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Migraine therapy and 5-HT receptor activity

5-HT in migraine – an introduction

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Introduction

Of the many factors that have been implicated from time to time in the pathophysiology of migraine, none seems to have a better claim than 5-hydroxytryptamine (5-HT; serotonin). Advances in the understanding of the role of 5-HT in migraine and in the pharmacology of this amine have now resulted in the development of the drug, sumatriptan, for the treatment of migraine. Since this drug is a selective agonist at a particular type of 5-HT_1-like receptors [5], it is desirable to sketch the current views on the classification and nomenclature of 5-HT receptors.

5-HT receptor classification

More than three decades ago Gaddum and Picarelli [3] reported that 5-HT stimulates two different types of receptor – "D" [phenoxybenzamine (dibenzyline)-sensitive] and "M" (morphine-sensitive) – which are present on the intestinal smooth muscle and intramural neurons, respectively. Already in the early 70's, it was, however, recognized that some pharmacological effects of 5-HT, for example vasoconstriction in the canine common carotid bed [6], are mediated by "atypical" receptors. Subsequently, it was demonstrated that two different binding sites, 5-HT_1 and 5-HT_2, exist in the rat brain membranes [4]. In 1986, Bradley et al. [1] proposed a new classification where the receptors for 5-HT were categorized into three main types, 5-HT_1-like (previously referred to as "atypical"), 5-HT_2 (previously referred to as "D") and 5-HT_3 (previously referred to as "M"). More recently, 5-HT_4 receptors have also been described [2].

Table 1 lists the agonists and antagonists at and the functional responses mediated by the different 5-HT receptors. It has to be emphasized that only 5-HT_2 and 5-HT_3 receptors have so far been well characterized using selective antagonists. No such substances are yet available for 5-HT_1-like and 5-HT_4 receptors. The 5-HT_1-like receptors, having a nanomolar affinity for 5-HT, are heterogeneous in nature but the exact association with the 5-HT_1 binding site subtypes is still unclear since suffi-

Table 1. Agonists and antagonists and some functional responses mediated by 5-HT receptors

Receptor type	Agonists	Antagonists	Binding site	Second messenger	Some functional responses
5-HT_1-like	5-HT 5-CT	Methiothepin[a], methysergide[a]	5-HT_1	See Table 2	
5-HT_2	5-HT, α-methyl-5HT	Ketanserin, cyproheptadine, methysergide, methiothepin	5-HT_2	PIte-specific PLA-C	Contraction of various vascular, gastrointestinal and bronchial smooth muscles, platelet aggregation, head twitch
5-HT_3	5-HT, 2-methyl-5HT	MDL 72222, ICS 205930, granisetron, ondansetron	5-HT_3	K^+	Membrane depolarization, dermal pain and flare response
5-HT_4	5-HT, renzapride, 5-CH_3O-T	ICS 205930 (high concentrations)	Not yet found	Positive coupling to AC	Gastrokinetic action, cholinergically-mediated guinea-pig ileum contraction, myocardial stimulation in the pig

[a] Non-selective antagonist (also blocks 5-HT_2 receptors)

AC, adenylyl cyclase; K^+, potassium channel; ICS 205930; (3α-tropanyl)-1*H*-indole-3-carboxylic acid ester; 5-CH_3O-T, 5-methoxytryptamine; MDL 7222, 1α*H*,3α,5α*H*-tropan-3yl-3,5-dichlorobenzoate; PIte, phosphoinositide; PLA-C, phospholipase C; 5-CT, 5-carboxamidotryptamine

Table 2. Putative subdivisions of the 5-HT_1-like receptors: agonists and antagonists and some functional responses

Subtype	Agonists	Antagonists	Binding site	Second messenger	Some functional responses
$5\text{-}HT_{1A}$	5-HT, 8-OH-DPAT, 5-HT, RU 24969	Cyanopindolol, methysergide, methiothepin	$5\text{-}HT_{1A}$	Negative coupling to AC, K^+	Behavioural changes, centrally evoked hypotensive response
$5\text{-}HT_{1B}$	RU 24969, 5-CT, 5-HT	Cyanopindolol, methiothepin, methysergide	$5\text{-}HT_{1B}$	Negative coupling to AC	Autoreceptor in the rat brain
$5\text{-}HT_{1C}$[a]	5-HT	Mesulergine, methiothepin, methysergide	$5\text{-}HT_{1C}$	PIte-specific PLA-C	Not yet convincingly demonstrated
$5\text{-}HT_{1D}$	5-CT, 5-HT, sumatriptan	Methiothepin	$5\text{-}HT_{1D}$	Negative coupling to AC	Not yet convincingly demonstrated
$5\text{-}HT_{1x}$[b]	5-CT, 5-HT, AH25086[c], sumatriptan, 8-OH-DPAT, RU 24969	Methiothepin, methysergide[d]	Not yet found[e]	Not yet known	Contraction of cephalic arteries (basilar, pial) and arteriovenous anastomoses in the carotid region, decrease of neuronal noradrenaline release
$5\text{-}HT_{1y}$[b]	5-CT, 5-HT	Methiothepin, methysergide	Not yet found[e]	Not yet known	Vascular smooth muscle relaxation, hypotension, tachycardia in the cat

[a] Shows little difference from the $5\text{-}HT_2$ receptor
[b] The receptor subtype is as yet unnamed and this name has been used for convenience to distinguish between the two unnamed 5-HT_1-like receptors
[c] Ligand binding profile is not yet reported
[d] Partial agonist
[e] Does not correlate with $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{1C}$ or $5\text{-}HT_{1D}$ binding sites

AC, adenylyl cyclase; AH25086, 3-aminoethyl-*N*-methyl-1*H*-indole-5-methane carboxamide; 5-CT, 5-carboxamidotryptamine; K^+, potassium channel; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetralin; PIte, phosphoinositide; PLA-C, phospholipase C; RU 24969, 5-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole

ciently selective drugs are not yet available, except for the $5\text{-}HT_{1A}$ site (Table 2; [5]).

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