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REVIEW ARTICLE

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Neuropharmacology of emesis and its relevance to anti-emetic therapy

Consensus and controversies

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Abstract Recent great advances in the neuropharmacology of the emetic pathways have led to better therapy and improved insight into pathophysiological processes in patients undergoing chemo- and radiotherapy. This article gives an overview of the area, outlines current controversies and makes recommendations for future clinical studies.

Key words Emesis · Neuropharmacology · Anti-emetic therapy

Introduction

In the past decade enormous advances have been made in our understanding of the neuropharmacology of the emetic pathways. These have led to improved anti-emetic therapy, and given important insights into the pathophysiological processes occurring in patients treated with cytotoxic drugs and radiation. This document is divided into three parts: (1) a general overview of the area based around aspects of the topic on which there is a large measure of consensus; (2) areas of controversy, uncertainty and current research; (3) recommendations of clinical studies which would assist understanding of basic mechanisms.

Current concepts of the neuropharmacology

The discovery [10, 22] that blockade of one sub-type of the 5-hydroxytryptamine (5-HT) receptor, the 5-HT_3 receptor, could block the "acute" emetic response (retching and vomiting) induced by cisplatin in an animal model (ferret) was the key advance. In some ways this was a fortuitous event. Granisetron (Kytril), ondansetron (Zofran) and tropisetron (Navoban), effectively abolished emesis observed over an acute 4-h period. If the authors had used a longer period of observation then the relative resistance of the delayed phase would have revealed an incomplete control. This would surely have jeopardised the progression of such compounds to developmental status, ensuring their failure to reach the clinic, and would have relegated emesis research to obscurity. Such is life! The importance of the $5HT_3$ receptor antagonists is that they provided a precise pharmacological tool with which to study the pathways involved in cisplatin-induced emesis as a protypical cytotoxic drug. With the identification of the site of action of the 5-HT_3 receptor antagonists the role of the vagal afferent – enterochromaffin cell (EC cell) functional unit in the emetic response was identified [5]. In addition, the introduction of 5-HT_3 receptor antagonists stimulated clinical research and improved the quantification of nausea and emesis.

The identification of the site of action of the $5HT_3$ receptor antagonists stimulated research into emetic mechanisms in general, and as a consequence there has been a major reappraisal of the relative involvement of the area postrema (AP, popularly referred to as the "chemoreceptor trigger zone for emesis") and the abdominal visceral afferents, particularly the vagus, and this continues (for reviews see [1, 3]). In particular, the involvement of the AP in the emetic response to all systemic agents is a matter of debate. The recognition of the significance of the nucleus tractus solitarius (NTS, the main integrative nucleus for visceral and some somatic functions in the brain stem, subjacent to the AP) in emesis has grown in prominence, particularly the realisation that the dendrites from the NTS neurones invade the AP [27]. Thus, surgical ablation of the AP inevitably causes damage to these dendrites, some of which receive inputs from the abdominal vagal afferents terminating in the subnucleus gelatinosus of the NTS. Therefore lesions directed at the area postrema may damage these vagal pathways and, if emesis is affected, may give rise to the erroneous conclusion that the AP was the primary site at which the emetic agent was acting (see [3] for review).

The focus of the above mechanistic studies was the acute phase of emesis induced by cytotoxic drugs, as this is the most intense phase, but such studies need to be repeated in the recently described models of delayed emesis [16, 31, 33].

The application of electrophysiological and molecular techniques to emesis has provided novel insights into the action of cytotoxic drugs at the cellular level. For example, cisplatin acutely increases the excitability of cultured neurones at concentrations reported clinically, but chronic exposure produced complex effects indicative of interference with calcium homeostasis [35] (cf. proposed mechanisms of renal toxicity). Some of the chronic toxic effects of cisplatin were reduced by dexamethasone.

Studies by Matsuki et al. [19] have provided evidence showing that free radical generation is probably the key step in the mechanism by which cytotoxic drugs evoke the calcium-dependent exocytotic release of 5-HT from the ECs. This raises the question of why the ECs are so sensitive to cytotoxic drugs and radiation; if they were not, it is probable that emesis would be less of a problem with cytostatic agents.

Studies of the way in which the release of 5-HT is controlled have continued and appear to support the proposal that it involves a positive feedback via $5\text{-}HT_3$ receptors. Whilst there is some evidence for a negative feedback (saturating at low concentrations of 5-HT) via $5\text{-}HT_4$ receptors, this is still a matter of debate (for reviews see [25, 37]. Evidence from human studies supporting the hypothesis that cytotoxic drugs release 5-HT from the ECs has continued to accumulate, and further insights have been provided by the measurement of plasma chromogranin A [13]. However, an interesting anomaly has appeared with cyclophosphamide, where apart from the sensitivity of the emetic response to $5\text{-}HT_3$ receptor antagonists, the urinary 5-HIAA, measurements provide no evidence for an involvement of 5-HT. This requires further investigation.

The activation of the early immediate oncogene *c-fos* has been used to map some of the central neuronal pathways involved in the emetic response to a range of emetic agents, including cisplatin [27]. These studies reveal that even when the emetic response is blocked by administration of a $5\text{-}HT_3$ receptor antagonist, *c-fos* (an index of neuronal activation) activation still occurs in some brain stem regions, most notably the AP. This indicates that the AP may have a permissive role, or alternatively that an action here may be responsible for some of the other effects of the cytotoxic drugs, such as nausea, reduced food intake and conditioned taste aversions, which are less affected by $5\text{-}HT_3$ receptor antagonists than emesis. This observation should also serve to remind us that even if a patient does not have nausea or vomiting the cytotoxic drug will still have damaging effects on the patient, which may be responsible for other deleterious effects.

The above brief outline of some of the key aspects of basic research gives an insight into the progress that has been made from a preclinical perspective. However, it would be erroneous to think that now that the $5\text{-}HT_3$ receptor antagonists are well established clinically throughout the world, basic studies no longer have a place (see below).

Controversial and novel areas

Are the emetic pathways in man the same as in animals?

A Darwinian approach to the emesis in anti-cancer therapy

Whilst it is impossible to answer this question by direct experimentation, a large body of circumstantial evidence supports the view that the vagus – EC cell functional unit plays a key role in the emetic response to cytotoxic drugs and radiation. Viewing the emetic reflex from an evolutionary view as a protective reflex also supports this view. In addition, from an evolutionary perspective it is nausea rather than vomiting that serves to generate the aversive response, and it is well known that once anticipatory nausea and vomiting have developed they are difficult to treat. This preclinical observation leads to the conclusion that optimal anti-emetic treatment (e.g. oral/i.v. $5\text{-}HT_3$ receptor antagonist with a steroid) should be given on the *first course* of anti-cancer therapy and not reserved for patients who have failed on conventional anti-emetics.

The continuing problem of nausea

It is clear that nausea is much less effectively dealt with than vomiting by the $5HT_3$ receptor antagonists, although the reason for this is not clear. Nausea (the warning) is often considered to be induced by "low"-intensity activation of a pathway that, when more intensely activated, leads to retching and vomiting. The observation that nausea is less affected than vomiting by $5HT_3$ receptor antagonists suggests that the genesis of nausea may involve activation of additional pathways to the vagal afferent–EC unit.The AP would be a likely site, and such a mechanism is supported by the lack of effect of the $5HT_3$ receptor antagonist granisetron on cisplatin-induced *c-fos* expression in the ferret [27]. Because of the severe limitations of studying a subjective sensation in animals, mechanistic studies of nausea must be undertaken in man.

The recent studies of Miller et al. [21] provide an excellent beginning. Measuring human cortical activity (using a noninvasive magnetic source imaging) during vestibular and ipecacuanha-induced nausea, they recorded a cortical locus in the inferior frontal gyrus that demonstrated a greater number of dipoles during intense than during milder nausea. Such changes were not recorded to other forms of sensory stimulation. Future studies using other emetogenic challenges and antiemetic regimens may help to elucidate the detail of the cortical and other brain systems and finally the mechanisms involved in nausea (and emesis). The techniques may also allow for an objective rather than subjective assessment of nausea.

In connection with this, it appears that the value of ipecacuanha to nausea and emesis research is frequently overlooked and better use could be made of this agent. Thus, ipecacuanha-induced nausea and emesis may be a particularly useful model to investigate the antiemetic actions of $5\text{-}HT_3$ receptor antagonists. In animal models, ondansetron and other $5\text{-}HT_3$ receptor antagonists exert a selective action, to inhibit emesis induced by cytotoxic drugs, radiation and ipecacuanha. The great advantage of using ipecacuanha in humans is that it can be safely used in human volunteers to assess the potency and antiemetic efficacy of $5\text{-}HT_3$ receptor antagonists [23] and other antiemetics, such as the NK_1 receptor antagonists, and generally makes it possible to avoid the difficulties inherent in using cancer patients. It remains unlikely that its mode of action precisely reflects that of cytotoxic drugs.

Are there animal models of patients?

When apparent differences are described between humans and animals the phrase often used is "species differences". However, this does not explain what is involved and is often used to suggest that the data from the non-human animal is "wrong". This is a patently unsupportable view, and particularly so when such an phylogenetically ancient and significant protective reflex as emesis is being considered. In studying the response of animals to cytotoxic drugs or radiation, we are essentially studying the basic reflex pathways, primarily at the level of the brain stem. Whilst this has provided key insights into pathways, as exemplified by the use of $5HT_3$ receptor antagonists, the limitations of such models must be borne in mind in assessment of the insights they provide into the mechanisms operating in cancer patients who are undergoing therapy.

One important aspect that needs to be addressed in comparing pathways in man and animals is the role of the cerebral cortex. There is little doubt that the cerebral cortex and related structures provide an important modulatory input to the brain stem, probably at both conscious and subconscious levels. In animals it is impossible to assess the role of the cortex. However, it is not unreasonable to suppose that except perhaps in the highest non-human primates there is little conscious input in terms of "rationalising" the experience. What is meant here is not that the animals do not find the experience distressing to some degree, but that they do not contextualise it, which must add to the globally stressful nature of the experience. In most of the animal studies it is therefore the basic reflex mechanism of emesis induced by cytotoxic drugs and radiation that is being studied, rather than chemo*therapy* and radio*therapy*. These mechanisms may be further modified by the presence of the tumour and concomitant medication, neither of which is present in the animal models.

Why do patients "fail" on $5\text{-}HT_3$ receptor antagonists in the acute phase of emesis?

Provided that an adequate dose of a long-lasting $5\text{-}HT_3$ receptor antagonist has been given, then "failure" cannot be attributed to inadequate blockade of the receptor. One possible conclusion is that another receptor or pathway is involved. Animal studies have revealed that the emetic system shows a degree of "plasticity" [6, 20]. It is possible that patients who fail on $5\text{-}HT_3$ receptor antagonists have a greater expression of this pathway than patients in whom the drugs are "successful". It is apparent from these experiments that clinical studies should be directed towards careful investigation of the failures so that the pharmacology of the non-$5HT_3$ pathways can be elucidated. This could be achieved by systematic characterisation of the effect of well-defined pharmacological agents on these patients.

There remain major differences between drug action to antagonise the emetic effects of single drug challenges in animals or human volunteers and the nausea and emesis occurring in the cancer patient undergoing

therapy. Thus, in man, visual, auditory or olfactory stimuli, e.g. the sight, sound or smell of someone being sick, or the psychological stimuli of anxiety, can contribute to the occurrence and intensity of nausea and vomiting. The cancer itself, if causing obstruction in the lower or upper intestinal system, raised intracranial pressure, hypercalcaemia, renal failure, pain, gastric irritation, etc., can all contribute to nausea and vomiting. Also, associated drug treatments, e.g. opioids, non-steroidal anti-inflammatory agents, drug abuse or alcohol, may all exacerbate nausea and vomiting. The more advanced the cancer, the greater their contribution. In palliative care units the incidence of nausea/vomiting may be as high as 90% [9]. The contribution these many factors make to anti-emetic drug treatments remains less than certain. However, given that various stimuli may contribute to the emesis induced by chemotherapy, the success of the 5-HT_3 receptor antagonists in completely controlling emesis in some 60–80% of patients during the acute phase is remarkable. Failure in the remaining patients during the acute phase may reflect the input of additional stimuli resistant to 5-HT_3 receptor blockade; this may also account for the less than adequate control of nausea and vomiting during the delayed phase. It should be borne in mind that even the failures are having less nausea and vomiting than if they had not received any anti-emetic treatment.

Whilst the involvement of 5HT and $5HT_3$ receptors (peripheral and central) in emesis induced by anti-cancer therapies is well accepted, Cubeddu et al. have recently published an apparently anomalous piece of evidence but nevertheless one that may give a clue to other mechanisms [12, 13]. In man, a raised urinary level of 5-HIAA following cisplatin treatment has been taken to reflect a release of 5-HT from the ECs, and hence a supportive of a role for 5-HT in emesis [12, 13]. However, although cyclophosphamide-induced emesis is affected by $5HT_3$ receptor antagonists in man and animals, cyclophosphamide fails to increase urinary 5-HT levels; it is imperative that further studies, using a much broader range of cytotoxic drugs and radiation, be carried out to substantiate a raised urinary 5-HIAA level with an emetic potential.

What mechanisms are involved in delayed emesis?

Delayed emesis remains a problem, although the new animal models may provide rapid advances as the pathways and the pharmacology of this phase are investigated. However, as there have been relatively few studies of the physiological changes occurring in patients during the delayed phase, it is not clear how closely the animal models mimic man. The efficacy of conventional doses of metoclopramide in the delayed phase suggests that gut motility may be perturbed during this phase. It is proposed that detailed studies of gastrointestinal function be undertaken in patients. This may provide some insights into the mechanism of delayed emesis, but also and of equal importance, be of use in assessing the damage caused to the gut by the anti-cancer treatments, which can influence the patients' return to a normal diet.

Studies (Andrews, Bingham and Davidson, unpublished observations) have been undertaken in rats showing a long-lasting (4 days) reduction in gastric emptying following a single injection of cisplatin, but it is not clear how the effect comes about or whether this could contribute to delayed emesis. Recently a ferret and a piglet model of delayed emesis have been published [16, 31], but as yet the pathways have not been investigated. Information is urgently needed about the pathways involved in these animal models, in order to identify therapeutic approaches to the outstanding problem of delayed emesis. Whilst the animal models of delayed emesis may superficially resemble the condition seen in man, it is important that food intake, gastrointestinal tract, autonomic nervous system function and tissue damage are monitored in man in the delayed phase, so that these can be compared with the events happening in the animals. It is highly likely that delayed nausea and vomiting are multifactorial, perhaps with different mechanisms operating at different times, but this has not been investigated experimentally in man.

It should be remembered that the poor efficacy of 5-HT_3 receptor antagonists in man in the delayed phase does not exclude a role for 5-HT, acting on some other receptor, in this phase of the response, and the piglet studies of [16] support such a proposal.

The quest for the perfect anti-emetic

The "holy grail" or "El Dorado" of anti-emetic research has been the identification of an anti-emetic agent that blocks the response to all stimuli. The reason for this is that it obviates the need to understand the precise mechanism or pathway by which a particular emetic stimulus acts, and obviously such an agent would have widespread clinical utility. Two approaches to this problem are highlighted below.

Continuing involvement of 5HT receptors

Recognising the involvement of 5HT in the central components on the emetic pathway, one approach to reducing 5-HT function has come from the use of 5-HT_{1A} receptor ligands (agonists), e.g. 8-OH-DPAT, buspirone (currently used in psychiatry), flesinoxan and lesopitron, which, in animals, can reduce motion-, copper sulphate- and cisplatin-induced emesis [18, 24, 30,

32]. Activation of somatodendritic 5-HT_{1A} autoinhibitory receptors in the raphé nuclei reduces 5-HT cell firing and 5-HT release throughout the central serotonergic system. This argues for an important role of central 5-HT mechanisms to modulate the emetic reflex. The clinical value of such agents, administered with or without a 5-HT_3 receptor antagonists, is currently being assessed. Although initial clinical studies with buspirone have been disappointing [12], this may not be the optimal compound to use in testing the hypothesis.

Substance P and its receptor(s): a way forward?

1993, Andrews and Bhandari showed that the ultrapotent capsaicin analogue resinferatoxin (RTX) markedly reduced the emetic response to emetic agents acting centrally (loperamide) or peripherally (total-body radiation, intragastric copper sulphate) [2]. It was proposed that the blockade was due to a release and subsequent depletion of substance P or CGRP in the nucleus tractus solitarius in the brain stem. In the past few years a number of animal studies (in ferret, dog, cat, house musk shrew) have been published demonstrating that selective non-peptide antagonists for the neurokinin-1 (NK1) receptor (one of the receptors at which substance P or a closely related substance acts) have the ability to block the retching and vomiting response to a wide variety of emetic stimuli, including cisplatin, radiation, apomorphine, intragastric copper sulphate, and motion [14, 15, 36, 38]. Thus, they can block the responses to stimuli acting centrally and peripherally, which gives them a clear potential clinical advantage over the $5HT_3$ receptor antagonists. It is suggested that the anti-emetic effect of the NK1 receptor antagonists is due to antagonism of the action of substance P at a critical point in the emetic pathway, probably the NTS [38]. To date, there is no evidence that NK1 receptor antagonists affect any other reflexes that involve the NTS. It is proposed that antagonists of the human NK1 receptor offer the best novel approach to complete blockade of retching and vomiting. However, it is not possible to comment on their efficacy against nausea, as this cannot be assessed directly in animals (it is a subjective sensation), and because of this the results of clinical studies are eagerly awaited, not only to see whether these agents offer a way forward but also to help better define the predictability (or otherwise) of the animal models of nausea and emesis.

Proposals for clinical studies that would facilitate understanding of the neuropharmacology

Pharmacological characterisation of anti-emetic failures

The question of whether failure is due to an inadequate (or inappropriate) drug or to the patient is, somewhat surprisingly, still unresolved. This question has two components. First, studies can only be undertaken in patients who have had optimal anti-emetic treatment (i.e., a $5HT_3$ receptor antagonist and a steroid) for the acute phase of their first course of cytostatic therapy. The rationale for this is outlined above, and on scientific grounds it is indefensible to use suboptimal therapy on the first course of treatment and "wait for the patient to fail". If this comes about, such patients may have a problem (e.g. anticipatory emesis) not amenable to anything other than behavioural therapy. If a patient fails on a pharmacologically well-defined agent (e.g. a $5HT_3$ receptor antagonist), then by judicious use of other equally well-defined agents (e.g. domperidone, as opposed to prochlorperazine) progress will be made in teasing out the neuropharmacology of the pathways in different patient populations. If a non-systematic approach is used, we believe this is a retrogressive step, returning to the of polypharmacy era, with regimens involving multiple drugs, each with multiple actions. Our consensus is that this is not progress. However, we recognise that in man, for total control of emesis and perhaps even more of nausea, it may be be necessary to block a number of different brain stem receptor sites.

Dexamethasone: the Cenerentolla of anti-emesis

It can be argued that the only disadvantage of dexamethasone is its low cost. Because of this, whilst it has demonstrable efficacy there is little interest in understanding the mechanism of action, as there may be little to be gained (financially) by making a "better" dexamethasone. Pharmacologically, dexamethasone is a fascinating agent, because of its ability to enhance the anti-emetic efficacy of diverse antiemetic agents (e.g. ondansetron, [32]). Whilst basic studies are revealing novel actions of dexamethasone (e.g. a possible neuroprotective action against cisplatin, [35]), virtually nothing is known about the mechanism of its anti-emetic effects. This is perhaps best exemplified by the absence of a dose–response curve for dexamethasone. Such information is needed urgently, as it would presumably provide important insights into its mechanism. The efficacy of dexamethasone in delayed emesis is of particular interest, as it may indicate whether an inflammatory process is involved in the delayed phase of emesis.

What is the true spectrum of anti-emetic action of the $5HT_3$ receptor antagonists?

The clinical efficacy of $5HT_3$ receptor antagonists against cytostatic anti-cancer therapy is not in doubt. A predominantly peripheral site of action (vagal afferents) with a central contribution for some compounds is

consistent with this spectrum of action. However, it should also be noted that there are preliminary indications from over 20 studies (many uncontrolled) that a $5HT_3$ receptor antagonist (ondansetron) has some efficacy in ameliorating the nausea and vomiting caused by drug-induced gastric irritation, obstruction or distension, uraemia, neurological trauma and the carcinoid syndrome (e.g. [7, 17, 26, 34]). This antiemetic potential is worthy of much more detailed investigation in the cancer patient, with or without chemotherapy.

Patient predictive factors

In some ways this aspect is the most amenable to study and may provide significant insights into the endogenous factors that determine individual emetic sensitivity. For example, ferrets challenged with apomorphine show different intensities of emetic response [11]. Humans also show differing sensitivity to emetic challenge. Thus, women who show sensitivity to the nausea and emesis-inducing effects of the contraceptive pill show a clear trend to a greater and consistent incidence of nausea and vomiting during pregnancy and with travel sickness and migraine [39]. Pharyngeal stimulation can readily evoke the gag reflex in some people and not in others. Female sex hormones may alter the threshold of the emetic reflex [4, 8, 28]. Nausea and vomiting decrease with age [29], and, generally speaking, women appear to be more sensitive to nausea and/or emesis than men.

There have been no systematic attempts to compare gender differences in establishing a simple behavioural profile or emetogenic/nausea challenge that would be revealing of emetic sensitivity. Success here would be a major advance in better prediction of an effective use of costly medication.

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