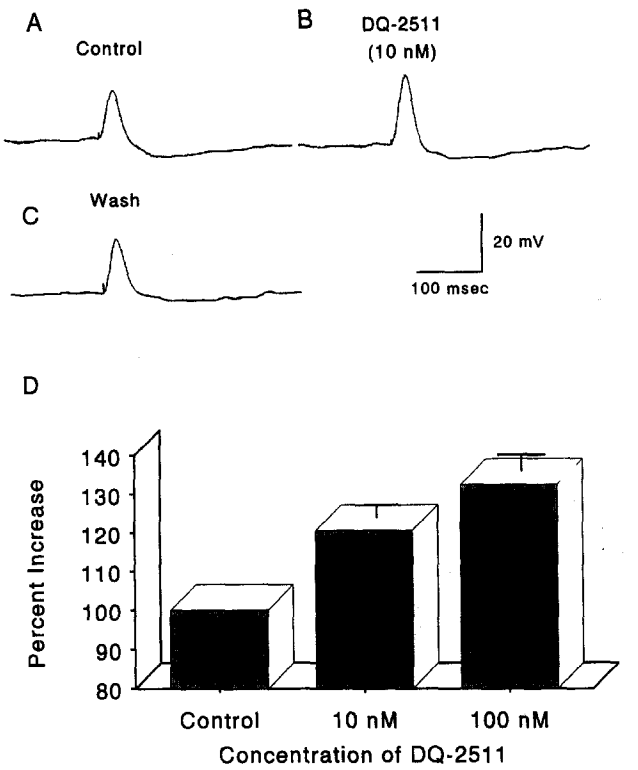

Fig. 2. DQ-2511 increased the amplitude of fast EPSPs in enteric neurons. (A) Control fast EPSP in an S/type-1 neuron of the submucous plexus. The EPSP was evoked by a single electrical shock applied to one of the fiber tracts that entered the ganglion. (B) The amplitude of the fast EPSP was increased after 8 min in the presence of DQ-2511 in the bathing solution. (C) Washout of the drug reversed the effect on the EPSP. (D) Increases in EPSP amplitude were greater for 100 nM than for 10 nM with both concentrations increasing the EPSP amplitude above control values. Each mean represents results for 6 or 8 neurons.

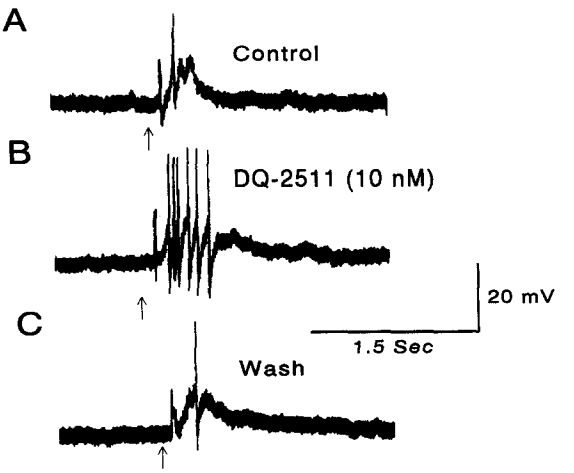

Fig. 3. DQ-2511 increased the amplitude of slow EPSPs in enteric neurons. (A) Control slow EPSP in an S/type-1 neuron of the submucous plexus. The EPSP was evoked by a single electrical shock applied to one of the fiber tracts that entered the ganglion. (B) The amplitude of the slow EPSP was increased after 10 min in the presence of DQ-2511 in the bathing solution. (C) Washout of the drug reversed the effect on the EPSP.

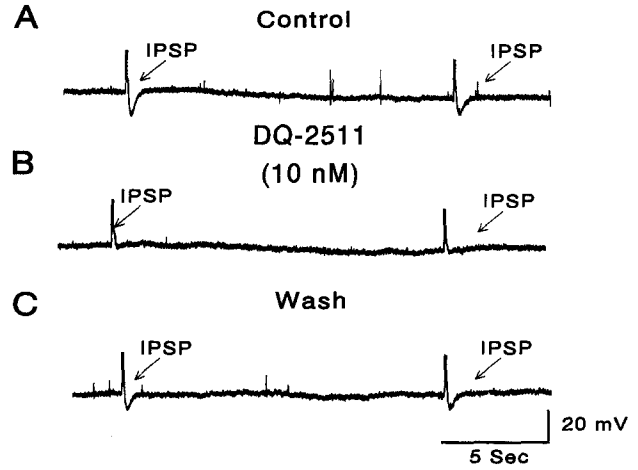

Fig. 4. DQ-2511 suppressed slow IPSPs in submucous neurons. (A) Control slow IPSPs in an S/type-1 neuron of the submucous plexus. The IPSPs were evoked by a train of 3 electrical shocks applied to the surface of the ganglion. (B) The IPSPs were abolished after 10 min in the presence of DQ-2511 in the bathing solution. (C) Washout of the drug reversed the effect on the IPSP.

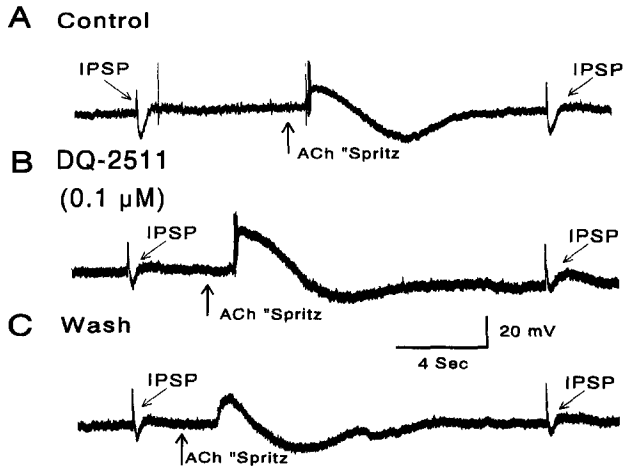

Fig. 6. DQ-2511 enhanced excitatory responses to micropressure application of acetylcholine. (A) Control response to a microejection pulse of acetylcholine ('Spritz') was biphasic with depolarization followed by hyperpolarization. Spike discharge occurred during the rising phase of the depolarization. Two IPSPs were evoked during the course of the record. (B) After 15 min exposure to DQ-2511 in the bathing solution, the amplitude of the depolarizing response to acetylcholine and associated spke discharge were increased whereas the stimulus-evoked IPSPs were suppressed relative to control onset. (C) The effects of the drug were reversed after washout.

3.2.5. Effects on responses to exogenous acetylcholine or norepinephrine

Exogenous norepinephrine or acetylcholine was applied by pressure microejection ('Spritz') before and after application of the drug. Micropressure application of norepinephrine evoked well-known hyperpolarizing responses in the submucous neurons (Surprenant, 1989; Shen et al., 1990). DQ-2511 (10–100 nM) had no effect on the hyperpolarizing action of norepinephrine (Fig. 5). Fig. 5 illustrates how the hyperpolarizing action of norepinephrine was unaffected while the stimulus-evoked slow IPSPs were suppressed by the drug.

Application of acetylcholine by pressure microejection evoked characteristic depolarizing responses accompanied by action potential discharge (Fig. 6). The depolarizations consisted of rapidly and slowly activating phases. Results published elsewhere show that the rapidly activating phase is mediated by nicotinic receptors and the slow depolarization by muscarinic receptors (Surprenant, 1989; Tonini et al., 1989; Wood, 1994a). Application of DQ-2511 in the nanomolar range increased the amplitude of the slowly activating response together with enhanced excitability reflected by a greater intensity of spike discharge (Fig. 6b). This action was reversed by washout. Fig. 6 shows that suppression of stimulus-evoked slow IPSPs by DQ-2511 occurred at the same time that excitatory responses to

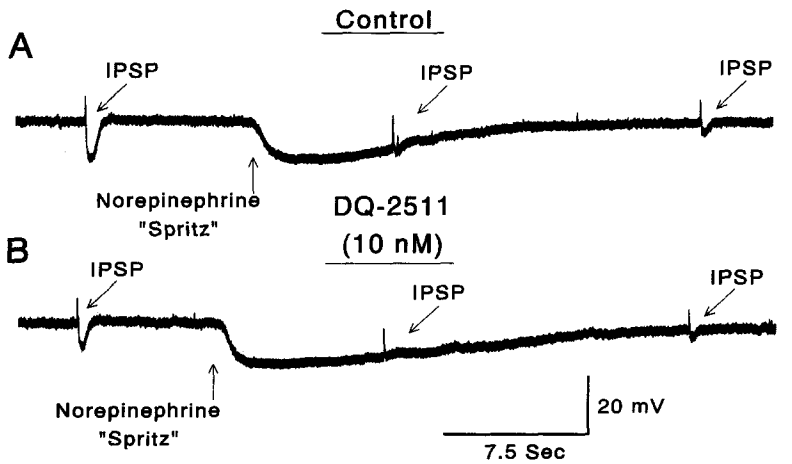

Fig. 5. DQ-2511 did not suppress hyperpolarizing responses to micropressure application of norepinephrine. (A) Control response to a microejection pulse of norepinephrine ('Spritz') was membrane hyperpolarization. Three IPSPs were evoked during the course of the record. Reduction in the amplitude of the IPSPs after norepinephrine reflects presynaptic inhibition of the IPSP mediated by presynaptic autoreceptors for norepinephrine. (B) After 10 min exposure to DQ-2511, the hyperpolarizing response to norepinephrine was unaffected whereas the first IPSP was reduced relative to control.

acetylcholine were enhanced. Effects on the nicotinic component of the cholinergic response were not clearly defined.

4. Discussion

4.1. DQ-2511 in micromolar concentrations

DQ-2511 in the micromolar concentration range was inconsistent in its actions but generally suppressed synaptic transmission. This is reminiscent of the actions of the prokinetic drug cisapride which, like DQ-2511, most often suppresses excitatory neurotransmission and responses to 5-hydroxytryptamine when applied in the micromolar range of concentrations in studies on enteric neurons (Nemeth et al., 1985; Tonini et al., 1989; Tack et al., 1991; Wood, 1992).

4.2. DQ-2511 in nanomolar concentrations

4.2.1. Effects on electrical behavior

The effects of DQ-2511 on electrical behavior differed from what is generally observed with the prokinetic drug, cisapride. Cisapride in nanomolar concentrations generally does not affect the electrical behavior of the cell bodies of the enteric neurons. Insufficient evidence precludes unequivocal interpretation of the excitatory action of DQ-2511. It could reflect a direct effect on the neuron from which the electrical record was obtained. Or, it could result from stimulation of release of excitatory neurotransmitters from other neurons in the same ganglion. The enhancing effects of the drug on slow as well as fast EPSPs within the synaptic microcircuits of the preparations could result in the accumulation of any number of excitatory neurotransmitters. The characteristics of the excitatory effects of the drug mimicked slow synaptic excitation as well as the actions of putative mediators of slow synaptic excitation in the enteric nervous system (for details of enteric slow EPSPs, see Wood, 1989, 1994a). This is consistent with interpretation of the DQ-2511 effect on excitability as due to the release of neurotransmitters for slow synaptic excitation.

4.2.2. Effects on fast EPSPs

The enhancing effects of nanomolar concentrations of DQ-2511 on fast EPSPs were essentially the same as observed in our earlier studies and those of others with the prokinetic drug cisapride (Nemeth et al., 1985; Tonini et al., 1989; Tack et al., 1991; Wood, 1992). Fast EPSPs in the enteric microcircuits throughout the gastrointestinal tract are mediated by the action of acetylcholine at nicotinic postsynaptic receptors (Wood, 1989, 1994b). Enhancement of the fast EPSPs by cisapride occurs without any change in the nicotinic responses to application of acetylcholine. This fulfills criteria for a presynaptic action of the drug to enhance the release of acetylcholine at nicotinic synapses on the neurons. Enhancement of release of acetylcholine and increased amplitude of the EPSPs at the fast nicotinic synapses is expected to 'energize' the circuits that control gastrointestinal motility and can be invoked as part of the mechanism underlying the prokinetic action of cisapride.

The mechanism of action of DQ-2511 to enhance the fast EPSPs was not clearly delineated. It could have resulted from augmented release of acetylcholine at the presynaptic terminal or could have reflected increased input resistance produced by DQ-2511. Moreover, a combination of the two mechanisms cannot be excluded.

4.2.3. Effects on slow EPSPs

The effect of low concentrations of DQ-2511 to enhance slow EPSPs could result from either of two actions that were not distinguished in this study. The drug could act to augment the release of the neurotransmitter for the slow EPSP by an action at the presynaptic terminals. It may also enhance the EPSP through a postsynaptic excitatory action, such as was seen as augmentation of the slow excitatory responses to acetylcholine (Fig. 6). A combination of pre- and postsynaptic actions could also be involved.

4.2.4. Effects on slow IPSPs

The action of DQ-2511 on slow IPSPs was opposite to the effects on excitatory neurotransmission. Stimulus-evoked slow IPSPs were suppressed by the drug. The stimulus-evoked slow IPSPs in the submucous plexus of the small intestine result from activation of nerve fibers projecting from prevertebral ganglia of the sympathetic nervous system (Surprenant, 1989; Wood, 1989, 1994a). They are mediated by the action of norepinephrine at postsynaptic α_2-adrenoceptors on the neurons. The slow IPSPs occur primarily in secretomotor neurons to the intestinal crypts (Cooke, 1988; Surprenant, 1989). Failure of DQ-2511 to alter the hyperpolarizing action of exogenously applied norepinephrine during the time when stimulus-evoked IPSPs were suppressed by the drug suggests that the mechanism of suppression of the IPSPs is inhibition of norepinephrine release from sympathetic nerves.

4.3. Conclusions

The neuropharmacology of DQ-2511 in the enteric nervous system may be unique. All of the actions observed in the present study are those desired of a prokinetic drug. The property of enhancing fast and slow excitatory neurotransmission would be expected to 'energize' the microcircuits that control propulsive motility. Increased gastric emptying is predicted by its actions if they should occur in the stomach and increased intestinal transit is anticipated through the energizing action in the microcircuitry of the intestine.

Intravenous application of DQ-2511 suppresses spontaneous and cholecystokinin-induced firing in vagal afferents from the stomach of the rat (Niijima et al., 1995). Enhanced firing in the vagal efferent innervation of the stomach occurs conincident with suppression of the afferent activity. This suggests that the gastric prokinetic effects of the drug may include actions on intramural afferent nerves as well as the enteric microcircuits.

DQ-2511 appears to suppress the inhibitory influence of the sympathetic nervous system on gastrointestinal functions while at the same time enhancing both propulsive motility and secretion. Suppression of sympathetic transmission to the secretomotor neurons in the submucous plexus would be expected to have an anticonstipation effect in conjunction with strengthened propulsive motility.

Secretomotor neurons in the submucous plexus project collaterals to precapillary arterioles in the submucosa (Evans et al., 1994). The colaterals release acetylcholine, that in turn releases nitric oxide from the arteriolar endothelium leading to dilation of the vessels and increased blood flow in support of stimulated secretion from the intestinal crypts (Andriantsitohaina and Surprenant, 1992). The inhibitory action of DQ-2511 to prevent sympathetic inhibition of the secretomotor neurons would not only promote secretion, but would also be expected to increase mucosal blood flow. Asano et al. (1990) found that DQ-2511 did increase mucosal blood flow in the rat stomach.

References

Andriantsitohaina, R. and A. Surprenant, 1992, Acetylcholine released from guinea-pig submucosal neurones dilates arterioles by releasing nitric oxide from endothelium, J. Physiol. (London) 453, 493.

Asano, M., Y. Kurebayashi, Y. Ryokawa, T. Hashizume and A. Akashi, 1990, Antiulcer effects of 3-[[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]-amino-*N*-methylbenzamide in experimental gastric and duodenal ulcers, Arzneim. Forsch. Drug Res. 40, 276.

Cooke, H.J., 1988, Complexities of nervous control of the intestinal epithelium, Gastroenterology 94, 1087.

Evans, R.J., M.M. Jiang and A. Surprenant, 1994, Morphological properties and projections of electrophysiologically characterized neurons in the guinea-pig submucosal plexus, Neuroscience 59, 1093.

Frieling, T., H.J. Cooke and J.D. Wood, 1991, Electrophysiological properties of neurons in submucous ganglia of the guinea-pig distal colon, Am. J. Physiol. 260, G835.

Hatanaka, S., K. Kawarabayashi, M. Iseri, K. Tsubokura and K. Furuhama, 1995, Enhancing effect of DQ-2511 on gastric emptying of spontaneously hypertensive rats, Life Sci. 56, 377.

Hirohashi, M., K. Takasuna, Y. Kasai, C. Usui, K. Tamura and H. Kojima, 1993a, General pharmacological profile of the new anti-ulcer drug 3-[[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]-amino-*N*-methylbenzamide, Arzneim. Forsch. Drug Res. 43, 569.

Hirohashi, M., K. Takasuna, M. Asano, Y. Ryokawa and K. Tamura, 1993b, Cardiovascular properties of the new anti-ulcer drug 3-[[[2-(3,4-dimethoxyphenyl)ethyl]carbamoyl]methyl]-amino-*N*-methylbenzamide Arzneim. Forsch. Drug Res. 43, 578.

Hosokami, T., M. Kuretani, K. Higashi, M. Asano, K. Ohya, N. Takasugi, E. Mafune and T. Miki, 1992, Syntheses of 2-(3,4-dimethoxyphenyl)ethylamine derivatives and their antiulcer activities, Chem. Pharm. Bull. 40, 2712.

Kawarabayashi, K., S. Hatanaka, M. Iseri, K. Tsubokura and K. Furuhama, 1995, Potential of DQ-2511 as a gastroprokinetic agent: improving action on delayed gastric emptying in experimental animals, J. Pharmacol. (Japan) 67, 197P.

Nemeth, P.R., C.S. Ort, D.H. Zafirov and J.D. Wood, 1985, Interaction between serotonin and cisapride on myenteric neurons, Eur. J. Pharmacol. 108, 77.

Niijima, A., Hatanaka, S. and K. Furuhama, 1995, Effect of DQ-2511 on the efferent and afferent activity of the gastric vagus nerve in the rat, J. Pharmacol. (Japan) 67, 197P.

Shen, K.Z., C. Barajas-Lopez and A. Surprenant, 1990, Functional characterization of neuronal pre and postsynaptic alpha adrenoceptor subtypes in guinea-pig submucosal plexus, Br. J. Pharmacol. 101, 925.

Surprenant, A., 1989, Synaptic transmission in neurons of the submucous plexus, in: Nerves and the Gastrointestinal Tract, Falk Symposium 50, eds. M.V. Singer and H. Goebell (MTP Press, Boston) p. 253.

Tack, J.F., W. Janssens, J. Janssens, G. Vantrappen and J.D. Wood, 1991, Effect of cisapride on myenteric neurons in the guinea-pig gastric antrum, J. Gastroint. Mot. 3, A203.

Tack, J.F. and J.D. Wood, 1991, Serotonergic mechanisms in the myenteric plexus of the guinea-pig gastric antrum, Gastroenterology 100, A500.

Tonini, M., J.J. Galligan and R.A. North, 1989, Effects of cisapride on cholinergic neurotransmission and propulsive motility in the guinea pig ileum, Gastroenterology 96, 1257.

Wood, J.D. and C.J. Mayer, 1978, Intracellular study of electrical activity of auerbach's plexus in guinea-pig small intestine, Pflüg. Arch. 374, 265.

Wood, J.D., 1987, Physiology of the enteric nervous system, in: Physiology of the Gastrointestinal Track, 2nd Ed., eds. L.R. Johnson et al. (Raven Press, New York) p. 67.

Wood, J.D., 1989, Electrical and synaptic behaviour of enteric neurones, in: Handbook of Physiology, The Gastrointestinal System, Motility and Circulation, Vol. 1, Sect. 6, ed. J.D. Wood (American Physiological Society, Bethesda) p. 465.

Wood, J.D., 1992, Integrated circuits: the basis of gastrointestinal motility programs, in: Gastrointestinal Dysmotility Focus on Cisapride, eds. R.C. Heading and J.D. Wood (Raven Press, New York) p. 15.

Wood, J.D., 1994a, Physiology of the enteric nervous system, in: Physiology of the Gastrointestinal Track, 3rd Ed., eds. L.R. Johnson et al. (Raven Press, New York) p. 423.

Wood, J.D., 1994b, Application of classification schemes to the enteric nervous system, J. Auton. Nerv. Syst. 48, 17.