**On serotonin and migraine: a clinical and pharmacological review**

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Migraine patients have chronically low systemic 5-HT, predisposing them to develop migrainous headache once an attack has been initiated. Changes in platelet 5-HT content are not causally related, but reflect similar changes at a neuronal level. Stimulation of vascular 5-HT₁ receptors, probably located in the vessel wall within the dural vascular bed, may alleviate the headache and associated symptoms, but does not interact with earlier mechanisms within the pathophysiological cascade. These receptors are of an as yet unidentified 5-HT₁ subtype, closely resembling, but not identical to 5-HT₁D receptors. Activation of these receptors results in vasoconstriction, inhibiting depolarization of sensory perivascular afferents within the trigemino-vascular system and thus stopping the headache. Additional inhibition of the release of vasoactive neuropeptides may be involved, but seems to be of only secondary clinical importance. • 5-HT receptors, metabolism, migraine, neuronal effects, receptors, serotonin, sumatriptan, vascular effects

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Migraine is a recurring disease of unknown cause. Serotonin (5-hydroxytryptamine, 5-HT) has long been implicated in its pathophysiology (1). The exact role of 5-HT in migraine has not been established. The purpose of this article is to review the current status of 5-HT and 5-HT receptors in the pathophysiology of migraine, in particular to try to bridge the gap between clinical observations and pharmacological mechanisms. The following questions will be addressed: (i) Is 5-HT causally related to migraine and, if so, in what phase of the attack? (ii) Is migraine a low or a high 5-HT disorder? (iii) Is the mechanism of 5-HT mediated via a peripheral (i.e. vascular) or central (i.e. neuronal) action? (iv) Which 5-HT receptor subtype is involved?

**Physiology of 5-HT**

**Distribution and metabolism**

The distribution, biosynthesis and metabolism of 5-HT have been reviewed recently (2). In humans, significant levels of 5-HT are found within the enterochromaffin cells of the gastro-intestinal mucosa, the brain, the pineal gland and the blood (at least 90% within the platelets). In addition, 5-HT can be detected in blood vessels and several other organs. 5-HT is synthesized in most of the tissues in which it is stored, but not in the blood platelet, where the essential synthesizing enzyme tryptophan hydroxylase is virtually lacking. Notwithstanding, the blood platelet is believed to be an excellent peripheral model for the pre- and post-synaptic function of 5-HT neurons (3, 4). Accordingly, platelet 5-HT has been studied extensively in various diseases including migraine (vide infra). All 5-HT present in platelets is taken up from the plasma, the bulk originating in the intestinal mucosa, and subsequently stored within dense granules in large, functionally inactive, aggregates with ADP, ATP and Ca²⁺. Under normal conditions very little platelet 5-HT is metabolized. Platelet 5-HT can be released by exocytosis and drugs. In contrast to platelet 5-HT, extracellular plasma 5-HT potentially is pharmacologically active. Plasma 5-HT levels, however, are generally lower than 20 ng/ml (5), which is considered to be too low to exert measurable vascular effects. Several rapidly acting and high capacity processes tend to limit any increase in plasma 5-HT concentration. Accordingly, if an increase is detected this probably reflects a major rise of 5-HT in the plasma. It thus appears that there are two compartments of 5-HT in blood, the 5-HT in platelets in the μmol range, representing a pharmacologically inactive slow turnover, reserve pool, and the plasma 5-HT in the nmol range, which has a rapid turnover and is potentially pharmacologically active (6). Plasma 5-HT and 5-HIAA levels show marked and opposite seasonal changes (7) and correlate significantly with 5-HT and 5-HIAA levels in the CSF (8).

**Neuronal effects**

5-HT predominantly serves as an inhibitory neurotransmitter in brain (9). The anatomy and function of the central 5-HT system have recently been reviewed (10). The main center is in the raphe nuclei in the brainstem. Major ascending and descending
projection systems exist, which transmit signals via both conventional junctional synapses and non-direct contacts. The central 5-HT system shows clear circadian and annual rhythmicity and has a close interaction with the noradrenergic system originating in the locus coeruleus (11). Excitatory effects of 5-HT are mediated by neuronal 5-HT \(_3\) receptors, which have been found in areas in brainstem and peripheral nervous system involved in the mechanism of vomiting and critical to nociceptive processing (12-19).

**Vascular effects**

Depending on vessel tone, diameter, vascular bed, species and administration route (luminal or adventitial), 5-HT can cause vasodilation and vasoconstriction. Vasodilation is mediated directly via vascular smooth muscle and indirectly via the release of endothelial derived relaxing factor and presynaptic inhibition of release of NA from vascular sympathetic adrenergic nerve terminals (20). Vasoconstriction appears to be mediated via 5-HT\(_2\) receptors in peripheral blood vessels and via 5-HT\(_1\)-like, presumably 5-HT\(_1d\), receptors in the cranial vasculature (21-26). Infusion of 5-HT in baboons caused constriction of the ipsilateral internal carotid artery without change in rCBF, presumably because 5-HT does not cross the blood-brain barrier (27, 28). Microapplication of 5-HT in situ caused dilation of cerebral arterioles with a diameter of less than 70 \(\mu\)mol, which can be blocked by propranolol, and constriction of larger cerebral arteries with a diameter greater than 200 \(\mu\)mol (29), which can be blocked by the universal 5-HT receptor blocker methysergide (30) and the 5-HT\(_2\) receptor antagonist ketanserin (31).

Interesting links between the central and peripheral vascular 5-HT systems are suggested by the observations that 5-HT nerve fibers originating from the raphe nuclei innervate pial vessels (32-34) and that activation of nucleus raphe dorsalis in the monkey increases CBF about 20% via a facial nerve pathway (35).

**Biochemical findings in migraine**

**Platelet 5-HT and 5-HIAA**

In patients with migraine without aura, not diet restricted, platelet 5-HT levels were normal between attacks (36), but reduced by 30% during attacks (Table 1) (36-47). In migraine with aura no such an ictal decrease could be demonstrated (36). Patients with migraine with aura who were put on a 5-HT and tyrosine (48, 49) or a phenylethylamine and tyramine restricted diet (50) had significantly higher basal platelet 5-HT levels (48, 49) and more \(^3\)H-spiperone platelet-membrane binding sites (50) compared with migraine without aura patients and healthy control subjects. Basal platelet 5-HIAA levels were about 50% decreased in both the patients with and those without aura (48, 49).

**Release of platelet 5-HT: specific or non-specific response?**

It has been claimed that the release of platelet 5-HT during migraine attacks is specific for migraine (38). This claim, however, is not supported by experimental data (51). In addition, release of platelet 5-HT has been found in other diseases (52, 53) and no release of platelet 5-HT was found during migraine attacks with aura (36). Therefore, release of platelet 5-HT is probably non-specific and only indirectly related to the migraine mechanism.

**Mechanism of platelet 5-HT release**

Several groups have suggested that the release of platelet 5-HT is caused by a specific "serotonin releasing factor" appearing in the plasma during migraine attacks (46, 53-55). This hypothesis was based on "in vitro" incubation experiments, which however suffered from several methodological flaws (for review see (51) and (56)). Further, in a recent large study Ferrari et al. (56) were unable to confirm this hypothesis. Remarkably, they found a substantial and specific release of methionin-enkephalin, a peptide which is co-stored with 5-HT and other monoamines in the dense granules (57, 58).

**Platelet 5-HT uptake**

Contradictory findings concerning platelet 5-HT uptake in migraine have been reported, due to methodological differences and confounding factors such as mood disorders and use of medication (for review see (59)). In the most extensive study so far, basal values of the Michaelis-Menten constant \(K_m\) were significantly increased in patients with migraine without aura or tension headache, but not in patients with migraine with aura or cluster headache (59). This difference was independent of age, sex, presence of anxiety or depression and drug intake during the previous week, but appeared greater in the morning than in the afternoon. Thus platelet 5-HT-uptake sites of patients with migraine without aura or with tension headache have reduced affinity for 5-HT, particularly in the morning.

**Plasma 5-HT and 5-HIAA**

Correct interpretation of 5-HT metabolism in blood of migraine patients has been hampered by inconsistent definition of plasma 5-HT (for review see (51)). Many authors have used this term also to describe the 5-HT content of platelet-rich plasma or whole blood, i.e. largely the 5-HT content of the platelets. In this review the term plasma 5-HT refers...
to the potential pharmacologically active extracellular platelet-free plasma portion of 5-HT in blood.

Plasma levels of 5-HT and 5-HIAA have been studied only once in migraine (36). Between attacks, 5-HT levels were about 60% lower compared to healthy control subjects, and 5-HIAA levels about 20% higher. During attacks, 5-HT levels increased more than 100% and 5-HIAA levels decreased. The changes in plasma were the same in migraine with and without aura, in contrast to the changes in platelets (vide supra). No changes were demonstrated for 5-HT precursor plasma levels.

**Depression of enzyme activities involved in 5-HT metabolism**

Platelets contain virtually all monoamine oxidase (MAO) and phenolsulphotransferase (PST) present in blood. Although platelet MAO is not involved directly in 5-HT degradation, its activity appears to reflect central 5-HT turnover and MAO activity in other organs (60-62). PST-M catalyses the sulphoconjugation of 5-HT and other monoamines (63). These platelet enzyme activities are decreased by about 20% during migraine attacks both with and without aura (36, 64). This decrease is not due to numerical reduction but rather to a functional change of the enzymes (36), possibly reflecting a similar depression of these enzymes and 5-HT metabolism in brain.

**5-HIAA in urine**

Several groups have reported an increase of 5-HIAA in the urine during migraine attacks (36, 65, 66), but these claims have not been backed up by appropriate statistical analyses. Other groups clearly failed to detect such an increase (67-69). Comparison of these studies is difficult because of methodological differences in sampling and urine acidification, circadian rhythmicity, and wide inter-individual and sex differences. In fact, by comparing the same patients outside and during an attack and by accounting for circadian rhythm, Ferrari and Odink (68) found reduced diurnal urinary excretion of 5-HIAA per mol creatinine during migraine attacks when compared with diurnal excretion during headache-free periods. This finding, and the observation that urine 5-HT was increased during attacks (55, 70) is in keeping with the hypothesis that systemic 5-HT degradation is less during an attack.

Between attacks, Bousser et al. (71) have found a 31% reduction of urinary 5-HIAA per mol creatinine in females, but not in male migraine patients compared with age- and sex-matched control subjects. This was thought to be related to the proneness of females to develop migraine. It is difficult to assess the true relevance of this finding to migraine because female control subjects had significantly higher excretion of 5-HIAA than male control subjects. From the methods description it was not clear whether these measurements were done in 24 h, diurnal, nocturnal or mixed urine samples. This is relevant because in the study of Ferrari and Odink (68), diurnal (but not nocturnal) urinary 5-HIAA tended to be lower in migraine patients (mainly female), although not reaching statistical significance. In fact the main finding in that study was a reversal in the circadian rhythm of urinary 5-HIAA excretion in migraine patients compared to controls.
Finally, it should be noted that the differences in urinary 5-HIAA excretion (71, 72) are far beyond the expected differences due to changes in platelet 5-HT content alone (72-75), but suggest instead a systemic disturbance of 5-HT storage and metabolism in migraine patients (71, 72).

5-HIAA in CSF

Recently, 5-HIAA levels were found to be elevated about 40% in suboccipital CSF of migraine patients (76). This is in agreement with the 5-HIAA findings in plasma (36, 77) and would point to enhanced turnover of 5-HT in the CNS.

Biochemical findings: conclusion

In summation, only fragmentary and often conflicting data concerning 5-HT in body fluids of migraine patients are available and only limited conclusions can be drawn. On the basis of the available evidence, the following can be concluded: (i) Changes in platelet 5-HT are not specific for, and not causally related to migraine; these changes, however, are different in migraine with and without aura, both outside and during attacks. (ii) The ictal release of platelet 5-HT occurs only in patients with migraine attacks without aura; there is no evidence that this release is caused by a specific "serotonin releasing factor". (iii) Migraine patients have a systemic disturbance of 5-HT metabolism. Between attacks 5-HT turnover is enhanced resulting in low 5-HT and during the attack the degradation of 5-HT is reduced, resulting in increased 5-HT levels; the ictal rise of plasma 5-HT may reflect a self-defense mechanism against headache, rather than its cause.

Migraine-provoking factors interacting with 5-HT and/or 5-HT receptors

5-HT depleting drugs

Kimball (78) and others (38, 79) reported that 2.5 mg reserpine im, a 5-HT reuptake inhibitor, caused a "typical headache" in 19 of 21 migraineurs, but only discomfort in 2-non-migrainous subjects. The headache claimed to be identical to but less severe than a spontaneous migraine attack-started between 1 and 5 h after reserpine and lasted between 2 and 20 h. No mention was made of associated migraine features. There was a reduction of platelet 5-HT in most already 1 h after the reserpine, with a maximum between 7 and 48 h. Kimball et al. reported that five patients with reserpine-induced headache were treated successfully with iv 5-HT (78). Anthony et al. reported that three patients with reserpine-induced headache received a slow iv infusion of 2 to 7.5 mg serotonin creatinine sulphate (0.1%): the headache disappeared completely in one and partially in two patients (38). Aura symptoms have never been reported to occur after reserpine. From these experiments the following may be derived: (i) im injection of reserpine may cause headache, but probably not migraine, (ii) there is no solid information on whether this effect is restricted to migraine patients, (iii) an additional local factor appears unnecessary, but migraine patients may experience the headache more often unilaterally, e.g. due to a localizing predilection, (iv) reserpine also causes depletion of platelet 5-HT which outlasts the headache and probably reflects a general loss of 5-HT, (v) the initial depletion of 5-HT and not the putative subsequent rise in plasma 5-HT appears causally important, because replenishment of 5-HT resolved the headache. Other reports with respect to the effect of 5-HT depleting agents and headache are more difficult to interpret, but it seems that these agents all have headache as a prominent side effect (67, 80-84).

Activation of 5-HT1c receptors

Activation of 5-HT1c receptors by m-chloro-phenylpiperazine (m-CPP) induced headache and associated symptoms (but not aura) in patients with eating disorders who had a personal or family history of migraine, but not in patients or healthy subjects who had not such a history (85, 86). This occurred 4 to 12 h after the administration of mCPP, suggesting a slowly developing mechanism. The headache rating correlated significantly with the peak plasma concentrations of mCPP, 2 to 3 h after administration. Placebo or tryptophan administration did not cause migraine symptoms (0 of 52) (85, 86). This exact role of 5-HT1c receptors remains to be defined because mCPP also causes depletion of 5-HT in the CNS (87).

Anti-migraine drugs interacting with 5-HT receptors

Clinical effects

Very few anti-migraine drugs have been tested rigorously in formal trials (88, 89). On the other hand, ergotamine tartrate generally has an accepted clinical efficacy (90, 91). The drug shows wide intra-and interindividual variation in bio-availability, metabolism, receptor affinity, clinical efficacy and side-effect profile, and is mostly given in combination with other drugs (90, 91). The efficacy of ergotamine alone has never been compared formally against placebo (90). When given early in the attack via the parenteral route, ergotamine can provide relief in individual patients, alleviating the headache and associated symptoms within 30 min (90, 91). When tested in groups, however, the clinical response rate of ergotamine probably does not exceed 50% (91, 92) and only when given early in the
attack. Recurrence of the attack within 45 h is uncommon in clinical practice although in a recent study up to 30% of successfully treated attacks recurred within 48 h (92). When ergotamine is used frequently (≥ 1 dose per week), so-called "rebound" or "ergot-dependent headache" may develop (93, 94). Patients with ergotamine-dependent headache show a progressive increase of attack frequency and ergotamine consumption. Ultimately, patients become addicted and require ergotamine daily to prevent severe migraine-like rebound attacks within 12 to 24 h of the last dose. Treatment is complete withdrawal of ergotamine, which causes severe headache, vomiting, diarrhea and other withdrawal symptoms for several weeks. Recently it was suggested that sumatriptan is able to abolish these ergotamine withdrawal symptoms (95) (and personal experience, vide infra).

Dihydroergotamine (DHE)

DHE iv is considered to be a highly effective acute treatment of migraine (96, 97). In comparison with ergotamine tartrate it is said to induce less nausea and no physical dependency. Clinical experience with DHE iv is largely confined to North America. Very few controlled trials with DHE iv have been published; most deal with treatment in the emergency room and none studied the effects of DHE alone, hampering true evaluation of the effects of DHE. Studies evaluating the efficacy of DHE nasal spray have been unconvincing (99-101).

Sumatriptan

Sumatriptan is highly and rapidly effective against all features of the headache phase of migraine attacks (headache, nausea, vomiting, photo- and phonophobia), with and without aura (102-107). Following oral administration, the bioavailability of sumatriptan is only about 14%, compared to 96% following sc administration (108). The response rates are also lower, but still considerable and better than placebo (103, 105), or ergotamine (92). In contrast to ergo-famine, sumatriptan also is effective when given late in the migraine attack (102).

The effects of sumatriptan on aura symptoms are as yet unknown. Aura symptoms are believed to be due to either vasoconstriction (109) or spreading depression (110). The vasoconstriction may be either at the arterial level or at the arteriolar level (112). Following systemic administration, sumatriptan primarily causes constriction of large cerebral conductance vessels and is not known to cause significant rCBF changes (vide infra). Therefore, sumatriptan is not expected to interfere with the aura symptoms and hence could be given safely during the aura phase. Anecdotal reports of three patients with familial hemiplegic migraine, who have used the drug during the hemi-plegic phase of an attack, indeed confirm this notion.

A conspicuous feature of treatment of migraine attacks with sumatriptan is that in at least one third of the cases the headache recurs within 24 h after initial relief (102). Median time to recurrence is about 10 to 14 h after sc administration (102) and 18 h after oral administration (92). Interestingly, headache recurrences have also been found in 18% of placebo treated patients, after a median time of 9 h (102), in 30% of oral ergotamine-treated patients, at a mean time of 23 h (92), and in 5-HT treated spontaneous and reserpine-induced attacks (79, 80). Headache recurrences following treatment with sumatriptan may be severe, but usually can be treated with a repeated dose of sumatriptan (personal observation). The exact mechanism of these recurrences is unknown. It appears that, because of the short plasma half-life of sumatriptan of about 2 h (108), the original attack breaks through again, after initial suppression of the migraine symptoms for several hours.

5-HT

Although only tested in a few patients, 5-HT appears to have a dramatic alleviating effect on migraine pain and associated features, but with significant side effects, precluding application in clinical practice. Kimball et al. (78) were the first to report that 5 mg iv 5-HT relieved spontaneous and reserpine-induced migraine attacks in five patients. The 5-HT precursor 5-HTP also alleviated spontaneous migraine attacks in three patients. Unfortunately, no detailed clinical information was given and no mention was made as to the total number of patients studied. Lance et al. (79) reported that slow iv infusion of 5-HT creatinine sulphate (0.1%) to a total of 2.0 to 7.5 mg abolished spontaneous migraine attacks completely in two and partially in one patient. A similar response was seen in three patients with reserpine-induced headache (vide supra) (38). Interestingly, in both the spontaneous and the reserpine-induced group, headache recurred within 24 h of initial disappearance in one patient. 5-HT does not cross the blood-brain barrier readily, suggesting a peripheral mechanism of action.

5-HT<sub>3</sub> antagonists

Based on the hypothesis that 5-HT<sub>3</sub> antagonists may block 5-HT-induced neurogenic dural inflammation in the distribution area of the trigeminal nerve and thus could potentially prevent migraine (pain) (113), five highly selective and potent 5-HT<sub>3</sub> antagonists have been tested in both the acute and prophylactic treatment of migraine (114-119). Except for some anti-emetic effect, none of these drugs have proven effective in the treatment of migraine. This
may have been partly due to the complex (bell-shaped) dose-response relation of these compounds, making exact titration of the correct dosage difficult. In a recent study (118) promising results were claimed for granisetron, but at the doses used the results were not clinically relevant.

**Prophylactic drugs**

In general, the clinical efficacy of prophylactic anti-migraine drugs is poor (response rates of 50% at most), unpredictable and extremely variable. It appears that most drugs modify attack frequency and some the duration and severity of the attack. Propranolol probably provides the highest chance of success in an individual patient and methysergide the best results in terms of reducing attack frequency.

No reliable information is available on the effect of prophylactic drugs on premonitory signs. It has been suggested that the peripheral dopamine D₂ receptor antagonist domperidone may stop the full development of migraine attacks when given during the premonitory phase (120), but clinical experience does not confirm this. Finally, it has been claimed that blockade at 5-HT₂ receptors may be important in the prophylaxis of migraine attacks (121). Selective 5-HT₂ antagonists are ineffective, however (122).

**Pharmacological effects**

**Sumatriptan**

Important general properties include a lack of antinociceptive effects (123) and good experimental evidence that sumatriptan does not readily cross the blood-brain barrier in animals (124-126). No data on humans are available and it is possible that functional properties of the blood-brain barrier may alter during a migraine attack (27, 28). Rare, but sometimes prominent side effects such as transient drowsiness, sedation, dizziness, vertigo and fatigue may point to some central effects of sumatriptan during an attack (102, 127). Although these symptoms may also be considered as part of the recovery phase of a migraine attack, it should be emphasized that these putative central effects occur only minutes after administration, may also be observed in cluster headache, and are not seen so prominently after successful treatment with other drugs including NSAIDs. Furthermore, sumatriptan caused dysphoria and apathetic sedation in a controlled study (128).

Sumatriptan is a potent vasoconstrictor of primarily cerebral vessels in animal and man (129). The drug contracts dog isolated saphenous vein (130) (via the same receptor as adenylate cyclase is inhibited (131)), isolated basilar arteries of various species (132-134) and man (135) (the latter via a 5-HT₁-like receptor) and blood vessels within human isolated perfused dura mater (which effect can be blocked by methiothepin (136)). In vivo animal studies sumatriptan caused a dose-dependent decrease in carotid arterial blood flow and increase of carotid arterial vascular resistance, without change in arterial blood pressure (137), due to a selective vasoconstriction of arteriovenous anastomoses (AVAs) within the carotid vascular bed and no noticeable effect on the cerebral or extracerebral circulation (138, 139). The sumatriptan-induced constriction of AVAs was fully blocked by methiothepin, but not by ketanserin (139, 140), indicating a 5-HT₁ receptor mediated mechanism, whereas ergotamine-induced constriction of AVAs was only partly blocked by methiothepin 3 mg kg⁻¹ (139-141). Perivascular application of sumatriptan caused concentration-related constriction of pial vessels, while iv administration of sumatriptan caused constriction of the carotid vascular bed but not of pial vessels (125). Thus, after systemic administration, sumatriptan does not seem to penetrate the vessel wall intima and does not affect rCBF.

Limited information is available on the vascular actions of sumatriptan in humans. Sumatriptan increases blood flow velocity (BFV) in the internal carotid artery (ICA) and middle cerebral artery (MCA) (142-144), but not in the external and common carotid artery (143, 144), in migraine patients both during (142-144) and between (Caektebeke et al. in prep.) migraine attacks. During attacks, the increase of BFV appears related to the clinical response and dose (143, 144). Six mg was found to be optimal both in terms of clinical improvement (102) and increase of BFV (143, 144). Because rCBF, as measured with Xe inhalation, was not changed (142), because increase in BFV with constant hematocrit usually reflects vasoconstriction (145, 146) and because of the known vasoconstrictor effect of sumatriptan in animals (vide supra), it was concluded that sumatriptan constricts large cerebral conductance vessels such as the ICA and MCA, and that this effect may be related to the clinical efficacy of the drug. When re-examining the patients outside an attack, response of BFV to sumatriptan was similar to the attack. Those patients who had clinically improved most during the attack showed the greatest increase in BFV outside the attack, again suggesting a relationship between the degree of vasoconstriction and clinical efficacy. Thus far no in vivo human data have been published on the effects of sumatriptan on dural vessels, but preliminary results from our center indicate a clear and rapid vasoconstricting effect.

Diener et al. (95) investigated BFV in the MCA and basilar artery (BA) of six patients during the withdrawal phase from ergotamine-induced headache, before and after 4 mg sc sumatriptan. Despite (transient) clinical improvement, they failed to demonstrate a significant change in BFV. In the
study of Caekebeke et al. (143, 144), 3 mg sc sumatriptan mildly increased BFV in the MCA during migraine attacks. The lack of change in BFV may have been related to the lower dose of sumatriptan used, to the small number of patients investigated or to differences of vasoreactivity in ergotamine-dependent patients. This would suggest that the clinical effect of sumatriptan in treating ergotamine-withdrawal symptoms may be independent of its vasoconstrictor action on large conductance vessels.

The effects of sumatriptan on rCBF, i.e. at the microvasculature level, are complex. When considering cortical (carotid) blood flow only, no consistent uniform changes could be demonstrated after sumatriptan (142, 147). However, by directly comparing the basilar and carotid blood flow, a differential opposing effect of sumatriptan on both vascular areas was found during migraine attacks, normalizing the balance of the carotid/basilar flow towards at-tack-free values (147).

Vasoconstriction within the carotid circulation appears important for anti-migraine action of drugs because efficacious drugs such as ergotamine, sumatriptan and 100% oxygen all share this ability (26). Recently it was shown that the vasoconstrictor actions of sumatriptan and ergotamine on the carotid circulation probably are mediated via different receptor subtypes (140), which may not even belong to the known 5-HT1 binding subtypes, including the 5-HT1D (141). Further, resolution of ergotamine-withdrawal symptoms by sumatriptan may be independent of its vasoconstrictor action on large conductance vessels (95). The possibility remains, however, that constriction of dural vessels is involved.

Neurogenic inflammation (vasodilation and plasma protein extravasation) in dura mater following stimulation of the trigeminovascular system, may be important to the mechanism of the headache in migraine (148, 149). Neurogenic inflammation is, at least in part, mediated by release of vasoactive neuropeptides such as substance P, neurokinin A and the powerful vasodilator calcitonin gene-related peptide (CGRP) (150), which are contained within the ganglia and perivascular sensory fibers of the trigeminovascular system (148, 150-152). In the rat model, systemic infusion of capsaicin may cause plasma extravasation within dura mater via an axonal reflex, whereas treatment with substance P or neurokinin A may cause plasma extravasation via a direct post-synaptic mechanism (133). Electrical trigeminal ganglion stimulation causes, in addition to plasma extravasation within dura mater (153, 154), ultra-structural changes in blood vessels and mast cells within dura mater (155-159), plasma extravasation within extracranial cephalic tissues including conjunctiva, lip and eyelid (151, 153, 157) and increase of CGRP in the superior sagittal sinus (160).

Moskowitz and colleagues (151, 152, 161, 162) demonstrated that pretreatment with clinically relevant doses of antimigraine drugs such as ergotamine tartrate, DHE, methysergide (long-term), sumatriptan and indomethacin and aspirin, or pretreatment with (non-selective) 5-HT1b/1d receptor agonists such as 5-carboxydimotryptamine (5-CT), 5-benzyloxytryptamine (5-BT) and 8-hydroxydipropylaminotetraeline (8-OH-DPAT), selectively blocks plasma extravasation from blood vessels in dura mater but not extracranial tissues, after electrical trigeminal ganglion stimulation. With respect to 5-HT1 receptors, the rank order of effective blocking doses was 5-CT < 5-BT < DHE < sumatriptan < 8-OH-DPAT, which is most consistent with a 5-HT1b/1d receptor mediated response. Sumatriptan, ergotamine tartrate and DHE also blocked plasma extravasation following systemic capsaicin or bradykinin (sumatriptan only), but not after systemic treatment with substance P or neurokinin A. No blocking effect was noted after pretreatment with 5-HT, and 5-HT2 or 5-HT3 antagonists. The blocking effect of sumatriptan on plasma extravasation was partially antagonized by pretreatment with the non-specific but high affinity 5-HT1b/d receptor antagonist metergoline, but not by pretreatment with the non-selective 5-HT1-like receptor antagonist methiothepin or 5-HT2 and 5-HT3 antagonists. Remarkably, 5-CT-blocked plasma extravasation was not attenuated by pretreatment with metergoline. Pre-treatment with sumatriptan or DHE also attenuated CGRP increase in superior sagittal sinus and ultra-structural changes in blood vessels and mast cells within dura mater following electrical trigeminal ganglion stimulation (160). It was concluded that the blocking effect of sumatriptan and ergot-alkaloids on neurogenic plasma extravasation is not related to their vasoconstrictor action, nor to a post-synaptic effect, but rather to a pre-synaptic action, presumably by inhibition of the release of vasoactive neuropeptides mediated by activation of 5-HT1b/1d auto-receptors on sensory fibers (151, 152).

Well in line with these conclusions is the observation that intra-cerebral infusion of sumatriptan, but not peripheral administration, reduced extracellular levels of 5-HT in the frontal cortex in a dose-dependent fashion (124), suggesting that sumatriptan inhibits release of 5-HT by stimulating terminal 5-HT auto-receptors and that sumatriptan crosses the blood-brain barrier only poorly. Thus the mechanism of sumatriptan action is located peripherally.

Important issues are (i) whether inhibition of neurogenic plasma extravasation in rat represents a true model for anti-migraine effects in humans, (ii) whether vasoconstriction alone is sufficient to block neurogenic plasma extravasation, and (iii) to what extent vasoconstricting and neuronal mechanisms are involved in the anti-migraine action of sumatriptan.

Besides anatomical considerations (148, 149, 163) and the observation that dural vessels are among the
few pain-sensitive intra-cranial tissues (164), the major argument in favor of the contention that blockade of neurogenic plasma extravasation in rat (as a measure of neurogenic perivascular inflammation) represents a good model for anti-migraine efficacy in human, is that clinically effective anti-migraine drugs share this ability (151). Human evidence can be derived from the elegant studies of Goadsby et al. which demonstrated that (i) thermocoagulation of the trigeminal ganglion causes marked elevation of plasma levels of substance P and CGRP in the ipsilateral external jugular vein (165), (ii) during migraine attacks there is selective increase in plasma levels of CGRP (166), and (iii) sumatriptan normalizes these elevated CGRP levels but increased neuropeptide Y levels (167).

Several reservations against a clinically important role of neurogenic inflammation should also be considered. First, the blocking drugs were given as pretreatment before trigeminal stimulation. No data are available whether or not plasma extravasation may be blocked when drugs are given after or during the stimulus, which would reflect more closely the clinical situation. Second, the clinical effect of sumatriptan is extremely rapid, particularly in cluster headache. It is hard to conceive that this rapid onset of improvement can be entirely due to inhibition of neurogenic perivascular inflammation alone. Interestingly, increase of BFV as a measure of vasoconstriction can be detected very early after the administration of sumatriptan (142-144) as well as dural vasoconstriction (in prep.). Likewise, it is hard to conceive how sumatriptan would be able to increase headache severity a few minutes after subcutaneous injection (vide supra) via a purely neuronal mechanism. Third, inhalation of 100% oxygen is an extremely potent abortive treatment of cluster headache attacks (168) and causes strong vasoconstriction in the carotid vascular bed (169). Breathing 100% oxygen (8 1/min) beginning 5 min prior to stimulation did not block neurogenic plasma extravasation (154). Fourth, patients with ergotamine-dependent headaches suffer from daily migraine-like attacks (93, 94). It is difficult to conceive that recurrent neurogenic inflammation may occur on a daily or even twice-daily basis. It would be interesting to see whether chronic treatment of rats with ergotamine, followed by acute withdrawal, would cause dural plasma extravasation. Fifth, nitrovasodilators are known to induce headache. These agents activate sensory fibers to release CGRP, which in turn relaxes cerebral vascular smooth muscle by activating guanylate cyclase (170). Accordingly, vasodilation seems the final pathway and not neuronal mechanisms. Finally, chronic pretreatment with propranolol, probably the most effective prophylactic anti-migraine (but not anti-cluster headache) drug in clinical practice, was not able to prevent plasma extravasation (154).

If neurogenic inflammation indeed is important to the clinical situation, the next question is whether vasoconstriction alone is sufficient to block it. Major arguments raised by Moskowitz and colleagues against this notion are that vasoconstricting agents such as phenylephrine and angiotensin did not block plasma extravasation (154, 161), neither did phenylephrine inhibit the release of CGRP in superior sagittal sinus following electrical trigeminal stimulation (160). Ergot alkaloids did not prevent plasma extravasation in extra cranial tissues despite a claimed arteriolar and venular constriction (154, 161). It has never been convincingly demonstrated, however, that these drugs indeed caused vasoconstriction in these models. Therefore, vasoconstriction cannot be excluded. On the contrary, sumatriptan did not block plasma extravasation into guinea-pig hind paw following stimulation of saphenous and fibularis nerves, a model in which sumatriptan is devoid of vasoconstricting effects (171).

Several lines of experiments suggest that in human sumatriptan acts via a 5-HT$_{1d}$ receptor-mediated mechanism. First, sumatriptan selectively binds to 5-HT$_{1d}$ receptors (Table 2) and activates functional biochemical models of 5-HT$_{1d}$ receptors (25, 172-174). Sumatriptan possesses also some affinity for 5-HT$_{1a}$ and 5-HT$_{1b}$ receptor subtypes, but the 5-HT$_{1b}$ receptor has not yet been identified in humans. Second, the rank order of effective plasma extravasation-blocking doses of sumatriptan in Moskowitz's rat model was most consistent with a 5-HT$_{1d}$ receptor mediated response (vide supra) (151). Finally, sumatriptan is essentially equipotent to other clinically effective abortive anti-migraine agents with respect to 5-HT$_{1d}$ agonism (172-174).

The 5-HT$_{1d}$ receptor is the most common type of 5-HT receptor subtype in human brain (175-177) and functions as an auto-receptor controlling the release of 5-HT (124) and other neurotransmitters such as NE and Ach (178, 179). The 5-HT$_{1d}$ receptor is also believed to closely resemble the vascular 5-HT$_1$-like receptor (23, 24, 130, 132, 135, 137, 180). Indeed, sumatriptan concentration dependently inhibited PG E$_2$ stimulated cyclic AMP accumulation in dog saphenous vein, via the same receptor which mediated contraction (131). Recently it was shown that a 5-HT$_1$-like receptor, which correlated with human caudate 5-HT$_{1d}$ binding sites or functional 5-HT$_{1d}$ receptor-coupled adenylate cyclase, was responsible for 5-HT induced vasoconstriction in human pial arterioles (23, 24). It thus seems that sumatriptan is a highly selective agonist at a subpopulation of 5-HT receptors (25, 172-174), designated "5-HT$_1$-like" in the vasculature (181) and 5-HT$_{1d}$ in nervous tissue (130, 132, 135, 137, 180).

Several reservations with respect to a 5-HT$_{1d}$ receptor mediated mechanism of action of sumatriptan should be considered. First, contraction of iso-
Table 2. Receptor binding profile of sumatriptan at a variety of neurotransmitter binding sites (22).

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Tissue</th>
<th>[3H]ligand</th>
<th>pK_i</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT_{1A}</td>
<td>Rat frontal cortex</td>
<td>8-OH-DPAT^a</td>
<td>6.6</td>
</tr>
<tr>
<td>5-HT_{1B}</td>
<td>Rat frontal cortex</td>
<td>5-HT</td>
<td>6.8</td>
</tr>
<tr>
<td>5-HT_{1C}</td>
<td>Pig choroid plexus</td>
<td>5-HT</td>
<td>5.1</td>
</tr>
<tr>
<td>5-HT_{1D}</td>
<td>Bovine caudate</td>
<td>5-HT</td>
<td>7.2</td>
</tr>
<tr>
<td>5-HT_{2}</td>
<td>Rat frontal cortex</td>
<td>Spiperone</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>5-HT_{3}</td>
<td>Mouse neuroblastoma</td>
<td>Ondansetron</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>a_{1}-adrenoreceptor</td>
<td>Total rat brain</td>
<td>Prazosin</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>a_{2}-adrenoreceptor</td>
<td>Total rat brain</td>
<td>Clonidine</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>β-adrenoreceptor</td>
<td>Rat cerebral cortex</td>
<td>Dihydro-alprenol</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Dopamine D_{1}</td>
<td>Rat caudata</td>
<td>Dopamine</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Dopamine D_{2}</td>
<td>Rat corpus striatum</td>
<td>Spiperone</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Histamine H_{1}</td>
<td>Total rat brain</td>
<td>Mepyramine</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>Total rat brain</td>
<td>QNB^b</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Tryptamine</td>
<td>Rat cerebral cortex</td>
<td>Tryptamine</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>μ-Opiate</td>
<td>Total rat brain</td>
<td>Naloxone</td>
<td>6.1</td>
</tr>
<tr>
<td>K-Opiate</td>
<td>Total rat brain</td>
<td>EKC^c</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>d-Opiate</td>
<td>Total rat brain</td>
<td>D-Alanine</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>g-Aminobutyric acid</td>
<td>Rat cerebellum</td>
<td>Muscimol</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Glycine</td>
<td>Rat medulla and pons</td>
<td>Muscimol</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>me-Thyrotrophin releasing hormone</td>
<td>Total rat brain</td>
<td>Thyrothrophin</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Cholecystokinin_{A}</td>
<td>Pancreas</td>
<td>Cholecystokinin-8</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Cholecystokinin_{B}</td>
<td>Rat cerebral cortex</td>
<td>Cholecystokinin-8</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

^a DPAT-8-Hydroxy-2-(di-n-propylamino)tetraline; ^b QNB-Quinuclidinyl-3-benzylate; ^c EKC-Ethyl ketocyclazocine.

Related dog saphenous vein and dog carotid artery by sumatriptan is potentially blocked by the non-selective 5-HT_{1D}-like receptor antagonist methiothepin, but not by the non-selective 5-HT_{1D} receptor antagonists metergoline, rauwolscine and vohimbine, even at very high concentrations (181). Next, Den Boer et al. (141) recently concluded that the constrictor carotid 5-HT_{1D}-like receptors are not related to the known 5-HT_{1D} binding subtypes, including the 5-HT_{1D} sub-type, because the reduction in carotid arteriovenous shunting by sumatriptan was not antagonized by metergoline, despite being susceptible to blockade by methiothepin. Finally, Buzzi et al. (151) raised several arguments, suggesting "that an additional, as yet unidentified subtype(s) of 5-HT_{1} receptor might be more involved in the inhibition of plasma leakage" in their model. Most importantly, the plasma extravasation-blocking action of sumatriptan could not be inhibited by pretreatment with methiothepin and only partially by metergoline, and the blocking effects of 5-CT showed an unexpectedly high potency, which could not be inhibited by metergoline. Further, 5-HT itself was relatively inactive in their model.

**Ergotamine tartrate and DHE**

In contrast to sumatriptan, ergot alkaloids show high affinity for a wide range of receptor sites (91, 121, 183) making interpretation of pharmacological experiments difficult. In animal studies, ergotamine tartrate and DHE show neuronal and vascular effects similar to sumatriptan. As discussed before, acute pretreatment with ergotamine tartrate and DHE blocked neurogenic plasma extravasation in the rat (161) and ergotamine reduced carotid blood flow in pig and cat predominantly by a reduction in AVA blood flow (184). In contrast to sumatriptan, ergotamine-induced constriction of AVAs was not inhibited by methiothepin up to 3 mg kg^{-1} (139-141), suggesting mediation via a different receptor sub-type. In humans, ergotamine caused 17-33% increase in BFV in MCA, without affecting CBF (185), an effect which is similar to that observed for sumatriptan (142-144). In comparison to ergotamine, DHE possesses mainly venoconstrictor and only modest arterial constrictor action (186, 187).

Recently, ^3H-DHE binding sites were found in cat brain, predominantly in medial and dorsal raphe nuclei and to a lesser degree in dorsal horn cervical spinal horn, medulla nucleus solitarius, area postrema, descending spinal trigeminal nucleus, mesencephalon and cortex (188). A role in the anti-migraine effect of DHE has been postulated for these binding sites. If this assumption is correct, the mechanism of action of DHE may be different from sumatriptan, which does not cross the blood-brain barrier readily, and would not reach these binding sites in significant quantities.
**Prophylactic drugs**

Prophylactic anti-migraine drugs show affinity for many different receptor sites and a great variety of pharmacological actions. Based on binding studies in human frontal cortex (121) and rat brain (189), affinity for 5-HT1A and/or 5-HT2 receptor sites may be important common mechanisms. However, clinical studies with agents selectively interacting with 5-HT2 receptors have been disappointing (122). No clinical data are available on agents selectively interacting with 5-HT1A receptors.

5-HT1C receptors are a prominent central class of 5-HT receptors which located as neurons in thalamic sensory relay nuclei and neurons involved in the central processing and regulation of nociceptive transmission (190). Activation of central 5-HT1C receptors has been claimed to provoke migraine attacks (vide supra) (85) and 5-HT1C antagonism has been suggested as a putative mechanism for prophylactic anti-migraine drugs (86). Although most prophylactic anti-migraine drugs show high affinity for 5-HT1C receptors, propranolol, clinically among the most effective drugs, shows only modest affinity (86, 191). As yet, no clinical information is available to support the 5-HT1C blocking hypothesis, but further investigations in this direction seem worthwhile.

Antagonism to 5-HT3 receptors has also been suggested as potential mechanism of action of prophylactic drugs (113). However, a controlled trial with ICS 205-930, a potent 5-HT3 receptor antagonist, produced unconvincing results (116).

**Concluding remarks**

Substantial, though still indirect, evidence indicates an important role of 5-HT and 5-HT receptors in the mechanism of the headache of migraine and possibly also cluster headache. Whereas the true etiology of the disease migraine, i.e., being struck by recurrent attacks, and the actual mechanism of the initiation of attacks are largely unknown, the last part in the migraine cascade, causing the headache, seems to involve reduced activation at cranial 5-HT1-like receptors. Whether or not these receptors are of the 5-HT1D subtype is a matter of debate. Likewise, the relative importance of vascular receptors mediating vasoconstriction of large cerebral conductance arteries, arteriovenous-shunts within the carotid circulation and extra-cerebral dural vessels, versus pre-junctional neuronal auto-receptor mediated inhibition of vasoactive neuropeptides and neurogenic inflammation, has not been fully established.

Our interpretation of the available data is that migraine patients suffering from recurrent attacks have chronically low systemic 5-HT, predisposing them to develop headache once an attack has been initiated. Changes in platelet-5-HT content are not causally related, but reflect similar changes at a neuronal level. Stimulation of vascular 5-HT1 receptors, probably located in the vessel wall within the dural vascular bed, may alleviate the headache and associated symptoms, but does not influence earlier mechanisms within the pathophysiological cascade. These receptors are of an as yet unidentified 5-HT1 subtype, closely resembling, but not identical to 5-HT1D receptors. Activation of these receptors results in vasoconstriction, inhibiting depolarization of sensory perivascular afferents within the trigemo-vascular system and thus stopping the headache. Additional inhibition of the release of vasoactive neuropeptides may be involved, but seems to be of only secondary clinical importance.

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