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The serotonergic system in migraine

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Abstract Serotonin (5-HT) and serotonin receptors play an important role in migraine pathophysiology. Changes in platelet 5-HT content are not casually related, but they may reflect similar changes at a neuronal level. Seven different classes of serotoninergic receptors are known, nevertheless only 5-HT_{2B-2C} and $5HT_{1B-1D}$ are related to migraine syndrome. Pharmacological evidences suggest that migraine is due to an hypersensitivity of 5-HT_{2B-2C} receptors. *m*-Chlorophenylpiperazine (mCPP), a 5-HT_{2B-2C} agonist, may induce migraine attacks. Moreover different pharmacological preventive therapies (pizotifen, cyproheptadine and methysergide) are antagonist of the same receptor class. On the other side the activation of 5-HT_{1B-1D} receptors (triptans and ergotamines) induce a vasocostriction, a block of neurogenic inflammation and pain transmission.

Key words Serotonin • Migraine • Triptans • *m*-Chlorophenylpiperazine • Pathogenesis

Introduction

Serotonin (5-HT) and serotonin receptors play an important role in migraine pathophysiology. This neurotransmitter is found in many body tissues. High concentrations are present in the gastrointestinal tract, platelets, and brain. There are seven known classes of 5-HT receptors: 5-HT_{1-7} excluding 5-HT_3, are G protein-coupled receptors; the 5-HT_3 receptor is coupled to an ion channel [1]. There is also a 5-HT transporter.

The 5-HT receptor subfamilies

5-HT_1 receptors

There are five subtypes of 5-HT_1 receptors (A, B, D, E and F); all have inhibitory actions.

The 5-HT_1 receptor family is distinguished from all other 5-HT receptors by the absence of introns in the genes; in addition all are inhibitors of adenylate cyclase [1].

The 5-HT_{1A} receptor has a high selective affinity for 8-hydroxy-2,2-(di-*n*-propylamino)tetralin (8-OH-DPAT). Activated human 5-HT_{1A} receptors expressed in Hela cells inhibit forskolin-stimulated adenylate cyclase activity. Buspirone and similar drugs act as agonists in cell lines expressing large numbers of 5-HT_{1A} receptors and as antagonists in cell lines with few receptors [2].

Both human and rodent 5-HT_{1B} and 5-HT_{1D} receptors, which are closely similar to each other, have been cloned; the rodent 5-HT_{1B} receptor is 97% identical to human 5-HT_{1B}. The mRNAs of 5-HT_{1B} and 5-HT_{1D} are expressed in human trigeminal ganglia [3]. Immunolocalisation experiments have shown that 5-HT_{1D} receptors are present on trigeminal nerve endings, and that 5-HT_{1B} receptors are present on cranial blood vessels [3]. Triptans and ergot alkaloids have high affinities for human 5-HT_{1B} and 5-HT_{1D} receptors [4].

Unlike most other 5-HT_1 receptors, the cloned human 5-HT_{1E} receptor has low affinity for 5-carboxamidotriptamine (5CT) and for sumatriptan [5]. The 5-HT_{1F} receptor, which is genetically very similar to 5-HT_{1E}, also has low affinity for 5CT but high affinity for sumatriptan [6]; furthermore it does not produce vasoconstriction. Autoradiographic experiments have localised the 5-HT_{1F} receptor to the trigeminal nucleus caudalis and substantia gelatinosa of the spinal cord – areas associated with pain transmission [7]. The density of 5-HT_{1F} receptors in these areas is greater than that of 5-HT_{1D} receptors [7].

The selective receptor agonist LY334370 has about a 100-fold greater affinity for the 5-HT_{1F} receptor than for 5-HT_{1B} and 5-HT_{1D}; LY334370 inhibits the extravasation of dural plasma proteins at very low doses in guinea pigs.

Alniditan, able to abort migraine attacks, has high affinity for 5-HT_{1B} and 5-HT_{1D} receptors; however in contrast to sumatriptan, it has relatively low affinity for the 5-HT_{1F} receptor. Alniditan is a more potent blocker of neurogenic plasma protein extravasation than sumatriptan [8]. Thus, activation of 5-HT_{1F} receptors is not absolutely necessary for antimigraine activity but may be sufficient.

5-HT_2 receptors

The 5-HT_2 receptors stimulate the hydrolysis of phosphoinositol [1].

There are three 5-HT_2 receptors: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}; in humans they are all found in the central nervous system (CNS). They have closely similar amino acid sequences and similar gene structures. All stimulate phospholipase C via a G protein-linked transduction system. The original 5-HT_2 receptor is now called 5-HT_{2A}. The 5-HT_{2B} receptor was originally called the fundus receptor (5-HT_{2F}) as it was first identified in the stomach fundus. The 5-HT_{2C} receptor was originally called 5-HT_{1C} [1].

5-HT_3 receptors

5-HT_3 receptors are ligand-gated ion channel receptors, and thus differ from all other 5-HT receptor types [1]. Selective 5-HT_3 receptor antagonists are antiemetics and may be useful for the treatment of irritable bowel syndrome.

5-HT_4 receptors

The 5-HT_4 receptors are G protein-coupled and activate adenylate cyclase [1]. They were first characterised in the CNS, but are also found on gastrointestinal tract neurons. 5-HT_4 receptor activation may be involved in learning, memory, anxiolysis, and analgesia, but it is unclear whether these receptors are involved in migraine pathogenesis.

5-HT_5 receptors

5-HT_{5A} and 5-HT_{5B} subtypes have been identified but more studies are needed to clarify their roles and functions.

5-HT_6 receptor

The 5-HT_6 receptor is coupled to adenylate cyclase, which it activates, and is expressed in the CNS. In particular it is abundant in extrapyramidal and limbic areas, consistent, respectively, with the known serotoninergic influence on motor function and mood. There is some evidence that the antipsychotic activity of clozapine is due to interaction with the 5-HT_6 receptor.

5-HT_7 receptor

The 5-HT_7 receptor has been cloned and sequenced, and its functional properties characterised. It is expressed by neurons and other cells and is coupled to adenylate cyclase which it activates. Activation of this receptor may occur during cranial vasodilation and nociceptive processing.

Serotonin and migraine

In some patients, 5-HT levels decline in platelets and increase in urine during a migraine attack. Levels of 5-hydroxyindole acetic acid, the main metabolite of 5-HT, also increase in some patients [9]. However, changes in plasma levels of 5-HT do not seem to be important in influencing cerebral arterial tone, and it is generally thought that they reflect some other process occurring during migraine. Migraine-like headache can be induced by reserpine and fenfluramine, which are 5-HT releasers, and exacerbated by selective inhibition of 5-HT reuptake. Furthermore, such headaches do not occur if the subject is pretreated with the 5-HT_2 antagonist methysergide. Administration of 5-HT itself or 5-HT_1 agonists can relieve these headaches. Another substance that can trigger migraine-like headache is the trazodone metabolite *m*-

chlorophenylpiperazine (mCPP), possibly by activating the 5-HT_{2B} or 5-HT_{2C} receptors [10] although it is also a 5-HT_{1A} agonist.

The most effective drugs available today for aborting migraine attacks are the triptans. These are 5-HT_{1B} and 5-HT_{1D} agonists, as indeed are ergotamine and dihydroergotamine (DHE) which also have demonstrated efficacy against migraine. Activation of 5-HT_{1B} and 5-HT_{1D} blocks neurogenic inflammation and pain transmission, both supposed to play a pivotal role in migraine pain. Lipophilic triptans and DHE bind to the nucleus caudalis of the trigeminal complex in the brainstem where they inhibit its activity [11]. These drugs also close arteriovenous anastomoses and in general are vasoconstrictors. In addition to binding the 5-HT_{1B} and 5-HT_{1D} receptors, ergotamine, DHE and triptans also interact variably with the 5-HT_{1E} and 5-HT_{1F} receptors. Ergotamine and DHE also bind to the 5-HT_2, α1 and α2-noradrenergic, and dopamine receptors.

The current balance of opinion is that the acute antimigraine action of both triptans and ergotamines is due to their high affinity for, and agonism of, neuronal $5HT_{1D}$, $5HT_{1B}$ receptors or both. However the compound PNU 142633, a highly selective $5HT_{1D}$ agonist with the pharmacological effects expected for such a compound, only had the efficacy of placebo in a placebo-controlled double-blind trial. It is also noteworthy that 5-HT_{lF} receptor agonists, which are devoid of vasoconstrictive activity, have antimigraine activity. The lipophilic triptans and DHE pass through the blood-brain barrier (BBB) and label nuclei in the brain stem and spinal cord concerned with pain transmission and modulation. The trigeminal nucleus caudalis, the major relay nucleus for head and facial pain, is activated by stimulation of the sagittal sinus. Ergots and the lipophilic triptans (and sumatriptan after disruption of the BBB) suppress this activation at concentrations in the clinical range; these drugs may exert their antimigraine effect by this pathway in the CNS. It is possible that sumatriptan also works in the same way, as it may cross the BBB during a migraine attack as a result of increased porosity.

These drugs also constrict meningeal, dural, cerebral, and pial vessels via the stimulation of vascular 5-HT_{1B} receptors. However they do not seem to have any effect on blood flow through the cerebral hemispheres [12] and this suggests their efficacy in migraine may be independent of their vasoconstrictive effect.

The drugs pizotifen, cyproheptadine, and methysergide are well known 5-HT antagonists and are also effective as migraine prophylactics. Before the characterisation of 5-HT2 subtypes, it was believed that their efficacy was due to 5-HT_2 (now 5-HT_{2A}) receptor antagonism. It is now clear, however, that there is no correlation between the affinity of these drugs for the 5-HT_{2A} receptor and their clinical effectiveness, indicating that 5-HT_{2A} receptor binding plays no part in migraine efficacy. It is also relevant that other 5-HT_{2A} receptor antagonists, including ketanserin, mianserin, sergolexole, and ICI 169,369, are ineffective as migraine prophylactics.

Nevertheless, pizotifen, cyproheptadine, and methysergide are potent 5-HT_{2B} and 5-HT_{2C} receptor antagonists, while mCPP, an agonist of these, can induce migraine [13, 14]. These three drugs, along with amitriptyline, propanolol, ketanserin, ritanserin, and mianserin, do not discriminate between 5-HT_{2B} and 5-HT_{2C} sites [15]. Furthermore, the average daily prophylactic doses of the drugs in humans correlate with their affinities for both 5-HT_{2B} and 5-HT_{2C} receptors [15].

A role of the CNS in mCPP-induced migraine is suggested by the fact that the headache appears at the same time as the cortisol and prolactin increases following mCPP administration, which is known to be due to direct hypothalamic stimulation. In addition, migraineurs are more prone to develop mCPP-induced headache than controls, suggesting increased sensitivity of the receptors stimulated by mCPP [14]. In fact, migraineurs have a markedly increased prolactin response to mCCP [16]. It has also been suggested that mCPP-induced migraine is attributable to stimulation of 5-HT_{2B} endothelial receptors, which results in nitric oxide (NO) release [10].

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