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# Pharmacology of antimigraine drugs

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**Summary.** The drugs used in migraine therapy can be divided into two groups: agents that abort an established migraine attack and agents used prophylactically to reduce the number of migraine attacks. Both groups have drugs that are specific for migrainous headaches and that are non-specific, and are used to treat the accompanying headache (analgesics), vomiting (anti-emetics), anxiety (sedatives and anxiolytics), or depression (antidepressants). The main drugs with specific action on migraine include ergot alkaloids (ergotamine, dihydroergotamine), agonists (sumatriptan) or partial agonists (methysergide) at a specific subtype of 5-$HT_1$-like receptors, β-adrenoceptor antagonists (propranolol, metoprolol), calcium antagonists (flunarizine) and anti-inflammatory agents (indomethacin). The pharmacological basis of therapeutic action of several of these drugs is not well understood. In the case of the ergot alkaloids and 5-$HT_1$-like receptor agonists, however, it is likely that the antimigraine effect is related to the potent and rather selective constriction of the large arteries and arteriovenous anastomoses in the scalp and dural regions. In addition, these drugs inhibit plasma extravasation into the dura in response to trigeminal ganglion stimulation, but it is possible that this effect is related to the selective vasoconstriction in the extracerebral vascular bed. The selectivity of the pharmacological effects of these antimigraine drugs (constriction of the extracerebral arteries and arteriovenous anastomoses, poor penetration into the central nervous system and the absence of an antinociceptive effect even after intrathecal administration) strongly suggests that excessive dilatation in the extracerebral cranial vasculature, probably initiated by a neuronal event, is an integral part of the pathophysiology of migraine.

**Key words:** Antimigraine drugs – Migraine – Pathophysiology – Pharmacology – Prophylaxis

## Introduction

Migraine is a syndrome characterized by attacks of intense headache, usually localized on one side, and accompanied by anorexia, nausea, vomiting and photo- and/or phonophobia. On the basis of the presence or absence of an aura, consisting of certain sensory (pins-and-needles feeling or numbness), motor (weakness or paralysis) or focal neurological (characteristically a homonymous, spreading, scintillating scotoma) symptoms preceding the headache, two forms of migraine have been discerned [22].

The drugs used in the treatment of migraine can be divided into two groups: agents that abolish acute migraine attacks and agents used prophylactically to reduce the number of migraine attacks (Table 1). Both groups have drugs that are specific for migrainous headaches and those that are used on account of other properties (non-specific drugs).

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## Non-specific antimigraine drugs

Non-specific antimigraine drugs, such as analgesics, anxiolytics or sedatives, and antidepressants, are used in migraine to treat the symptoms of pain, nausea, vomiting, anxiety, fear and, occasionally, depression. The anti-emetic, metoclopramide, possesses a gastrokinetic action that enhances drug absorption, which is slow during migraine attacks [21]. The bioavailability of metoclopramide, however, after oral dosing is erratic and frequently results in insufficient blood levels [5]. Domperidone has similar pharmacological action but, unlike metoclopramide, does not cross the blood-brain barrier and, thus, is less likely to cause central effects [11].

## Specific antimigraine drugs

### *Drugs effective in abolishing attacks*

*Ergotamine.* Ergot derivatives have a complex mode of action, which is partially mediated by an interaction with 5-hydroxytryptamine (5-HT; serotonin), dopamine and noradrenaline receptors (agonism or antagonism), and partially by an interaction with still unclassified receptors [33, 40].

Ergotamine possesses a potent and very long-lasting vasoconstrictor activity, which is relatively selective for

**Table 1.** Classification of antimigraine drugs

| Acute attack therapy | | Prophylactic therapy | |
|---|---|---|---|
| Name | Daily dose (mg)[a] | Name | Daily dose (mg)[a] |
| *Non-specific drugs* | | *Non-specific drugs* | |
| Anti-emetics | | Antidepressive agent | |
| Cyclizine | 0–150; 100–300 (rec) | Amitriptyline | 30–75 |
| Domperidone | 10–40; 10 (i.m.); 30–60 (rec) | *Specific drugs* | |
| Metoclopramide | 5–30; 10–20 (i.m.); 10–30 (rec) | 5-HT-related drugs | |
| Prochlorperazine | 10–20 | Pizotifen | 3–5 |
| Analgesics | | Methysergide | 2–6 |
| Aspirin | 600–900 | β-Adrenoceptor antagonists | |
| Paracetamol | 500–1000 | Atenolol | 100–200 |
| Meperidine | 75–100 (i.m.) | Metoprolol | 200–300 |
| Anti-inflammatory drugs | | Propranolol | 120–320 |
| Indomethacin | 50–200 | Timolol | 30–45 |
| Naproxen | 375–500 | Calcium channel blocker | |
| Ibuprofen | 1200–1600 | Flunarizine | 10–20 |
| Anxiolytics/sedatives | | $\alpha_2$-Adrenoceptor agonist | |
| Chlorpromazine | 5–50 (i.v.) | Clonidine | 0.05–0.15 |
| *Specific drugs* | | Anti-inflammatory drugs | |
| Ergot alkaloids | | Indomethacin | 50–200 |
| Ergotamine | 2–4; 0.125–0.5 (i.v., i.m., s.c.); 2 (rec) | | |
| Dihydroergotamine | 2–4; 2–4 (i.n.) | | |
| 5-$HT_1$-like receptor agonist | | | |
| Sumatriptan | 100–300; 2–4 (i.v.); 4–8 (s.c.) | | |

[a] Unless otherwise stated, these are oral doses for adults; im., intramuscular; rec., rectal; s.c., subcutaneous; i.v., intravenous; i.n., intranasal

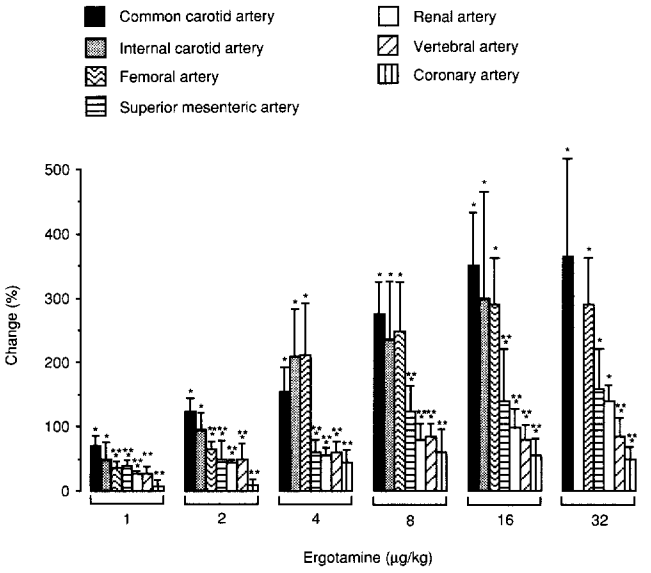



**Fig. 1.** Effect of ergotamine on change in regional vascular resistances (mean ± SEM % increase). * $P < 0.05$ vs control value; ** $P < 0.05$ vs corresponding effect on the common carotid vascular bed. From Saxena and de Vlaam-Schluter [49]

the external carotid arterial bed in the dog (Fig. 1) [49], as well as in man (Fig. 2) [39]. In anaesthetized animals, this selectivity extends further, at least with lower concentrations, to the arteriovenous anastomotic (non-nutrient) fraction of the vasculature, since the drug has little influence on the perfusion of tissues, including the brain (Table 2) [46, 47]. Furthermore, there is a good correlation between the reduction in arteriovenous shunting and the increase in the difference in oxygen content between arterial and jugular venous blood [46]. It should be noted that the vasoconstrictor action on arteriovenous anastomoses, which are predominantly present in the head skin, tongue, eyes and dura mater [28a, 41, 53], does not seem to be mediated by α-adrenoceptors, 5-$HT_1$-like or 5-$HT_2$ receptors [8, 56] and, therefore, may involve novel receptors.

Ergotamine also inhibits extravasation of plasma in the dura mater following "neurogenic inflammation" due to stimulation of the trigeminal ganglion [43]. Since ergotamine and dihydroergotamine, but not angiotensin II or phenylephrine, inhibit neurogenic and capsaicin-induced oedema, Saito et al. [43] concluded that the effect of the two ergot derivatives is independent of vasocon-

striction. These results, however, were not backed up by simultaneous measurement of dural (or carotid) blood flow or arterial blood pressure and, therefore, the effectiveness of angiotensin II and phenylephrine in inducing dural vasoconstriction, or even systemic vasoconstriction, is uncertain.

The use of ergotamine in the treatment of migraine attacks is associated with several problems: (a) for optimal effect the drug should be administered at the first sign of an attack; (b) the absorption of ergotamine after oral, rectal or sublingual administration is incomplete and unreliable, the bioavailability after oral and intramuscular administration being only 5% and 50%, respectively [28]; (c) although ergotamine may not decrease blood flow to the ischaemic myocardial segment in pigs with stenotic coronary vessels [57], the drug is best avoided in patients suffering from coronary disease because of a possible vasospastic effect; and (d) the safety margin of ergotamine is rather small and overdosing is characterized by nausea, vomiting and headache, symptoms which are difficult to distinguish from those found in migraine and can easily lead to a vicious cycle [69].

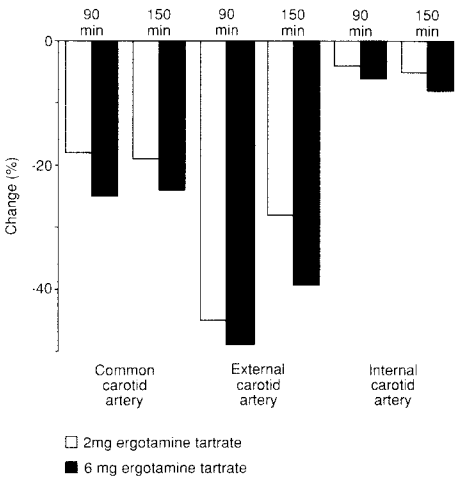



**Fig. 2.** The effect of oral administration of 2 and 6 mg ergotamine tartrate on the change in velocity of blood flow in the carotid vessels of migraine patients outside the headache period. Note that ergotamine mainly affects the external carotid circulation. Redrawn from Puzich et al. [39]

*Dihydroergotamine.* The basic pharmacological features of dihydroergotamine resemble those of ergotamine, but dihydroergotamine is less vasoconstrictive, has a stronger α-adrenoceptor antagonist activity and is more effective in constricting capacitance vessels rather than resistance vessels [40]. Like ergotamine, it decreases arteriovenous anastomotic blood flow (Table 2) [46].

Dihydroergotamine can be used in the treatment of acute attacks of migraine and in its prophylaxis; the latter preferably only for a short time. Side-effects, including nausea and vomiting, may occur but, in general, they are less frequent than with ergotamine.

*Sumatriptan.* The 5-$HT_1$-like receptor agonists AH 25086 and sumatriptan were developed on the premise that vasoconstriction within the carotid bed is responsible for the therapeutic action of ergot alkaloids [49]. That this can be achieved more selectively via stimulation of "spe-

**Table 2.** Effect of antimigraine drugs and some other 5-HT receptor agonists on arterioles and arteriovenous anastomoses (AVAs) in the porcine carotid artery bed

| Drug | Arterioles | AVAs | Antagonism by | Resistance to | Receptor |
|---|---|---|---|---|---|
| Ergotamine | 0 | ++++ | | Methiothepin | Not known |
| Dihydroergotamine | 0 | ++++ | | | Not known |
| Methysergide | − | +++ | | | 5-$HT_1$-like? |
| Sumatriptan | 0 | ++++ | Methiothepin | Ketanserin<br>Metergoline | 5-$HT_1$-like |
| AH 25086[a] | 0 | ++++ | | | 5-$HT_1$-like |
| 5-HT | −−−− | ++++ | Methiothepin | Cyproheptadine<br>Ketanserin,<br>MDL 72222 | 5-$HT_1$-like |
| 5-CT | −−−− | ++++ | | Cyproheptadine | 5-$HT_1$-like |
| BEA 1654 | −− | +++ | | Ketanserin | 5-$HT_1$-like |
| 8-OH-DPAT | − | ++++ | Methiothepin | Ketanserin<br>Pindolol | 5-$HT_1$-like |
| Indorenate | − | ++++ | Methiothepin | Ketanserin<br>Metergoline | 5-$HT_1$-like |
| Ipsapirone | 0 | 0 | | | |

AH 25086, 3-aminoethyl-*N*-methyl-1*H*-indole-5-methane carboxamide; BEA 1654, *N*-(3-acetylaminophenyl)piperazine hydrochloride; 5-CT, 5-carboxamidotryptamine; MDL 72222, 1α*H*,3α,5α*H*-tropan-3-yl-3,5-dichlorobenzoate; 8-OH-DPAT, 8-hydroxy-2-(di-*N*,*N*-n-propylamino) tetralin

−, Dilatation; +, contraction; 0, no or very little effect. The number of − and +, indicate the magnitude of effect

[a] Data in cat

Based on Saxena et al. [56]

cial" or "atypical" type (later identified as 5-$HT_1$-like) receptors [55] stems from observations that the anti-5-HT drugs cyproheptadine and mianserin do not antagonize the carotid vasoconstrictor response to 5-HT (Fig. 3) [44, 49, 54], and that the antagonism by the antimigraine drug methysergide takes place at doses that elicit a selective carotid vasoconstriction, probably by an agonist action at the 5-HT receptors [45]. Subsequently, it has been shown that the vasoconstriction induced by 5-HT occurs within the arteriovenous anastomotic part of the carotid circulation and that the arteriolar part displays

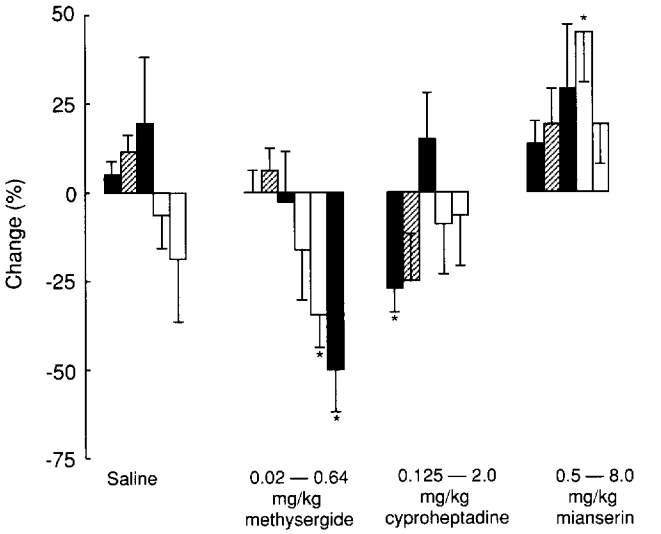



**Fig. 3.** Modification (mean ± SEM) by saline, methysergide, cyproheptadine and mianserin on the change in carotid vasoconstrictor responses to 5-HT (25 μg, i.a.) in the anaesthetized dog. The doses of the different drugs used were sequentially: methysergide, 0.02, 0.04, 0.08, 0.16, 0.32 and 0.64 mg/kg, i.v.; cyproheptadine, 0.125, 0.25, 0.5, 1.0 and 2.0 mg/kg; and mianserin, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg. Note that cyproheptadine (except the first dose) and mianserin fail to antagonize the 5-HT-induced carotid vasoconstriction. The response to 5-HT is significantly reduced by methysergide only at its two highest doses (0.32 and 0.64 mg/kg), which also causes carotid vasoconstriction (see Fig. 5). * $P < 0.05$ vs baseline. Data from Saxena [44] and Saxena et al. [54]

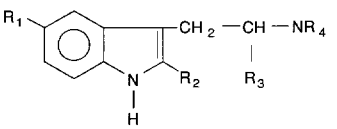
vasodilatation [51]; both these effects are mediated by similar, but not identical, subtypes of 5-$HT_1$-like receptors (Table 2) [56]. Humphrey et al. [26, 27] showed that the vasoconstrictor 5-$HT_1$-like receptor was also present on the dog saphenous vein and they identified a number of derivatives of 5-HT – 5-carboxamidotryptamine, AH 25086 and sumatriptan – with an agonist action on this subtype of 5-$HT_1$-like receptors (Table 3). With these drugs, therefore, it was possible to constrict the large arteries and arteriovenous anastomoses in the extracerebral cranial circulation more selectively than using the ergot alkaloids.

The concept that such 5-$HT_1$-like receptor agonists can alleviate migraine was initially tested with AH 25086, a highly polar lipophobic substance unsuitable for oral use. It was shown that intravenous injections of AH 25086 efficiently aborted acute migraine attacks, including nausea, vomiting and photophobia [10, 16]. Early studies with sumatriptan, which is a less polar compound than AH 25086, indicated that the drug was highly effective in the treatment of acute migraine attacks after either intravenous, subcutaneous or oral administration [38, 67].

Sumatriptan causes contraction of different isolated blood vessels: dog saphenous vein and middle cerebral artery, primate basilar artery [25, 26, 27] and human basilar artery [31]. In vivo, sumatriptan selectively increases carotid vascular resistance in the dog, cat and pig and, in the latter two species, the increase in carotid resistance has been shown to be confined to its arteriovenous anastomotic fraction (Table 2; Fig. 4) [14, 14a, 17, 26, 37]. Unlike ergotamine, no peripheral vasoconstriction has been observed with sumatriptan in man [34]. Sumatriptan has also been reported to inhibit the extravasation of plasma from dural vessels following trigeminal ganglion stimulation or local capsaicin application in the rat [12], but it is not known whether or not this effect is secondary to the selective vasoconstriction of the cephalic blood vessels.

In spite of the fact that experience with sumatriptan is still limited it seems to be a promising new antimigraine agent. Only few side-effects have been noticed and

**Table 3.** Chemical structure of some derivatives of 5-HT which have selective action on 5-HT receptors




| Compound | Substitution | | | | |
|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Known receptor profile |
| 5-HT | OH | H | H | $H_2$ | All receptors |
| 5-CT | $CONH_2$ | H | H | $H_2$ | All 5-$HT_1$-like, except 5-$HT_{1C}$ |
| 5-$CH_3O$-T | $CH_3O$ | H | H | $H_2$ | 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_4$ |
| AH 25086 | $CH_2CONHCH_3$ | H | H | $H_2$ | 5-$HT_{1X}$ |
| Sumatriptan | $CH_2SO_2NHCH_3$ | H | H | $(CH_3)_2$ | 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1D}$, 5-$HT_{1X}$ |
| α-$CH_3$-5-HT | OH | H | $CH_3$ | $H_2$ | 5-$HT_2$, 5-$HT_4$ |
| 2-$CH_3$-5-HT | OH | $CH_3$ | H | $H_2$ | 5-$HT_3$ |

5-CT, 5-carboxyamidotryptamine; 5-$CH_3O$-T, 5-methoxytryptamine; AH 25086, 3-aminoethyl-*N*-methyl-1*H*-indole-5-methane carboxamide; α-$CH_3$-5-HT, α-methyl-5-HT; 2-$CH_3$-5-HT, 2-methyl-5-HT

those that do occur are invariably of a mild character, such as sensations of heaviness, pressure, warmth, or tingling in the head or extremities [38, 67].

*Drugs used in migraine prophylaxis*

*Methysergide.* Methysergide is a synthetic substance derived from the ergot alkaloid ergonovine. It is readily demethylated into methylergometrine, to which the drug may owe part of its activity [65]. Methysergide possesses a marked 5-$HT_2$ receptor antagonist activity and, more recently, it has also been demonstrated to have an affinity for 5-$HT_1$ binding sites, albeit less marked than for 5-$HT_2$ binding sites [36], being capable of both stimulating and antagonizing the 5-$HT_1$-like receptors [9, 45]. In experimental animals, it induces a selective decrease in carotid blood flow (Fig. 5) [45] by closing arteriovenous anastomoses (Table 2) [52]; this effect is much less marked than that of ergotamine. Methysergide has been shown to decrease carotid blood flow during migraine attacks but to increase flow between attacks, an action which could be related to its mixture of agonistic and antagonistic properties [3].

The side-effects of methysergide include nausea, vomiting, sleeplessness, dizziness and symptoms of peripheral vasoconstriction (pains in the chest and extremities, with or without paraesthesia, and decrease in arterial pulsations). Long-term (usually more than 6 months) uninterrupted use can lead to retroperitoneal and/or pleuropulmonary fibrosis, which may become life-threatening; therefore, the use of methysergide must be interrupted for 3–4 weeks after every 4–5 months.

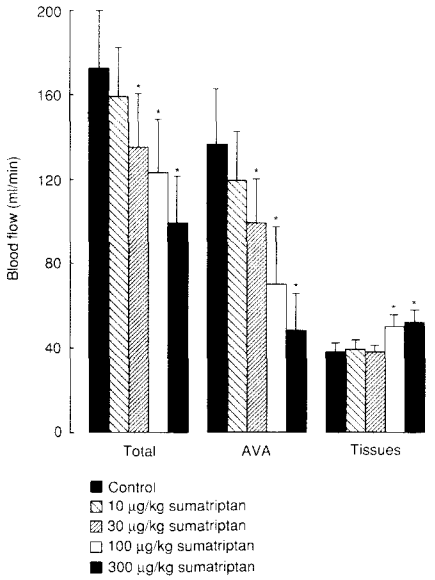



**Fig. 4.** Effect of intravenous sumatriptan on the total common carotid blood flow and its arterioveneous anastomotic (AVA) and nutrient (tissue) fractions in anaesthetized pigs. All values have been presented as means ± SEM. * $P < 0.05$ vs baseline. Data from Den Boer et al. [14]

*Pizotifen.* Pizotifen is a potent antagonist at 5-$HT_2$ and histamine $H_1$ receptors [62] and its vasoconstrictor activity has been demonstrated in animals [32] and man [1]. Besides a slight sedation, pizotifen exerts some antidepressant activity but its mechanism of action is not known.

The most important side-effect reported for pizotifen is an increase in body weight due to increased appetite.

*β-Adrenoceptor antagonists.* In migraine prophylaxis propranolol has proved as effective as methysergide [6], but its action appears to be prolonged and wears off slowly after stopping therapy [15]. At first propranolol was thought to be the only β-adrenoceptor antagonist effective in migraine prophylaxis [6], although further investi-

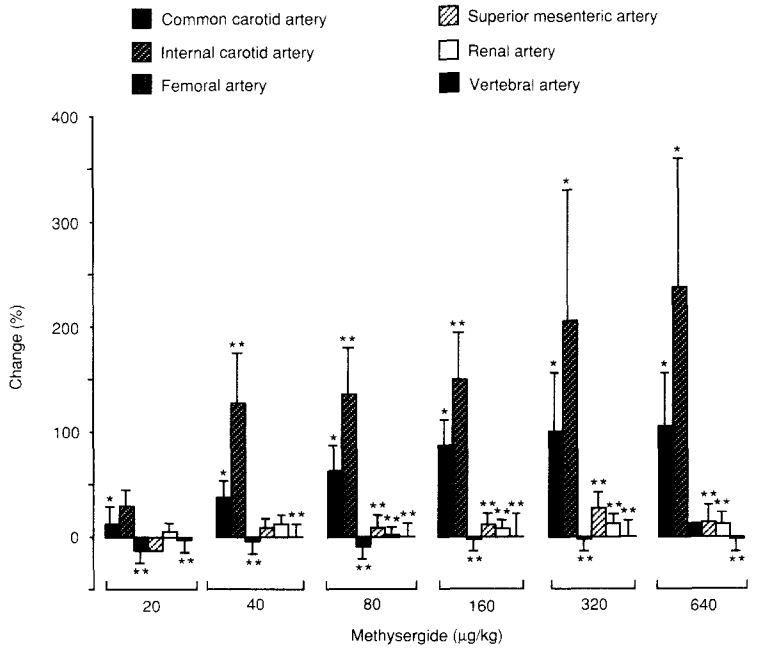



**Fig. 5.** Effect of methysergide on regional vascular resistances (mean ± SEM % increase). * $P < 0.05$ vs control value, ** $P < 0.05$ vs corresponding effect on the common carotid vascular bed. From Saxena [45]

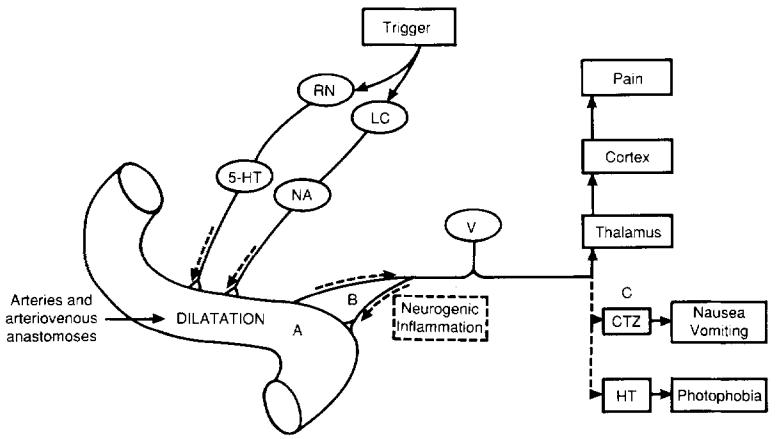



**Fig. 6.** Possible chain of events during migraine. Changes in the activity of raphe nuclei (RN) and/or the locus ceruleus (LC) efferents might induce dilatation of arteries and arteriovenous anastomoses in cephalic (dural and scalp) circulation. This can stimulate perivascular sensory afferents of the fifth cranial nerve (V) to cause headache and, possibly, nausea, vomiting and photophobia. CTZ, chemoreceptor trigger zone; HT, hypothalamus; NA, noradrenaline. In addition, neurogenic inflammation via retrograde release of vasoactive neuropeptides as well as local ischaemia due to arteriovenous shunting may accentuate pain sensation. Drugs like ergotamine and sumatriptan appear to abort migraine attacks by constricting the dilated cephalic vessels (A) and may also have inhibitory influence at the perivascular nerve terminals (B) and CTZ (C). From Saxena and Ferrari [50]

gations have extended antimigraine activity to both cardioselective (atenolol and metoprolol [18, 23, 64]) and non-selective (timolol [63, 66]) β-adrenoceptor antagonists. It appears, however, that β-adrenoceptor antagonists with a partial agonistic activity (e.g. pindolol, acebutolol, oxprenolol, alprenolol) are inactive [58, 68]. The mechanism of action of these drugs is not well understood, but seems to involve β-adrenoceptor blockade [46].

The side-effects of β-adrenoceptor antagonists are generally mild and include bradycardia, hypotension, dizziness and cold extremities. These drugs, however, should be avoided in patients suffering from respiratory diseases, myocardial insufficiency and, possibly, insulin-dependent diabetes mellitus.

*Calcium channel antagonists.* Although nimodipine, nifedipine and verapamil have been reported to be of some value in migraine prophylaxis [19, 61], recent clinical trials have not confirmed their effectiveness [2, 4, 31]. Perhaps among this class of drugs, only flunarizine is of value in the prophylactic therapy of migraine [29, 30].

Side-effects of flunarizine, which are usually mild, include sedation, tiredness, gastric complaints and weight increase.

*Clonidine.* This $\alpha_2$-adrenoceptor agonist was introduced for the treatment of migraine [69] because it had been reported to inhibit vasodilatation and vasoconstriction by vasoactive substances [70]. Unfortunately, these findings have not been reproduced, nor could any clinical effect of clonidine in the treatment of migraine be demonstrated [6, 42]. In view of the fact that side-effects (sedation, tiredness, hypotension, dry mouth, dizziness, gastric complaints) are frequent, there seems to be little place for this compound in the treatment of migraine.

*Indomethacin.* Indomethacin, which inhibits prostaglandin synthesis, is not particularly effective in common or classic migraine, but it does seem to have a beneficial effect because of its rapid onset of action in some migraine variants, such as chronic paroxysmal hemicrania [59, 60], although neither the pathogenesis of these disorders nor the mechanisim of action of indomethacin has been elucidated.

## Possible impact of the pharmacology of antimigraine drugs on the pathophysiology of migraine

Both neurogenic and vascular theories have been proposed to explain the origin of migraine [7, 20]. According to the neurogenic theories the cause of migraine is within the brain and the vascular changes are regarded as epiphenomena. On the other hand, the vascular theories suggest that migraine headache results from an excessive dilatation of extracerebral cranial (mainly scalp and/or dural) arteries and arteriovenous anastomoses [7, 24, 46, 47].

The clinical effectiveness of AH 25086 and sumatriptan [10, 16, 38, 67] in migraine attacks against the headache, as well as the nausea, vomiting and photo-/phonophobia, and the selectivity of their pharmacological effects – constriction of the cephalic arteries and arteriovenous anastomoses [14, 17, 25, 26, 27, 35, 37], lack of penetration into the central nervous system [13] and the absence of antinociceptive effects, even after intrathecal administration [25, 26, 27] – make a compelling case that excessive dilatation in the extracerebral cranial vasculature is connected to the symptomatology of the migraine syndrome. Other antimigraine drugs, such as ergotamine, dihydroergotamine and methysergide, also constrict large arteries and cephalic arteriovenous anastomoses [46] and some may only poorly cross the blood-brain barrier [48, 50]. Moreover, the cephalovascular pharmacology of 5-HT – constriction of large extracerebral arteries and arteriovenous anastomoses, and dilatation of arterioles (Table 2) [51, 55] – is in keeping with the suggestion that endogenous (humoral and/or neural) 5-HT activity is lowered at the initiation of a migraine attack [48, 50]. Despite some reservations [50], the present evidence, therefore, is in favour of the view that dilatation in the extracerebral cranial (scalp and/or dural) vasculature is an integral part of the pathophysiology of migraine. As suggested earlier [50], changes in the activity of raphe nuclei, with their 5-HT-containing neurons, and the locus ceruleus, with its noradrenaline-containing efferents, may induce dilatation of arteries and arteriovenous anas-

tomoses in cephalic (dural and scalp) circulation (Fig. 6). This, in turn, can stimulate perivascular sensory afferents of the fifth cranial nerve to cause headache and, possibly, nausea, vomiting and photophobia via putative neurons to the chemoreceptor trigger zone and hypothalamus. In addition, neurogenic inflammation via retrograde release of vasoactive neuropeptides, as well as local ischaemia due to arteriovenous shunting, may accentuate pain sensation. Drugs, such as ergotamine and sumatriptan, appear to abort migraine attacks by constricting the dilated cephalic vessels. These drugs may also exert an inhibitory effect on perivascular nerve terminals and, possibly, the chemoreceptor trigger zone, both of which are outside the blood-brain barrier.

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