RECEPTORS INVOLVED IN INHIBITION OF THE RESPONSE TO ACETYLCHOLINE RELEASED FROM THE MYENTERIC PLEXUS OF THE GUINEA-PIG ILEUM

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Although antiemetic drugs (e.g. chlorpromazine) block central dopamine receptors (Carlsson & Lindqvist, 1963), it is not yet known if there is a peripheral component in their action. The recent concept of presynaptic receptors which modulate neuro transmitter release (Endo & other, 1977) provides a possible target site for these drugs. Therefore the effects of dopamine and other agonists and antagonists were examined on the isolated guinea-pig ileum preparation stimulated either by added acetylcholine or by transmural electrical stimulation, firstly to seek any evidence for modification of transmitter release and secondly to identify the receptors involved.

Contractions were elicited either with an ED_{50} concentration of acetylcholine or by a single electrical pulse (0.5msec, supra-maximal voltage). Dopamine, apomorphine, noradrenaline and isoprenaline produced a dose related inhibition of the response to added acetylcholine but it did not exceed 40% of the maximum. Of the antagonists tested (phentolamine, propranolol, pimozide and domperidone) only propranolol (10^{-6}M) reversed the inhibition. Dopamine and the other agonists were also effective inhibitors of the response to transmural stimulation but they were effective at lower doses and capable of producing 100% inhibition. Unlike added acetylcholine they were not specifically antagonised by propranolol and therefore β-adrenoceptors were not implicated. However, as both pimozide and phentolamine were effective antagonists it seemed that either a dopamine receptor or an α-adrenoceptor could be involved. The EC_{50}'s for the agonists as inhibitors of the response to transmural stimulation are shown in Table 1 and compared with clonidine and phenylephrine. The order of potency is similar to that found for presynaptic α-adrenoceptors (Endo & others, 1977). Phenylephrine caused only a small transient inhibition of twitch so that no value could be obtained for its potency.

Table 1. Potency comparison of various agonists as inhibitors of the response to transmural electrical stimulation and their susceptibility to antagonism by phentolamine and pimozide.

Agonist	EC_{50} (M)	Mean pA_2 phentolamine ($\pm$ se)	Mean pA_2 pimozide ($\pm$ se)
Clonidine	10^{-8}	9.22($\pm$0.08)	<7.00
Noradrenaline	10^{-7}	6.69($\pm$0.05)	8.08 ($\pm$0.03)
Dopamine	10^{-5}	6.80($\pm$0.04)	7.99 ($\pm$0.09)
Apomorphine	10^{-5}	5.95($\pm$0.02)	7.98 ($\pm$0.04)
Phenylephrine	10^{-4}	-	-

However, that more than presynaptic α- adrenoceptors could be involved is suggested by comparison of pA_2 values (Schild, 1947), thus phentolamine was a weak antagonist of apomorphine, but a potent antagonist of clonidine, whereas with pimozide the opposite was true. The simplest explanation of these results is that clonidine and apomorphine act on different receptors and that dopamine and noradrenaline may act on both.

Carlsson, A. & Lindqvist, M. (1963). Acta Pharmacol. Toxicol., 20, 140-144.

Endo, T., Starke, K. & others (1977). N-S. Arch. Pharmacol. 296, 229-247.

Schild, H. O. (1947) Brit. J. Pharmacol., 2, 189-206.