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Pharmacology of the Gastric Pro-kinetic Drug Ecabapide (DQ-2511)

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Abstract

The pharmacology of ecabapide (DQ-2511; 3-[2-(3,4-dimethoxyphenyl)ethylcarbamoylmethyl]amino-*N*-methylbenzamide) is reviewed.

Evidence from basic studies in animal models suggests that the drug acts on peripheral mechanisms of neural control. In the stomach, ecabapide acts to suppress firing in vagal afferent nerves and thereby reduce the flow of sensory information into the dorsal vagal complex.

The enhancement of the efferent discharge provoked by ecabapide was completely blocked by bilateral vagotomy, as suggested by increased firing in vagal efferent fibres, preceded by suppression of activity in the sensory limb of the putative vago-vagal reflex pathway.

The mechanism of action of ecabapide in suppressing discharge in vagal afferent terminals appears to mimic that of nitric oxide by stimulating formation of cGMP and activation of an inhibitory transduction cascade in the sensory fibres. In this respect the mechanism of its pro-kinetic action differs from other promoter agents. In addition to selective actions in the stomach, evidence from electrophysiological studies of enteric neurons in the small intestine suggests that ecabapide might have actions similar to those of other substituted benzamides on synaptic transmission in the intramural nervous system of this specialized region of the digestive tract. These actions include enhanced release of acetylcholine at excitatory synapses and suppression of the release of noradrenaline at inhibitory synapses.

Ecabapide (DQ-2511; 3-[2-(3,4-dimethoxyphenyl)ethylcarbamoylmethyl]amino-*N*-methylbenzamide; Fig. 1) is a substituted benzamide first investigated as an anti-ulcer drug (Asano et al 1990; Hosokami et al 1992). Later, the drug was found to enhance gastric emptying significantly in rodent and non-human primate models, suggestive of pro-kinetic action (Hatanaka et al 1995a, b, 1996; Kawarabayashi et al 1995; Furuhama 1997). It also improves symptoms of non-ulcer dyspepsia in man.

The toxicity of single oral doses in mice and rats was found to be low (LD50 > 5 g kg^{-1}). Long-term toxicity studies found no adverse effects except for minor suggestions of haemolytic anaemia in dogs at very high oral doses of 600 mg kg^{-1} (Ohno et al 1993, 1996). No impairment of behaviour or of cardiovascular, respiratory or renal function (Hirohashi et al 1993a, b) was found in a variety of species orally administered 100 mg kg^{-1}. This dose is 20-fold higher than 100 mg three times a day (ca 5 mg kg^{-1}) which is the therapeutic dose used in later treatment trials for non-ulcer dyspepsia. Ecabapide did not alter the activity of acetylcholinesterase. Likewise, there were none of the effects on prolactin release or extrapyramidal motor behaviour characteristic of dopaminergic drugs (Pinder et al 1976; Brogden et al 1982).

Pharmacokinetic studies on rats revealed that intravenous bolus injection of ecabapide (60 μg kg^{-1}) resulted in a peak plasma concentration of 1 μM. Essentially, the same plasma concentrations were obtained 5 min after oral administration of 3 mg kg^{-1} in matched controls. After intravenous injection, isotopically-labelled ecabapide appeared first in the subserosal region of the stomach and later became heavily distributed in the gastric submucosal regions.

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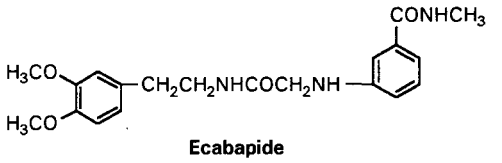
Effects on Gastric Emptying

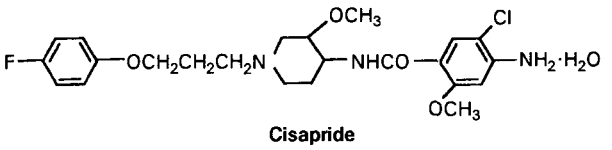
Most studies on the actions of ecabapide on gastric emptying in a variety of animal species utilized the phenol red method for evaluation of emptying of liquid meals and the paracetamol method for emptying of semi-solid meals (Hatanaka et al 1994). Actions of the drug were compared with those of cisapride which was taken as the standard for evaluation of propulsive actions. The effective dose in the respective models (Tables 1 and 2) means dosage levels resulting in significant differences ($P < 0.05$) when compared with the corresponding vehicle control.

Single oral doses of ecabapide or cisapride were tested for efficacy in reversing delays in gastric emptying induced in mice, rats and non-human primates induced by intraperitoneal injections of cholecystokinin-octapeptide (CCK8), dopamine or α-calcitonin gene-related peptide (CGRP). Gastric emptying in mice was suppressed significantly by CCK8 (5 μg kg^{-1}), dopamine (30 mg kg^{-1}) or CGRP (100 μg kg^{-1}). Gastric emptying in rats and non-human primates was suppressed by the same doses of CCK8. Oral administration of ecabapide or cisapride 90 min before treatment with CCK8, dopamine or CGRP offset the action of these chemical messenger substances to suppress gastric emptying (Table 1). Efficacy of action of ecabapide was superior or approximately equivalent to that of cisapride (Hatanaka et al 1995a, 1996; Kawarabayashi et al 1995).

Ecabapide, but not cisapride, was found to be efficacious in three other animal models of delayed gastric emptying. The



Ecabapide



Cisapride

FIG. 1. The molecular structures of ecabapide and cisapride.

first was the spontaneously hypertensive rat (SHR), the second was the stroke-prone spontaneously hypertensive rat (SHRSP) and the third was the unilaterally vagotomized rat. Gastric emptying in both spontaneously hypertensive models is significantly delayed relative to normotensive Wistar–Kyoto rats and this is exacerbated during stress (Ito et al 1991, 1992; Shichijo et al 1991; Hatanaka et al 1995b). Single or repeated dosing with ecabapide, either by gavage or inclusion in the diet, improved gastric emptying in all three models, with increased efficacy after repeated dosing for 2–4-week periods (Kawarabayashi et al 1995; Hatanaka et al 1996; Furuhama 1997). On the basis of the above results, it is proposed that ecabapide shows no possibility of tachyphylaxis (Furuhama 1997). Parallel studies with administration of cisapride in the same models found comparably less improvement in gastric emptying (Table 2). Apparent variability among the models was explainable by differences in the extent of suppression of gastric emptying among the different animal models. Dose-response relations for the improvement of gastric emptying in each of the models were bell-shaped. In this respect, ecabapide behaved similarly to other gastric pro-kinetic drugs (Foster & Dockray 1990; Chen et al 1993; Eglen et al 1993; Gullikson et al 1993).

Gastric Motility

Effects of ecabapide and cisapride on the phasic contractile behaviour of the gastric antrum were compared in urethane anaesthetized rats. Established methods of strain-gauge recording (Itoh et al 1978) were used to assess the effects of intravenous injections (60 $\mu g\ kg^{-1}$) of ecabapide or cisapride (Hatanaka et al 1996). Both drugs increased the motility indices for the gastric antrum at 60, 90 or 120 min post-injection of the bolus. No distinguishable differences were found between the actions of the two drugs in enhancing the phasic contractile behaviour of the gastric antrum.

Vagal Nerve Afferents

In this series of studies the effects of ecabapide and cisapride on action potential discharge in vagal nerve afferent fibres were compared. The methods used were micro-dissection of afferent nerve filaments in the ventral gastric branch of the vagus and multi-unit extracellular recording (Niijima 1991; Niijima & Yamamoto 1994; Niijima et al 1996). All electrophysiological recording (Fig. 2) was for rats anaesthetized with urethane.

Table 1. Effective doses of ecabapide or cisapride administered singly by gavage to various species, with delays in gastric emptying.

				Ecabapide ($mg\ kg^{-1}$)		Cisapride ($mg\ kg^{-1}$)
Species	Model	Dose	n	Dose used	Effective dose	Effective dose
Mice	CCK8	5 $\mu g\ kg^{-1}$	7	1 to 10	3 and 10	NE*
Mice	Dopamine	5 $mg\ kg^{-1}$	7	1 to 3	0·3 and 1	NE
Mice	CGRP	100 $\mu g\ kg^{-1}$	7	0·3 to 10	0·1, 0·3, 1 and 10	1 and 3
Rats	CCK8	5 $\mu g\ kg^{-1}$	5	0·01 to 3	0·1	3
Monkeys	CCK8	5 $\mu g\ kg^{-1}$	6–9	1 to 10	3 and 10	3

The effective dose means dosage levels resulting in a significant difference compared with the corresponding vehicle control in each model. Either ecabapide or cisapride was administered orally 90 min before cholecystokinin-octapeptide (CCK8), dopamine, or α-calcitonin gene-peptide (CGRP) treatment. *No effect. Permeability data were obtained from Kawarabayashi et al (1995); Hatanaka et al (1995a, 1996).

Table 2. Effective doses of ecabapide or cisapride administered singly or repeatedly by gavage to various rat models with delays in gastric emptying.

			Ecabapide ($mg\ kg^{-1}$)		Cisapride ($mg\ kg^{-1}$)	
Model	Administration period	n	Dose used	Effective dose	Dose used	Effective dose
Spontaneously hypertensive rat	2 weeks	5	0·1 to 1	1	0·1 to 30	NE*
Spontaneously hypertensive rat	2 weeks (diet)	7	2 to 22	2	–†	–
Spontaneously hypertensive rat	4 weeks (diet)	7	2 to 21	2 and 21	–	–
Stroke-prone spontaneously hypertensive rat	Single	5	1 to 30	1	1 to 30	NE
Stroke-prone spontaneously hypertensive rat	2 weeks	5 to 10	0·3 to 30	0·3 and 1	–	–
Stroke-prone spontaneously hypertensive rat	4 weeks (diet)	5	1·9 to 19·8	7·7	–	–
Unilateral vagotomy	2 weeks	8 to 10	0·3 to 10	1, 3 and 10	0·3 to 10	NE
Unilateral vagotomy	2 weeks (diet)	8 to 10	2 to 17	2 and 5	–	–

The effective dose means dosage levels resulting in a significant difference compared with the corresponding vehicle control in each model. *No effect. †Not tested. Permeability data were obtained from Kawarabayashi et al (1995); Hatanaka et al (1995a, b, 1996); Furuhama (1997).

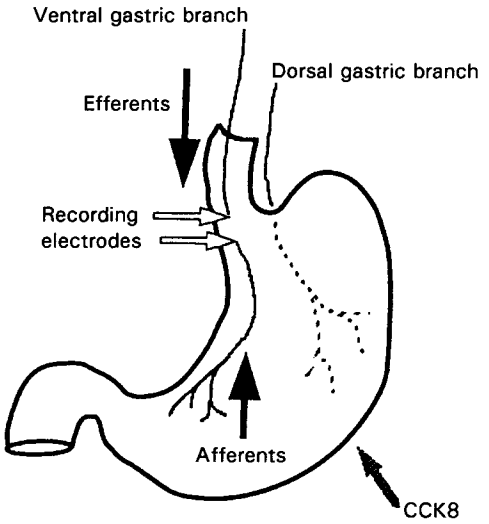


FIG. 2. The method used to record the effects of cholecystokinin-octapeptide (CCK8) on action potential discharge in the ventral gastric branch of the vagus nerve of rats. Recording electrodes detected multi-unit spike discharge in efferent and afferent fibres of the mixed nerve.

Bolus injections of ecabapide (6 and 60 $\mu g\ kg^{-1}$) given intravenously reduced the frequency of multi-unit afferent discharge in the vagal sensory fibres in a dose-dependent manner. The depression of spike discharge was time-dependent over intervals of 1 h (Fig. 3). Unlike ecabapide (Fig. 3), cisapride in doses of 6, 60, 120 and 360 $\mu g\ kg^{-1}$ did not suppress on-going sensory discharge in the vagal gastric nerve branches (Hatanaka et al 1996). Decreased firing rates in vagal afferents evoked by ecabapide were associated with increased firing in vagal efferent fibres (Hatanaka et al 1996). Involvement of the efferent limb of gastric vago-vagal reflex connections was confirmed by loss of activity after bilateral vagotomy (Fig. 4).

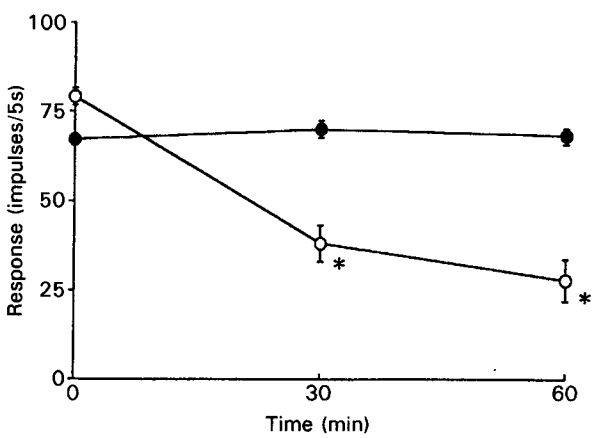


FIG. 3. Time-dependence of the effects of ecabapide and cisapride on rate of action potential discharge in afferent fibres of the ventral gastric branch of the vagus nerve. The data represent the rate of spike discharge 30 and 60 min after intravenous injection of ecabapide or cisapride. ○ Results from injection of 60 $\mu g\ kg^{-1}$ ecabapide (n = 7), ● results from injection of 60 $\mu g\ kg^{-1}$ cisapride (n = 5). Each point and vertical bar represents the mean and ± s.e.m., respectively. $*P < 0.05$ for differences between mean values at 0 min. Permeability data were obtained from Hatanaka et al (1996).

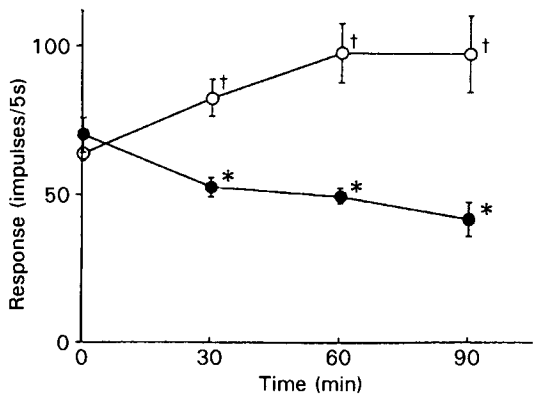


FIG. 4. Time-dependence of the effects of ecabapide (60 $\mu g\ kg^{-1}$) on rate of action potential discharge in efferent fibres of the ventral gastric branch of the vagus nerve before (○) and after (●) bilateral vagotomy. Each point and vertical bar represents the mean and ± s.e.m., respectively (n = 7). $*P < 0.05$ compared with ecabapide alone; $\dagger P < 0.05$ compared with 0 min. Permeability data were obtained from Furuhama (1997).

Treatment with CCK8

Administration of CCK8 resulted in well known increases in discharge rate in the gastric vagal afferents (Richards et al 1996). Decline in the firing rate of vagal efferent units occurred coincident with the increased firing rates at the sensory side of a presumed vago-vagal pathway. This action of CCK8 was prevented by treatment with ecabapide (Fig. 5). Atropine ($0.05\ mg\ kg^{-1}$) did not affect discharge of the sensory afferents, suggesting that the action of ecabapide in reducing sensory afferent firing was not a secondary effect of relaxation of tension in the gastric musculature (Hatanaka et al 1997a).

Ligand-binding Assays

Competitive ligand-binding assays were performed to address the question of whether the mechanism of action of ecabapide was antagonism at CCK_A, CCK_B, dopamine D_2, 5-hydroxytryptamine (5-HT) subtype (non-selective 5-HT, 5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_2, 5-HT_3 or 5-HT_4), CGRP, nicotinic or muscarinic M_3 receptors. Ecabapide showed no specific binding affinity for any of the mentioned receptor subtypes (Hatanaka et al 1995a). In contrast, cisapride had selective binding affinity for dopamine D_2 receptors and 5-HT_3 and 5-HT_4 receptor subtypes, with Ki values of 54·5, 52·3 and 9·4 nM, respectively.

cGMP Formation

Treatments with sodium nitroprusside ($0.5\ mg\ kg^{-1}$) suppressed vagal afferent discharge in a manner reminiscent of the effects of ecabapide. Intravenous administration of a cyclic guanosine monophosphate (cGMP) analogue (8-bromoguanosine-3,5-cyclic monophosphate sodium salt, $2\ mg\ kg^{-1}$) also reduced discharge in the gastric vagal afferents (Hatanaka et al 1997b). On the other hand, similar injections of the nitric oxide synthase inhibitor N^G-nitro-L-arginine ($5\ mg\ kg^{-1}$) induced significant increases in vagal afferent discharge rates. Pretreatment with the nitric oxide synthase inhibitor prevented the reduction in rates of afferent discharge that were evoked by ecabapide (Hatanaka et al 1997a).

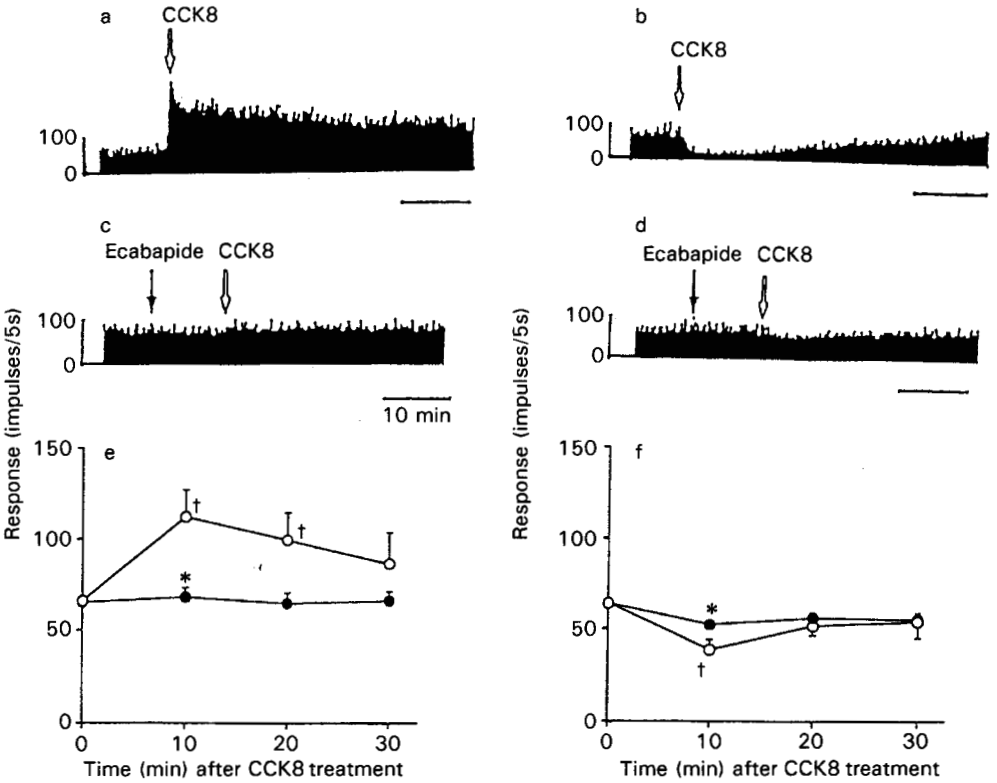


FIG. 5. Ecabapide blocked the action of cholecystokinin-octapeptide (CCK8) on afferent and efferent firing rates in the rat vagus nerve. a. Application of CCK8 (20 μg, open arrow) to the serosal surface of the stomach enhanced afferent discharge recorded at the peripheral cut end of the ventral gastric branch. b. The same application of CCK8 suppressed efferent discharge recorded at the central cut end of the dorsal gastric branch. c. Intravenous injection of ecabapide (60 $\mu g\ kg^{-1}$, closed arrow) before application of CCK8 prevented action of CCK8 on afferent discharge. d. The same application of ecabapide prevented the suppression of efferent discharge by CCK8. e. Quantitative analysis for time-dependent changes in afferent discharge rates in response to CCK8 before (○) and after (●) injection of ecabapide. f. Quantitative analysis for time-dependent changes in efferent discharge rates in response to CCK8 before (○) and after (●) injection of ecabapide. Each point and vertical bar represents the mean ± s.e.m., respectively (n = 5). $*P < 0.05$ compared with CCK8 alone, $\dagger P < 0.05$ compared with baseline discharge rates. Permeability data were obtained from Niijima et al (1996).

The findings for sodium nitroprusside, the cGMP analogue and nitric oxide synthase inhibitor suggest that ecabapide might act like nitric oxide to stimulate formation of cGMP in the vagal afferent endings. Elevation of cGMP in the sensory fibres, whether by application of a nitric oxide donor (e.g. sodium nitroprusside) or a cGMP analogue, appears to suppress spike discharge in afferent fibres of the gastric vagal innervation. This suggestion is consistent with findings of others that gastric vagal fibres of the rat express nitric oxide synthase (Foster & Southam 1993). It is also consistent with observations that inhibition of nitric oxide synthase leads to delayed gastric emptying in both dog and rat models (Orihata & Sarna 1994; Plourde et al 1994).

To test the hypothesis that ecabapide acts to stimulate intracellular cGMP formation, changes in cGMP levels in response to drug treatment were determined for rat arterial smooth muscle preparations and cell-rich suspensions of gastric parietal cells. Ecabapide was found to increase levels of cGMP in arterial smooth muscle (Hatanaka et al 1995c; Okamura et al 1995). In suspensions of gastric parietal cells, ecabapide stimulated cGMP formation in a time- and dose-dependent manner with an EC50 value of 0·2 μM (Fig. 6, Sakai et al 1996). The minimum concentration of ecabapide that stimulated cGMP formation had no effects on resting tension in arterial smooth muscle (Hatanaka et al 1995c).

Ecabapide Metabolites

The effects of ecabapide on gastric emptying were compared with those of the eight metabolites of the compound (Fujimaki et al 1995; Nakaoka et al 1996) illustrated in Fig. 7. Of these metabolites, MA-2 is the principal metabolite found in the blood. Ecabapide or a metabolite was injected intraperitoneally in mice 30 min before administration of CCK8 (5 $\mu g\ kg^{-1}$). Phenol red solution was used as the marker for liquid meal emptying. As in rat models, ecabapide (30–100 $\mu g\ kg^{-1}$) reversed the inhibitory action of CCK8 on gastric emptying. Of the eight metabolites, MA-2 was without significant effect on gastric emptying after CCK8 administration. One of the metabolites (MB-2) behaved like ecabapide with a minor effect in enhancing gastric emptying in the CCK8 model; one other metabolite (MB-6) further delayed gastric emptying. These observations suggest that the primary actions of ecabapide reflect the actions of the parent compound rather than one of its metabolites (Hatanaka et al 1995b).

Enteric Nervous System

Intracellular electrophysiological recording methods were used to investigate the effects of ecabapide on electrical and

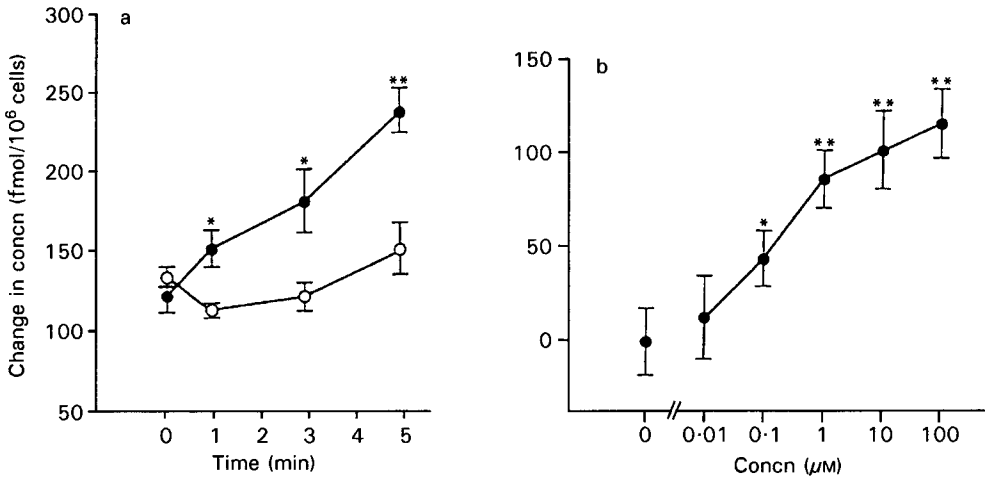


FIG. 6. Ecabapide-induced increases in cGMP in rabbit parietal cell-rich suspension. Each point and vertical bar represents the mean and ± s.e.m., respectively. a. cGMP was measured 1, 3 and 5 min after the addition of 10 μM ecabapide (●) or vehicle (○) (n = 4 or 5). $*P < 0.05$ and $**P < 0.01$ compared with result for 0 min. b. Concentration–response curve for increases in cGMP induced by ecabapide. The ecabapide-induced net increase in cGMP ([cGMP]i) was determined 5 min after addition of ecabapide or vehicle (n = 5 or 6). $*P < 0.05$ and $**P < 0.01$ compared with vehicle. Reproduced with permission from Sakai et al (1996).

synaptic behaviour of neurons in the enteric nervous system of the guinea-pig small intestine (Wood 1993, 1994a, b). The drug was found to depolarize some of the neurons and this was associated with an increase in input resistance and a state of enhanced excitability reminiscent of enteric slow synaptic excitation (Zafirov et al 1996). In nanomolar concentrations ecabapide augmented the amplitudes of fast excitatory post-synaptic potentials at nicotinic synapses. This was similar to actions reported for cisapride at cholinergic synapses in both guinea-pig small intestine (Tonini et al 1989; Tonini 1992) and gastric antrum (Wood 1992). Ecabapide, also in nanomolar concentrations, suppressed noradrenergic slow inhibitory postsynaptic potentials in neurons of the guinea-pig sub-mucous plexus (Zafirov et al 1996). This action resulted from suppression of stimulus-evoked release of noradrenaline from sympathetic post-ganglionic nerve fibres.

The results for the guinea-pig suggest that any beneficial actions that might emerge in the small intestine could result from two mechanisms of action, one being the enhanced release of acetylcholine within the neural circuitry and the other the suppression of inhibitory noradrenergic neuro-transmission in the enteric nervous system. Noradrenaline released from sympathetic nerve fibres acts at presynaptic α_2-adrenoceptors to suppress release of acetylcholine at nicotinic synapses in the enteric neural circuits (Wood 1994a, b). It acts also at inhibitory postsynaptic α_2-adrenoceptors on secreto-motor neurons in the intestinal submucous plexus. Suppression of noradrenaline release at synapses on secretomotor neurons removes an inhibitory brake from the neurons and thereby enhances secretion of electrolytes, water and mucus from the intestinal crypts.

Beneficial effects of enhanced release of acetylcholine at nicotinic synapses at the integrated systems level in the intestine are expected to be expressed as enhanced propulsive motility and augmented secretory behaviour. Further enhancement is derived from suppression of noradrenaline

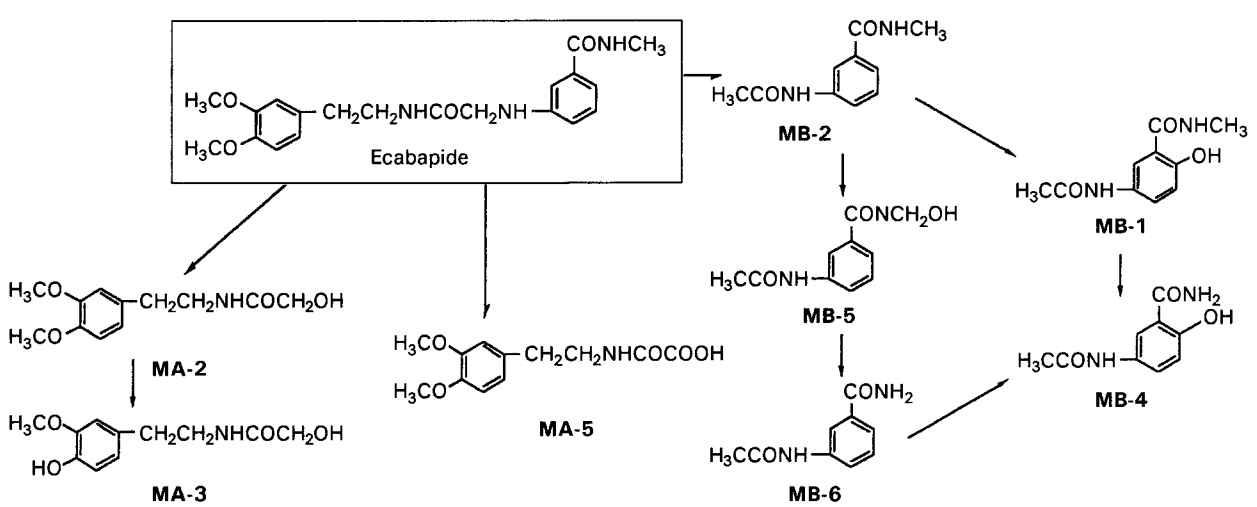


FIG. 7. Possible pathways of degradation for ecabapide and the resulting metabolites in rats and man. Permeability data were obtained from Fujimaki et al (1995) and Nakaoka et al (1996), with slight modifications.

release which removes an inhibitory brake from both nicotinic synapses in the neural circuits of both myenteric and submucous plexuses and secretomotor neurons in the submucous plexus (Wood 1993, 1994a, b). Mechanisms of this nature remain unclear as explanations of the gastric pro-kinetic action of ecabapide. This is because the drug has been tested mainly on gastric motility and not on motility and secretory behaviour in the intestine. On the other hand, actions of ecabapide have been investigated on electrical and synaptic activity of enteric neurons in the intestine, but not in the stomach.

Clinical Efficacy

Basic pharmacological observations on the actions of ecabapide suggested potential as a gastric pro-kinetic drug for the treatment of non-ulcer dyspepsia. This was tested in a blind fashion in clinical trials involving 300 patients selected on the basis of a diagnosis of non-ulcer dyspepsia with symptoms such as epigastric distress, early satiety, postprandial nausea and heartburn. The efficacy rates for a two-week trial with daily oral dosing of 300 mg day^{-1} were significantly improved relative to a low dose of 21 mg day^{-1} (Miwa et al 1996). A blind trial comparing ecabapide with cisapride (7·5 mg day^{-1}) showed the same efficacy as cisapride in relieving symptoms of functional dyspepsia (Matsuo et al 1996).

Conclusions

Ecabapide is a novel drug with gastric pro-kinetic properties that holds promise for treatment of functional disorders of gastric motility. Evidence from basic studies in animal models suggests that the drug acts on peripheral mechanisms of neural control. In the stomach, ecabapide acts to suppress firing in vagal afferent nerves and thereby reduce the flow of sensory information into the dorsal vagal complex.

The presence of excitatory CCK receptors on vagal afferent terminals is well documented (Richards et al 1996). Ecabapide appears to exert an opposite action on these same terminals and this might account for its ability to reverse the inhibitory effects of CCK8 on gastric emptying. Suppression of sensory afferent input to the dorsal vagal complex by ecabapide might result in the removal of inhibitory influences from the vagal excitatory motor neurons that make-up part of the efferent outflow to the stomach. The enhancement of the efferent discharge provoked by ecabapide was completely blocked by bilateral vagotomy. These are suggested by increased firing in vagal efferent fibres, preceded by suppression of activity in the sensory limb of the putative vago-vagal reflex pathway.

The mechanism of action of ecabapide in suppressing discharge in vagal afferent terminals might mimic that of nitric oxide by stimulating formation of cGMP and activation of an inhibitory transduction cascade in the sensory fibres (Hatanaka et al 1997a, b). In this respect the mechanism of its pro-kinetic action differs from other promoter agents including cisapride (McCallum et al 1988; Barone et al 1994; Wiseman & Faulds 1994) domperidone (Brogden et al 1982) and metoclopramide (Pinder et al 1976). In addition to selective actions in the stomach, evidence from electrophysiological studies of enteric neurons in the small intestine suggests that ecabapide might have actions similar to those of other substituted benzamides on synaptic transmission in the intramural nervous system of this specialized region of the digestive tract. These actions include enhanced release of acetylcholine at excitatory synapses and suppression of the release of noradrenaline at inhibitory synapses.

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