

Receptors of the enteric nervous system: potential targets for drug therapy

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It is recognised that the enteric nervous system (ENS) has a unique ability to mediate reflex activity independently of input from the brain or spinal cord.¹⁻⁴ This ability implies that the ENS contains sensory receptors, primary afferent neurones, interneurons, and motor neurones. The events that are controlled, at least in part, by the ENS are multiple and include motor activity, secretion, absorption, blood flow, and interaction with other organs such as the gall bladder or pancreas.¹⁻⁴

The extensive regulatory activities of the ENS are made possible by the presence and abundance of different types of neurones within the wall of the gastrointestinal tract. The ENS contains about 10^8 neurones, approximately the number of neurones found in the spinal cord. Morphological, electrophysiological, and pharmacological studies have revealed a substantial diversity of neurones within the ENS. Moreover, a surprisingly large number of established or candidate neurotransmitters can be found in enteric neurones. Most neurones contain several of these substances, and distinctive patterns of colocalisation of mediators allow identification of different functional classes of neurones.^{2,3} The presence of receptors on enteric neurones is another expression of their heterogeneity. Myenteric neurones can express receptors for both peptide and non-peptide (amines, amino acids, purines) neurotransmitters.¹⁻⁵ Generally, expression of a receptor is limited to a subset of myenteric neurones, with probably the only exception being expression of nicotinic cholinergic receptors on all myenteric neurones in the guinea pig stomach.^{6,7} Unfortunately, we know very little about the relationship between the functional role of enteric neurones and their expression of receptors.

The ENS is a target for pharmacotherapy of gastrointestinal disorders

A number of drugs, which are used clinically to alter gastrointestinal motility, act via the ENS. Prokinetic drugs, such as cisapride, motilin and erythromycin, stimulate gastrointestinal motility at least in part through release of acetylcholine from intrinsic cholinergic neurones.^{8,9} Cisapride enhances cholinergic neurotransmission via activation of a presynaptic 5-hydroxytryptamine (5-HT)₄ receptor.^{8,10} In addition, cisapride has a direct postsynaptic excitatory effect on a subpopulation of antral neurones, which is not mediated by a 5-HT₄ receptor.¹¹ Indeed, non-serotonergic effects have also been implicated in the prokinetic actions of cisapride.¹² Motilin and erythromycin can induce prolonged depolarisation in a subset of neurones in the guinea pig stomach, possibly by

activation of a motilin receptor.⁹ However, direct muscular effects are also involved in some of the effects of motilides.¹³ Inhibitors of gastrointestinal motility, such as clonidine, botulinum toxin, or sumatriptan, may inhibit release of acetylcholine or stimulate the release of nitric oxide from intrinsic neurones.¹⁴⁻¹⁷

The observation that drugs which are used clinically to alter gastrointestinal motility act via the ENS confirms the view that the ENS is a valid target for the pharmacotherapy of gastrointestinal motor disorders.

The ENS as a target for achieving improved specificity of pharmacological actions

Pharmacological treatment of gastrointestinal motility disorders is intended to stimulate or inhibit motility. Established sites of action of motility drugs are gastrointestinal smooth muscle, the ENS, autonomic ganglia, and the central nervous system. Drugs acting at different sites may cause a similar net effect on gastrointestinal motility. Enhancement of gastrointestinal motility can be achieved by direct stimulation of gastrointestinal smooth muscle, by activation of excitatory neural pathways, or by inhibition of inhibitory pathways. Similarly, inhibition of gastrointestinal motility can be achieved by a direct relaxant effect on gastrointestinal smooth muscle, by inhibition of excitatory neural pathways, or by activation of inhibitory pathways.

When stimulation or inhibition of contractile activity is achieved through agents that act directly on gastrointestinal smooth muscle (for example, cholinergics, cholinesterase inhibitors, nitrates, L-type calcium channel blockers), the effect is often non-specifically present throughout the gastrointestinal tract. Motilides may be an exception to this, as smooth muscular motilin receptors are mainly expressed in the stomach and proximal small intestine in humans.¹⁸

Most drugs affecting gastrointestinal motility do so by acting as an agonist or antagonist at specific cellular receptors. Stimulation or inhibition of contractile activity through receptors on enteric neuronal circuitry offers the potential of achieving higher specificity. Serotonin 3 (5-HT₃) receptor antagonists, for example, inhibit colonic motor activity in humans via a neural pathway but they have no clearly demonstrable effect on gastric emptying rate.^{19,20}

The selection of a drug therapy with optimal specificity requires both a precise knowledge of

Abbreviations used in this paper: ENS, enteric nervous system; 5-HT, 5-hydroxytryptamine.

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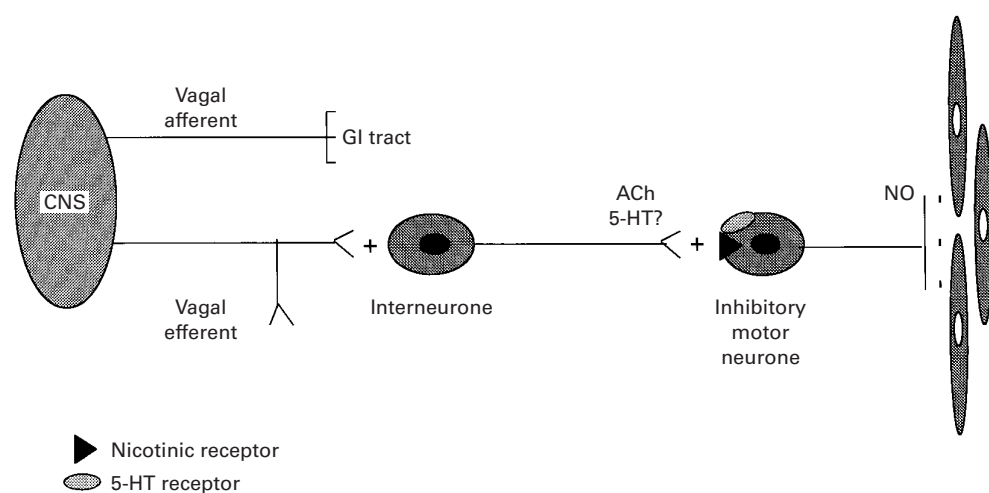


Figure 1 Neural pathways mediating gastric accommodation (animal studies). 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; NO, nitric oxide.

the type of change in motor behaviour that is required, as well as of the circuitry and the receptors that are involved in its control. This statement is best illustrated by an example. A subgroup of patients with functional dyspepsia has impaired accommodation of the proximal stomach to ingestion of a meal, and this is associated with symptoms of early satiety and weight loss.²¹ Several attempts have been made to improve defective gastric accommodation in these patients. Nitrates can enhance relaxation of the stomach after ingestion of a meal but produce several side effects related to their action on extraintestinal smooth muscle.²² In the mouse and guinea pig, involvement of 5-HT receptors on intrinsic neurones in the vagally mediated gastric relaxation has been demonstrated (fig 1).²³ Selective 5-HT re-uptake inhibitors act both centrally and peripherally to enhance the availability of physiologically released 5-HT.²⁴ We demonstrated that a selective 5-HT reuptake inhibitor can enhance gastric accommodation to a meal in humans.²⁵ However, probably because such drugs enhance the availability of 5-HT at vagal afferents that are activated by 5-HT₃ receptors, they are associated with nausea. Hence they are less well suited for therapeutic use in dyspeptic patients. More recently, it was demonstrated that 5-HT induced relaxations of the guinea pig stomach are mediated via release of nitric oxide through activation of a 5-HT₁-like receptor.²⁶ Combining 5-HT responsiveness with immunohistochemical studies in myenteric neurones of the guinea pig stomach revealed that a 5-HT_{1P} receptor is present on intrinsic nitrergic neurones (fig 2).²⁷ We recently demonstrated that sumatriptan is an agonist at the 5-HT_{1P} receptor on gastric antral myenteric neurones.²⁸ We confirmed that administration of sumatriptan can improve impaired gastric accommodation in dyspeptic patients with early satiety, with a resultant improvement in early satiety.²¹

The ENS in humans as a target for pharmacotherapy

Selection of a drug therapy with optimal specificity requires a precise knowledge of the

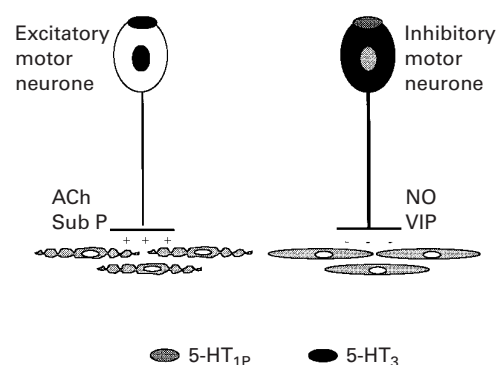


Figure 2 5-Hydroxytryptamine (5-HT) receptors on gastric myenteric neurones. ACh, acetylcholine; NO, nitric oxide; Sub P, substance P; VIP, vasoactive intestinal peptide.

circuitry and receptors that are involved in any given motor phenomenon in humans. Unfortunately, our knowledge of the ENS in humans is extremely limited, and most of the information available is extrapolated from animal studies, as has been illustrated above. The availability of human tissue for physiological and pharmacological studies is extremely limited. Hence labourious and slow techniques, such as intracellular electrophysiological studies of receptor responses, are not suitable for studying the human ENS. Immunohistochemical demonstration of receptor expression on human myenteric neurones may be one more fruitful approach. Recently, we investigated the use of optical imaging of neuronal calcium concentration as a technique to study the responsiveness of enteric neurones to neuroleptands. This technique, which was validated on cultured myenteric neurones, is also applicable to ex vivo preparations and on neurones that are retrogradely labelled with DiI.²⁹⁻³¹ In preliminary studies, we demonstrated that circular muscle motor neurones of the guinea pig small intestine showed characteristic responsiveness to groups of neuroleptands. We are currently adapting this technique for use on human specimens.

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