EFFECTS OF THE ANTIEMETIC DRUG DOMPERIDONE ON GUINEA-PIG ISOLATED GASTROINTESTINAL TISSUE

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Dopamine-receptor antagonists have antiemetic actions and have previously been presumed to act on the chemoreceptor trigger zone in the central nervous system. However, the dopamine-antagonists metoclopramide and domperidone have few central effects and yet are antiemetic. It seemed reasonable therefore to test whether there was a peripheral component in their action. In a previous communication (Ennis & others, 1977), dopamine was shown to inhibit cholinergic transmission in the isolated ileum preparation and it was thought possible that the antiemetics might act by preventing this action of dopamine on the cholinergic nerves of the gastrointestinal tract. However, in subsequent experiments domperidone was found to be inactive against this action of dopamine and therefore this could not explain its antiemetic action. Consequently we have been looking for alternative sites.

The ileum may not have been the most relevant tissue for this investigation since vomiting involves primarily the upper parts of the gastrointestinal tract. Therefore two different types of smooth muscle strip were made; one contained the gastroduodenal junction and the other the gastrooesophageal junction. Both types of strip were set up for isometric recording of tension changes in Krebs solution at 37°C aerated with 5% carbon dioxide in oxygen.

Both dopamine and noradrenaline produced dose-related relaxations of the smooth muscle strips and just submaximal concentrations of either drug were chosen for the remainder of the studies.

The relaxation of the gastroduodenal junction produced by addition of either dopamine (5×10^{-6}M) or noradrenaline (10^{-6}M) could be only partially blocked by phentolamine (2.5×10^{-6}M) or propranolol (3×10^{-6}M). However these relaxations were completely prevented by a mixture of phentolamine and propranolol. Domperidone (3×10^{-7}M) on the other hand was without effect on the response to either dopamine or noradrenaline.

The noradrenaline and dopamine-induced relaxation of the gastrooesophageal junction was also prevented by a mixture of phentolamine and propranolol. However in contrast to the results at the gastroduodenal junction domperidone (3×10^{-7}M) was found to be an effective antagonist of dopamine on this tissue. The antagonism appeared to be selective since this same concentration of domperidone did not antagonise noradrenaline. Pimozide a drug which blocks dopamine receptors in the central nervous system was also tested. In a concentration (5×10^{-9}M) known to block dopamine on ileal tissue, pimozide failed to block dopamine on the gastrooesophageal junction.

One possible explanation for these results is that dopamine is acting at the gastrooesophageal junction via a domperidone sensitive site to release noradrenaline, which in turn can itself be blocked by the phentolamine-propranolol mixture. The domperidone sensitive site does not appear to be similar to central dopamine-receptors since pimozide does not block it. This aspect of the work is at present under further study. However, whatever the precise mechanism underlying this effect, it is interesting that domperidone, an antiemetic, can antagonise dopamine at the gastrooesophageal junction, a site which could be relevant to its antiemetic action.

Ennis, Christine, Schnieden, H. & Cox, B. (1977). J. Pharm. Pharmac., 29, Suppl. 27P.