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Site(s) and mechanisms of the anti-emetic action of 5-HT_3 receptor antagonists: a discussion of Professor Naylor's paper

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Studies on the anti-emetic action of 5-HT_3 receptor antagonists have suggested two possible sites where these drugs could produce their effects. These are: (a) the vagal afferent peripheral nerve terminals which innervated the gastrointestinal mucosae, and (b) the central terminals of these same afferent nerves located in the vomiting system in the brain stem (i.e. the dorsovagal nucleus, the nucleus of the solitary tract and the area postrema). The evidence supporting these conclusions has been reviewed by Professor R.J. Naylor in this volume. While there are convincing arguments for a dual site of action, there are several pieces of the jigsaw still to be put in place. For example, the vagus nerve undoubtedly is richly populated with 5-HT_3 receptors along its whole length but the question still remains as to the source of the 5-HT which activates them. The most likely source is the enterochromaffin cells (ECL) which contain most of the 5-HT in the body and are located closely to the vagal afferent terminals in the duodenal mucosa. However, there is no evidence to show whether the 5-HT released by chemotherapeutic drugs or radiotherapy is due to a direct or indirect action on ECL cells.

It is possible that other actions, such as an inflammatory response, act indirectly on those cells which results in 5-HT release. Experiments in isolated cultured ECL cells need to be conducted. Whatever mechanism is determined it needs also to account for the delayed onset of vomiting seen with chemotherapeutic agents in both ferrets and patients. This delay may be due to a slowly developing stimulus or possibly due to an endogenous inhibitory response induced by the chemotherapeutic drug or radiation.

5-HT_3 antagonists injected directly into the brain stem in ferrets block the emetic response to parenterally administered cisplatin (Higgins *et al.*, 1989). However, the injection of 2-methyl-5-HT into the same brain stem area produces on slight retching and some nausea. While this is convincing evidence that there is an important central anti-emetic site of action, the question remains as to the source of 5-HT and why it is that emesis cannot be induced by direct application of a 5HT_3 agonist. It is unlikely that 5-HT released from the ECL cells reaches the brain stem via the plasma since 5-HT is rapidly metabolised and the 5-HT_3 receptors in the brain stem 'vomiting system' are probably inside the blood brain barrier across which 5-HT cannot readily pass. The pial membrane over the area postrema has specialised cells which contain 5-HT; it is possible that chemotherapy, or even activation of vagal afferents, causes 5-HT to be released from these cells which then activates the presynaptic 5-HT_3 receptors. Experiments which measure the changes in 5-HT levels in the brain stem vomiting system during treatment with chemotherapeutic drugs could assist in answering this question. An explanation for the lack of effect of centrally administered 2-methyl-5-HT may be that it is a partial agonist at 5-HT_3 receptors and therefore has insufficient efficacy to initiate a response; similar experiments with 5-HT, which has higher efficacy, should be conducted. An alternative possibility is that 5-HT acts synergistically with the primary afferent neurotransmitter of the vagus nerve. In this case both substances would be necessary to initiate an emetic response; blockade of either would be anti-emetic but neither agonist alone could initiate the response.

The question remains as to why 5-HT_3 antagonists are able to completely prevent emesis in ferrets but in patients there are still some resistant emetic episodes. The answer to this may come from examining the clinical components of the emetic response in cancer patients particularly the influences from higher brain centres. This comprises three parts: firstly, 'anticipatory nausea and vomiting' which can frequently precede treatment and occurs mostly in those patients who have vomited on previous treatment courses. Secondly, the acute induction of vomiting by the treatment itself, and thirdly, 'delayed vomiting' which can occur for several days after the treatment has stopped. Anticipatory vomiting is undoubtedly a conditioned response to the hospital environment and associated procedures which precede the unconditioned stimulus (chemotherapy). During the second treatment course there is most likely to be a continuation of this conditioned emetic response in addition to the acutely-induced response. This conditioned component may explain why some patients respond less well to anti-emetic therapy and may also explain the difference in effectiveness between that seen in the ferret, where there is no conditioned component, and in patients. It is likely that delayed vomiting is also partly a conditioned response and would be less effectively treated by anti-emetics – as appears to be the case. The effectiveness of 5-HT_3 antagonists against a conditioned emetic response in ferrets needs to be determined as well as against anticipatory vomiting in patients.

The 5-HT_3 receptor antagonists have undoubtedly improved the management of nausea and vomiting in cancer patients. However, there is still some way to go before com-

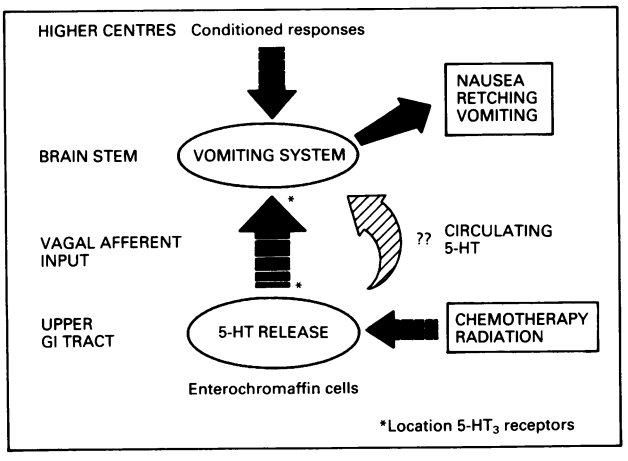

Figure 1 Site(s) and mechanism of the anti-emetic action of 5-HT_3 receptor antagonists.

plete control can be achieved. Combinations with dexamethasone significantly improve the effectiveness of 5-HT$_3$ antagonists but a further understanding of the mechanisms involved may lead to an even more effective anti-emetic regime.

Reference

HIGGINS, G.A., KILPATRICK, G.J., BUNCE, K.T., JONES, B.M. & TYERS, M.B. (1989). 5-HT$_3$ receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. *Br. J. Pharmacol.*, **97**, 247.