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Review

Looking beyond 5-HT$_3$ receptors: A review of the wider role of serotonin in the pharmacology of nausea and vomiting

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ABSTRACT

The concept that 5-hydroxytryptamine (5-HT; serotonin) is involved in the emetic reflex was revealed using drugs that interfere with its synthesis, storage, release and metabolism ahead of the discovery of selective tools to modulate specific subtypes of receptors. This review comprehensively examines the fundamental role of serotonin in emesis control and highlights data indicating association of 5-HT$_{1-4}$ receptors in the emetic reflex, whilst leaving open the possibility that 5-HT$_{5-7}$ receptors may also be involved. The fact that each receptor subtype may mediate both emetic and anti-emetic effects is discussed in detail for the first time. These discussions are made in light of known species differences in emesis control, which has sometimes affected the perception of the translational value of data in regard to the development of novel anti-emetic for use in man.

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1. Introduction

Nausea and vomiting (emesis) are symptoms of many diseases and side effects of many drug therapies. Despite years of pre-clinical research however, the precise anatomical pathways and biochemical mediators involved have been difficult to define. Vomiting is

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quantified relatively easily but unfortunately common laboratory animals (*e.g.* mice, rats and rabbits) lack a vomiting reflex. The study of emesis therefore requires animals possessing the capacity to vomit and is relatively expensive. Nausea represents an even greater challenge since it is subjective and very poorly understood.

Hints at how important serotonin (5-hydroxytryptamine, 5-HT) would turn out to be important in nausea and vomiting came in fact from the clinic, and the explosion of research that followed could be considered to be 'reverse-translational'. The puzzle of why metoclopramide was more efficacious at controlling chemotherapy-induced nausea and vomiting (CINV) than other dopamine antagonists contributed to the evolution of 5-HT receptor classification, and the synthesis of novel pharmacological tools with several avenues of therapeutic potential.

Subsequent research and development however focused on 5-HT_3 receptor pharmacology almost to the exclusion of other receptor subtypes even though much data generated from pharmacological manipulation of 5-HT synthesis, storage, and release had suggested a bigger picture. Potential leads for the development of alternative anti-emetic agents were followed no further, yet with increasing recognition that even combined use of all currently available recognized anti-emetic agents fails to eliminate emesis in the clinic, the need for something new has never been more pressing. By revisiting the pre-5-HT_3 receptor data and incorporating, with these, where possible, up-to-date clinical and molecular findings, this review will attempt to redress the balance.

2. 5-HT receptor classification

5-HT receptors are classified into 7 families (5-HT_{1-7}) (Barnes and Sharp, 1999; Hoyer et al., 2002). All are trans-membrane spanning G-protein-coupled receptors except for the 5-HT_3 receptor, which belongs to the cys-loop ligand-gated ion channel family. The 7 families are divided into subfamilies and, to date, a total of 14 5-HT receptors have been characterized. As recently as the 1980s however, only 2 receptors were known (D and M receptors). Our understanding was limited by the pharmacological tools available at the time. In the 'pre-molecular biology era' 5-HT receptor function had to be defined by drugs affecting the synthesis, release or activity of 5-HT by administering biosynthetic precursors, or by simply administering 5-HT itself. 'D' and 'M' receptors were subsequently reclassified as 5-HT_2 and 5-HT_3 receptors, respectively, preceding the characterization of 5-HT_1 and 5-HT_4 receptors, and all of which came before the molecular techniques which lead to the characterization of the full 5-HT pantheon which is appreciated today (Hoyer et al., 2002).

Understanding the role of 5-HT receptors in emesis requires an appreciation that 5-HT may both facilitate and inhibit emesis. The relative effects of different agents that interfere with the synthesis, storage, or release of 5-HT will be governed by their ability to reach different anatomical areas, which may be populated by receptors mediating the different functions. Specific ligands (agonists and antagonists) may have different effects according to their receptor selectivity and even then, different functions may still be mediated by identical receptors in neighboring tissues but on different neurons. To complicate issues even further, it is not even likely that 5-HT receptor ligands will behave in the same way in different species.

3. Emetic potential of drugs potentiating 5-HT function

3.1. 5-Hydroxytryptophan (5-HTP)

5-HT is found extensively in neurons in the central and peripheral nervous systems and following release, its actions are terminated by re-uptake and/or metabolism by monoamine oxidase (MAO). Serotonin is synthesized from dietary L-tryptophan via an intermediate compound, 5-hydroxytryptophan (5-HTP) by its rate-limiting enzyme tryptophan hydroxylase (TPH). 5-HT is also synthesized in GI tract enterochromaffin cells. Platelets, take up 5-HT as they pass through the GI tract and provide a circulating reservoir of the monoamine (Bertrand and Bertrand, 2010). In fact, L-tryptophan itself is known to induce nausea in man and emesis in pigs (see Chung et al., 1991).

5-HTP is an over the counter medicine in several countries where it is used as an antidepressant, appetite suppressant and also as a hypnotic to induce sleep (Byerley et al., 1987); it is also used in an attempt to avoid the depressive after effects of MDMA (3,4-methylenedioxy-N-methamphetamine, 'ecstasy'). 5-HTP is usually taken orally but diarrhea, nausea and vomiting are its known side effects (Li Kam et al., 1993; van Vliet et al., 1996) and 5-HTP administered intravenously also induces nausea and vomiting in humans. It is natural to assume that the mechanism may be related to a local conversion of 5-HTP to 5-HT which could then go on to stimulate any number of 5-HT receptors. 5-HTP is capable of crossing the blood brain barrier (BBB) yet depending on the species, evidence supports either a central or peripheral mechanism of action to induce emesis. The peripheral decarboxylase inhibitor, carbidopa does not prevent 5-HTP-induced emesis in man (Gijsman et al., 2002; Smarius et al., 2008; Van Woert et al., 1976). However, in marmosets and *Cryptotis parva* (the least shrew), the emesis induced by 5-HTP is suppressed by carbidopa (Campos and Rodrigues, 1987; Darmani and Johnson, 2004). The concept that there may also be differences between species will be a recurring one in this review.

If the emetic effects of 5-HTP are mediated directly by 5-HT, the question of which of the many 5-HT receptors are responsible remains. In the common marmoset 5-HTP-induced emesis is not prevented by cyproheptadine (a histamine H_1 antagonist with non-selective 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptor blocking properties), methysergide (an antagonist at 5-HT_{2B}, 5-HT_{2C} and 5-HT_7 receptors and partial agonist at 5-HT_1 receptors) or metergoline (an antagonist at 5-HT_2 and also 5-HT_{1D} receptors; also with moderate affinity for 5-HT_6 and high affinity for 5-HT_7 receptors) (Campos and Rodrigues, 1987). Data thus implicate the 5-HT_3, and possibly the 5-HT_5(?) receptor by process of elimination. In the least shrew, 5-HTP-induced emesis is antagonized by delta-9-tetrahydrocannabinol (Δ-9-THC) by a mechanism probably involving cannabinoid CB_1 receptors (Darmani and Johnson, 2004), cannabinoids however are now also known to act as non-competitive antagonists at the 5-HT_3 receptor (Xiong et al., 2008).

Interestingly, the contention that the action of 5-HTP to *induce* emesis is not entirely due to an interaction at 5-HT receptor sites was investigated in cats almost 50 years ago (Cahen, 1964). In this species, the emetic action of 5-HTP was prevented by chlorpromazine (a dopamine receptor antagonist that also weakly blocks histamine H_1 and alpha-adrenoceptors) and by compounds depleting catecholamines including alpha-methyl-dopa, alpha-methyl-tyrosine and reserpine; an anesthetic dose of pentobarbital also prevented the response (Cahen, 1970). Conversely, the non-selective MAO inhibitors, iproniazid, nialamide and isocarboxazid, all potentiated emesis induced by 5-HTP (Cahen, 1970). It was therefore suggested that 5-HTP-induced emesis may indirectly involve the release of noradrenaline (Cahen, 1970). If however we also look at reserpine-induced emesis in pigeons, (before depleting monoamines, reserpine first releases monoamines), 5-HTP did not modify the emetic response, which complicates our understanding of the mechanisms involved (Trivedi and Gupta, 1973).

5-HTP is also emetic in dogs (Bogdanski et al., 1958) and marmosets (Campos and Rodrigues, 1987) but in our own