# THE ROLE OF NON-ADRENERGIC NON-CHOLINERGIC SYSTEM IN THE PERISTALTIC REFLEX OF GUINEA PIG ILEUM

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#### ABSTRACT

The effect of some endogenous components -endogenous opiates, cholecystokinin (CCK), vasoactive intestinal polypeptide (VIP) and somatostatin-as inhibitory or excitatory transmitters in the local nervous pathways involved in peristaltic responses was examined. The peristaltic reflex was studied using a modification of the Trendelenberg preparation. In each preparation, the luminal distension pressure was increased in sudden steps of 1 cm H<sub>2</sub>O at intervals of 10, until peristalsis was initiated. Morphine inhibited the rhythmic peristaltic activity. The inhibitory effect of morphine was characterized by a decreased activity of both the longitudinal and circular muscle layers. Addition of naloxone to the organ bath reversed this inhibitory effect of morphine. Using distension pressures which evoke only tetrodotoxin-sensitive peristaltic contractions, the mechanism rapidly "fatigues". This fatigue can be reversed by naloxone. Higher distending pressure, which can evoke tetrodotoxin-resistant activity, produced persistent peristalsis with intermittent activity seize. Addition of naloxone reversed the blockade leading to a continuous uninterrupted peristalsis.

Proglumide or dbcGMP (selective inhibitor of the effects of CCK) increased the threshold pressure necessary to cause the peristaltic reflex and blocked all responses to threshold distension.

Cholecystokinin or caerulein decreased the threshold of distension pressure required to evoke the peristaltic reflex. Furthermore, it increased the height and duration of the responses. The excitatory effect of CCK or caerulein was blocked by proglumide or dbcGMP.

VIP increased the threshold of distension required to cause the peristaltic reflex and blocked the responses to threshold distension of longitudinal but not circular muscle layers.

Somatostatin has been proved to exert an unusual effect on peristalsis. At high concentration it decreased the duration of the responses but had no effect on the height of rhythmic activity. It is concluded that the activation of intramural neurones by distension causes the release of inhibitory and excitatory transmitters, such as endogenous opiates which interrupts peristaltic activity and CCK which enhance the peristaltic reflex at a synapse with cholinergic neurones since CCK releases acetylcholine from intrinsic nerves. VIP and somatostatin are involved in the peristaltic reflex but the mechanism of their actions are not studied in this work. *MJIRI, Vol. 7, No.2, 115-122, 1993.* 

#### INTRODUCTION

The gastrointestinal tract is able to coordinate the movement of its contents in an aboral direction, so allowing the contents to be exposed to a variety of digestive enzymes and to sites where digestion products may be absorbed. In mammals it is likely that ordered intestinal motility results from a balance between three factors: hormonal, myogenic, and neurogenic. However, unlike most involuntary organs, segments of intestine are able to produce coordinated movements after the severing of the connections with the central nervous system. It is generally accepted that the neurones and their connections, which lie in the enteric nervous system, contain all the neural pathways necessary to execute several simple reflexes.<sup>1,2</sup> The receptors for the peristaltic reflex were thought originally to be pressure receptors.<sup>3</sup>

It is suggested that there are two alternative ways in which these receptors might respond to an increase in pressure in the intestinal lumen. The first way could be by activating directly these stretch receptors, the other indirectly by releasing chemical mediators which stimulate the sensory endings.<sup>3</sup> The peristaltic reflex is abolished by hexamethonium and atropine indicating that it has at least one synapseand that the neuroeffector transmitter is mainly acetylcholine. The longitudinal and circular muscles are the effectors for the reflex. The longitudinal muscle is believed to have a lower threshold than the circular muscle and so contracts first.<sup>346</sup>

However, peristaltic reflex partially resistant to the inhibitory action of hyoscine or atropine has been demonstrated and no evidence for the involvement of 5-HT, substance P. bradykinin or histamine in the hyoscine-resistant peristaltic reflex was obtained. An atropine-resistant pathway has also been observed in the rabbit and guinea-pig colon and in the chick and rat ileum. In addition, the contraction of the guinea-pig ileum in response to electrical transmural stimulation was shown to be partially atropine-resistant. Therefore, peristaltic reflex is possibly regulated by nervous mechanisms releasing mainly ACh (atropine-sensitive) or other substances and probably by myogenic procedures.<sup>7,10</sup>

Generally, both substance P and 5-HT can initiate peristatic contractions and also improve peristatic efficiency.<sup>11-12</sup> Substance P, in the anaesthetized cat, also selectively stimulated the distal colonic motility.<sup>13</sup> It was further found that 5-HT is released into the intestinal lumen when the intraluminal pressure was raised.<sup>14</sup> There is still much uncertainty about the mechanism of action of 5-HT and substance P. In most gastrointestinal preparations, e.g. on the guinea-pig ileum, 5-HT acts on neuronal receptors enhancing motility by acetylcholine release.<sup>15</sup>

Somatostatin exerts an unusual effect on peristalsis. Its complete lack of an immediate action was, several minutes after the end of its infusion, followed by a marked impairment of pressure-induced peristalsis without recovery.<sup>11</sup> Vasoactive intestinal polypeptide (VIP) has a wide variety of actions which include inhibition of pentagastrin and histamine-stimulated gastric acid secretion. VIP which prolonged small bowel transit time in the rat has no effect on peristalsis in the isolated guinea-pig ileum.<sup>16-19</sup>

Usually enkephalin and morphine-like drugs inhibit the peristaltic reflex activity. This inhibition is mainly characterized by a delay in the appearance of the reflex and an inhibitory effect on the responses of both muscle layers.<sup>20:21</sup> Naloxone and other 'narcotic antagonists' reverse the inhibitory effect of all known morphine-like narcotics and enkephalin on the guinea-pig ileum whether activated by electrical stimulation or reflexly by pressureinduced distension.<sup>22:24</sup>

CCK has powerful motor effects in the intestine. These are indirect and involve the activation of intramural nerves.<sup>25-28</sup> Moreover, CCK has been found in the guineapig ileum myenteric plexus.<sup>29</sup> Therefore, it is possible that endogenous CCK, released by CCK-containing nerves, is



Fig. 1. Upper trace, effect of tetrodotoxin (TTX) on the peristaltic reflex in the guinea-pig ileum. TTX blocked the peristaltic reflex at just suprathreshold distension. In contrast it was without effect on the peristaltic response induced by higher level of distension (D+) (n=5). Lower trace, effect of morphine (Mr) on peristaltic reflex induced by near threshold distension (D). Morphine completely inhibited the peristaltic reflex. Addition of naloxone (N) restored the normal activity (n=6) (P<0.005).</p>

L= Longitudinal muscle activity,

C= circular muscle activity



Fig. 2. Effect of naloxone (N) on the peristaltic reflex of the guinea-pig ileum. Upper trace shows that peristaltic activity evoked by continuous distension of the lumen at the threshold distension (D) rapidly "fatigued" and remained so for several minutes. Middle trace shows that addition of naloxone (N) before stimulation prevented the "fatigue". Lower trace shows that addition of naloxone (N) reversed the "fatigue" (n=4) (P<0.005).

involved in the peristaltic reflex. However, peristaltic reflex is under the control of extrinsic nerves and some endogenous substances. This study is an attempt to investigate the role of some endogenous components, endogenous opiates. CCK, VIP and somatostatin as inhibitory or excitatory transmitters in the local nervous pathways involved inperistaltic responses to distension. A preliminary account of this work was presented to the Physiological Society.<sup>30,31</sup>

#### MATERIALS AND METHODS

Adult guinea-pigs (300-800 g) of either sex were killed by stunning and bleeding. The abdomen was opened by making a midline incision, a piece of ileum carefully but quickly removed from the abdomen and the oral end held by a pair of artery forceps. This made it possible to identify the ends when mounting the segment in the organ bath, with the oral end connected to the inflow of the system and the caudal end to the outflow. The lumen of a piece of intestine (usually the ileum) 4 to 5 cm long, again with the oral end clamped for identification, was washed with warm Krebs solution or it was left untouched for 10 to 15 min, until any pellets of faeces contained in the segments had been ejected. The preparation was then suspended horizontally in a 50 ml Perspex organ bath by means of a fixed cannula at the oral end which was attached to a rack and pinion holder. The second cannula at the caudal end was pivoted to allow free movement and was bent into an acute z-shape to reduce the height of the column of fluid at this point. The organ bath was filled with standard Krebs solution, bubbled with 95% O2,5% CO2 and maintained at 37°C via a water circulator pump. The fixed cannula was connected to a Marriotte bottle. A thin polythene tube, introduced through the fixed cannula was placed inside the lumen of the segment and was connected to a pressure transducer. The Marriotte bottle was filled to a chosen level with Krebs solution previously bubbled with 95% 0,, 5% CO<sub>2</sub>. This was done to guarantee sufficient oxygen supply to the mucosa during perfusion of the segment. The Krebs solution passed through a warm coil at about 37°C before entering the segment. The Marriotte bottle was kept on an adjustable platform which could raise and lower it manually. At the end of every cycle the height of the Krebs solution in the Marriotte bottle was kept at the original level before the beginning of the next cycle. Distension of the intestine was achieved by raising the Marriotte bottle (usually 2 to 3 turns for threshold stimuli). When the threshold intraluminal pressure was reached peristalsis occurred. Usually peristaltic contractions were recorded for less than one min then the preparation was allowed to rest for at least 5 min. The contractions of the longitudinal

muscle were measured by attaching the pivoted cannula by a silk thread to an isolated movement transducer (SRI type 7043) which was balanced by attaching a counterweight to the other arm of the transducer lever. This transducer was connected to a Devices M4 pen recorder.

The circular muscle contractions were measured as changes in the intraluminal pressure of the intestinal segment via a pressure transducer connected to a blood pressure monitor (CFP type 8138) which in turn was connected to the pen recorder. Drugs were added directly to the bath and the concentrations quoted are the final concentrations in the bath. Results were analyzed using student's t-test of paired or unpaired as appropriate and p<0.05 was taken as significant.

#### RESULTS

The peristaltic reflex was evoked at just suprathreshold pressures by slowly raising the intraluminal pressure of the segment until it reached a level sufficient to stimulate the peristaltic reflex. Rhythmic peristaltic activity at this near threshold pressure was recorded for one min. (control). Morphine  $(2 \times 10^{-7} \text{ M})$  blocked this peristaltic reflex induced by a mild increase in intraluminal pressure (6 mm H,O) applied slowly (15 s from 0 to 6 mm H,O). The inhibitory effect of morphine was characterized by a decreased activity of both the longitudinal and circular muscle layers. The frequency of the peristaltic movements also was reduced. At high concentration  $(4 \times 10^{-6} \text{ M})$ morphine blocked completely the rhythmic peristaltic activity. Addition of naloxone  $(4 \times 10^{-8} \text{ M})$  to theorgan bath reversed this inhibitory effect of morphine. (Fig. 1, lower trace).

However, if the distension was continued for a long period, the reflex activity eventually slowed down and then stopped. Addition of naloxone ( $8 \times 10^{-8}$  M) to the organ bath before distension prevented this phenomenon of "fatigue". Moreover, this phenomenon was reversed by addition of naloxone ( $8 \times 10^{-8}$  M) to the organ bath after a short period of fading of the peristaltic reflex (Fig. 2).

Distension of the guinea-pig ileum segment by a suprathreshold pressure (>20 mm H<sub>2</sub>O) and a counter balance of 2 g elicits regular peristaltic reflex activity which can last forseveral minutes. However, if the distension was continued for a long period, the reflex activity eventually slowed down and became intermittently interrupted. This interruption was reversed by addition of naloxone ( $6 \times 10^{-8}$  to  $10^{-7}$  M)to the organ bath (Fig. 3). However, over a much longer period of time, intermittent interruption could still occur in the presence of naloxone. This concentration of naloxone usually did not interfere with normal peristaltic activity. Regular rhythmic activity was restored within 30 s of addition of naloxone.





Rhythmic peristaltic activity in response to near threshold distension was blocked by adding atropine ( $10^{-8}$  to  $3 \times 10^{-5}$  M) or TTX ( $10^{-7}$  to  $2 \times 10^{+6}$  M) to the organ bath. However, these drugs in the same concentrations did not block rhythmic peristaltic activity in response to higher levels of distension which were achieved by raising the reservoir more than four times higher and more rapidly than the level that was necessary to evoke peristaltic activity at just suprathreshold levels (Fig. 1, upper trace).

Addition of VIP ( $10^{-a}$  --  $10^{-9}$  M) to the organ bath before distension, increased the threshold of distension required to cause the peristaltic rellex and blocked the responses to threshold distension of longitudinal but not circular muscle layers (Fig. 4)

Somatostatin ( $10^{-5}$  --  $10^{-4}$  M) has been shown to exert an unusual effect on peristalsis. In some experiments, somatostatin increased the threshold of distension and inhibited responses to threshold distension. At high concentration it decreased the duration of the responses but had no effect on the height of rhythmic activity.

Proglumide and dbcGMP ( $10^{-3}$  to  $2 \times 10^{-3}$  M) were added directly to the organ bath 10 to 30 min. before testing, 1t was found that dbcGMP or proglumide increased the threshold pressure necessary to cause the peristaltic reflex and blocked all responses to threshold



Fig. 4. Effect of vasoactive intestinal polypeptide (IVP) on the peristaltic reflex in the guinea-pig ileum. VIP increased the threshold of distension required to cause the peristaltic reflex and blocked the responses to threshold distension of longitudinal (L) but not circular muscle activity (C) (n=8) (A). Inhibitory effect of VIP on longitudinal muscle (L) activity (P<0.005) and lack of its effect on circular muscle (C) activity (B) (P<0.005).</p>

distention. However, in the presence of dbcGMP or proglumide higher levels of distension induced peristaltic activity in the same way as in the presence of atropine and TTX (Fig. 5). This, therefore, possibly represented the myogenic response to distension. Caerulein and CCK ( $10^{-10}$  to  $10^{-11}$  M) decreased the threshold of distension pressure required to evoke the peristaltic reflex. Furthermore, they increased the height and duration of the responses (Fig. 6).

#### DISCUSSION

The aim of this study was to consider the possible role of non-adrenergic, non-cholinergic or some families of



Fig. 5. Upper trace, effect of dbcGMP on the peristaltic reflex in the guinea-pig ileum. DbcGMP blocked the peristaltic reflex evoked by near threshold distension (D) but not that induced by higher level of distension (D+). The latter response was similar to that obtained in the presence of atropine or TTX (n=4). Lower trace shows the inhibitory effect of proglumide (PROG) on the peristaltic reflex evoked by near threshold distension (D) (n=5). Note its effect is similar to that of dbcGMP. The inhibitory effect of both proglumide and dbcGMP on the peristaltic reflex is reversible (P<0.005).</p>

neuropeptides (endogenous opiates, cholecystokinin-like peptides, VIP, and somatostatin), known to be present in the myenteric plexus, in local nervous control of gut motility. Since the peristaltic reflex is best known and most widely studied of the local nerve mechanisms in gut, it was selected for this study.

Morphine inhibited the peristaltic reflex of the guineapig ileum. The inhibition was mainly characterized by decreased activity of both the longitudinal and circular muscle layers and delay in the appearance of the reflex. The inhibitory effect of morphine on the peristaltic reflex was reversed by naloxone and suggested therefore the involvement of endogenous opiate receptors in the regulation of the peristaltic reflex. Moreover, prolonged threshold distension of a guinea-pig ileum segment leads to an



Fig. 6. Effect of cholecystokinin (CCK) on the peristaltic reflex in the guinea-pig ilcum. It shows the potentiation of the peristaltic reflex (length and frequency) by cholecystokinin (CCK) (n=6,P<0.005).</p>

immediate and permanent inhibition of the peristaltic reflex activity (fatigue). This fatigue was usually reversed by naloxone. In addition, prolonged suprathreshold elicits regular peristaltic reflex activity which remains for several minutes. Then the activity slows down and becomes interrupted. The period of blocking of peristaltic activity is interrupted by the reappearance of short bursts of peristaltic waves. Addition of naloxone during a period of quiescence immediately restores the continuous peristaltic activity.<sup>32</sup> These results provide evidence that endogenous opiates are released during distension, casuing inhibition of the peristaltic reflex activity.

It has been well established that endogenous opiates act on the cholinergic neurones inhibiting ACh release and their inhibitory action on the peristaltic reflex can thus be explained by the same mechanisms.<sup>23,24,32,33</sup> However, at high levels of distension or even occasionally at low levels, intermittent inhibition may occur much later even in the presence of naloxone. This finding might be comparable with the naloxone-resistant component of the nerve-mediated inhibition discussed by Najafi (1990). This intermittent inhibition of the peristaltic reflex is unlikely to be explained in terms of postsynaptic desensitization because it is not a permanent inhibition. It can be explained more easily by presynaptic modulation of ACh release by muscarinic receptors. As ACh release is inhibited by presynaptic muscarinic receptors so the reflex will be inhibited. However, as ACh release slows down, so will the presynaptic feedback,34 and ACh release may then increase and the reflex activation of peristalsis will resume. This postulated oscillation in ACh release would account for the

observed phenomenon but would not be a feature of a well controlled feedback system. However, evidence for this suggestion is weak. VIP is distributed in large quantities throughout the gastrointestinal tract and localized mainly in nerve fibres.<sup>35</sup> VIP has a wide variety of actions which include inhibition of gastric acid secretion and gastric motility.<sup>18,19,36</sup> Since VIP increased the threshold of distension and blocked the responses of longitudinal muscle layers, it will be involved in the regulation of the peristaltic reflex and may act as an inhibitory transmitter.<sup>36</sup>

Somatostatin is identified by its action as an inhibitor of growth hormone release.37 Somatostatin is thought to function as a neurotransmitter, primarily because somatostatin-like immunoreactivity has been demonstrated in axons and nerve cell bodies of the peripheral and central nervous system.<sup>38</sup> In isolated longitudinal muscle strips from guinea-pig ileum, somatostatin has been shown to cause relaxation. It is demonstrated that somatostatin inhibits ileal muscle contraction induced by electrical field stimulation, which is atropine-sensitive. In contrast, the contractile response of the ileal muscle strip to exogenous acetylcholine is not modified by somatostatin.39 Most of our results show that somatostatin inhibits peristaltic activity and will be involved in the peristaltic activity. The mechanism by which somatostatin acts to inhibit peristaltic activity is not clear and may act presynaptically to inhibit the release of acetylcholine.

Caerulein and CCK enhanced the peristaltic reflex by increasing both the frequency and the magnitude of contractions. On theotherhand, both dbcGMP and proglumide inhibited the peristaltic reflex evoked at threshold distension pressure. Since both dbcGMP and proglumide are specific antagonists to CCK and related peptides and do not affect either the responses to direct electrical stimulation of the intramural cholinergic neurones<sup>40-12</sup> or the myogenic response to distension (i.e., the response to high levels of distension which are TTX- and atropine-resistant), it is concluded that CCK or a related peptide may be acting as a transmitter in the local nervous pathway. CCKcontaining neurones exist in the myenteric plexus.<sup>29</sup> Dockray & Hutchison (1980) showed that a proportion of intestinal CCK may originate from, and act on, gut neurones.8 They demonstrated that CCK was localized in the myenteric plexus rather than smooth muscle since concentrations were reduced by 70% in muscle strips without plexus. Moreover, CCK acts indirectly via stimulation of myenteric plexus neurones to release ACh and does not act on muscle; therefore, it cannot be the neuromuscular transmitter. It can be suggested, therefore, that distension of the ileum segment releases CCK or related peptides eitner from the sensory neuron or an interneuron, thereby activating the cholinergic motor neuron. Another possibility, however, is that CCK functions not as a transmitterbut as a modulator of ACh release. The first of these

possibilities appears to be most likely since TTX blocks responses to CCK. However, neither of these possibilities can be positively confirmed or excluded without neurophysiological and neuropharmacological studies on myenteric plexus neurons.

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