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REVIEW

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# Success and failure of triptans

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**Abstract** Sumatriptan and the newer triptans (zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan and donitriptan) display high agonist activity at 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors. Most triptans, but not all (donitriptan, frovatriptan and rizatriptan), also have a high affinity at the 5-$ht_{1F}$ receptor. In anaesthetised animals, triptans decrease the arteriovenous anastomotic fraction of carotid blood flow. In isolated blood vessels, triptans cause contraction and this effect is more marked on cranial arteries. The 5-$HT_{1B}$ receptors and not 5-$HT_{1D}$ or 5-$ht_{1F}$ receptors mediate the vasocontrictor effect of triptans. In animal studies, the triptans exert an inhibitory effect within the trigeminovascular system. The therapeutic effect of triptans is mediated mainly by their cranial vasoconstrictor property. Whether the inhibitory effects of the triptans on the trigeminovascular system contribute to their efficacy in migraine is still a moot point. The biggest success of triptans is that they provide an excellent therapeutic option for migraine therapy. This success has generated awareness for migraine in patients, clinicians and researchers alike. This, in turn, has increased our knowledge of the disease pathophysiology, which will ultimately lead to even better drugs in future. Among the failures of triptans, one may mention that a minority of patients respond poorly and others may have headache recurrence and chest symptoms. Overall, however, the advantages of triptans far outweigh their disadvantages and they represent a significant advance in medical therapy.

**Key words** 5-HT receptors • Migraine • Migraine therapy • Coronary artery constriction • Sumatriptan • Triptans

## Introduction

The triptans belong to a class of drugs known as 5-$HT_{1B/1D}$, formerly 5-$HT_1$-like/5-$HT_{1D}$ [1, 2] receptor agonists. The first of this class, sumatriptan, was introduced for the acute therapy of migraine more than a decade ago and is considered to represent a significant milestone in the battle against this affliction [3, 4]. Since sumatriptan's introduction, several new triptans have come onto the market (e.g. zolmitriptan, rizatriptan and naratriptan), while others are likely to follow (Fig. 1). In this short review, the success and failure of these drugs is discussed against the background of their pharmacology.

## Pharmacology of triptans

Pharmacodynamic effects

*Receptor binding profile*

All triptans have a high affinity at 5-$HT_{1B}$, 5-$HT_{1D}$ receptors (Table 1). Many, but not all (e.g. rizatriptan, frovatriptan and donitriptan) also have high affinity for the 5-$ht_{1F}$ receptor [5, 6].

*Vasoconstriction*

The main pharmacological effect of these drugs is the constriction of cranial extracerebral blood vessels. Sumatriptan

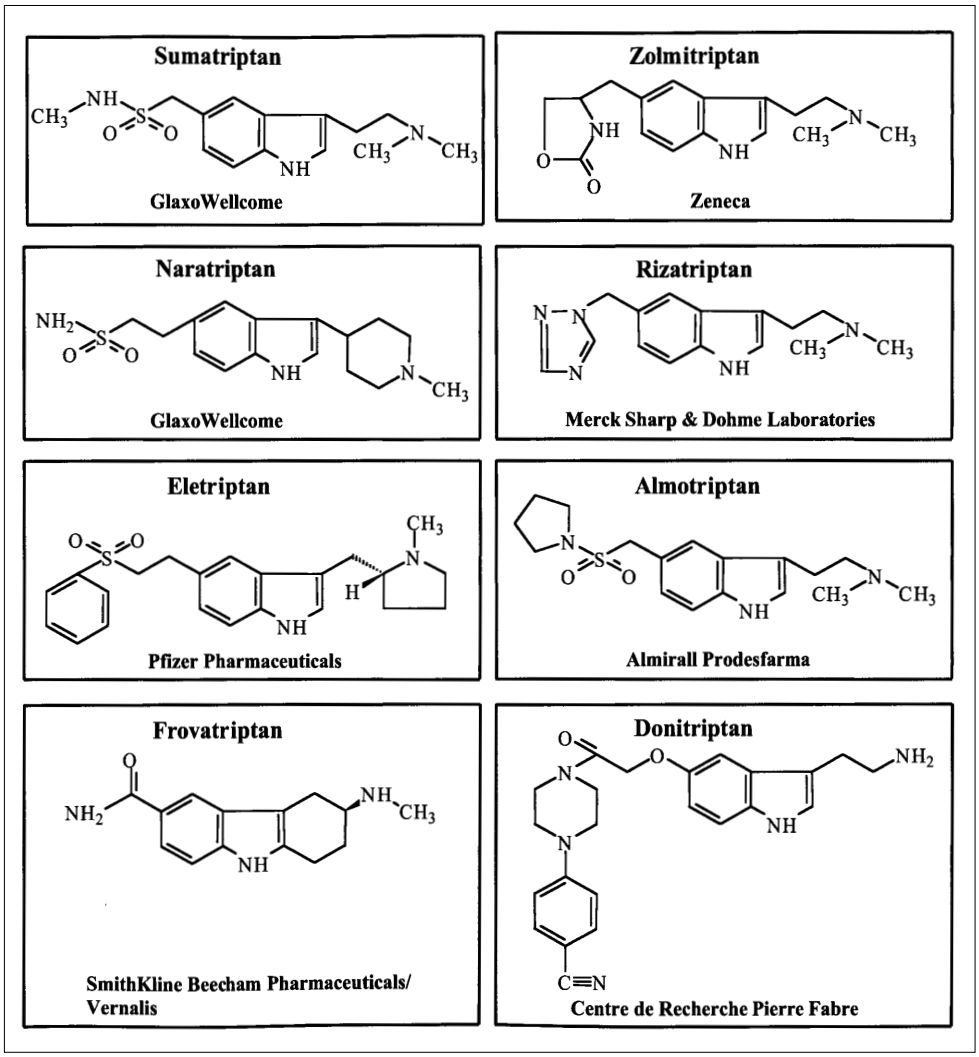


**Fig. 1** Chemical structures of triptans

**Table 1** $pK_i$ values of triptans at human 5-HT receptors. Except as otherwise indicated, the values refer to the human receptor

| Receptor | Sumatriptan | Zolmitriptan | Naratriptan | Rizatriptan | Eletriptan | Almotriptan | Frovatriptan |
|---|---|---|---|---|---|---|---|
| 5-$HT_{1A}$ | 6.4, 6.9 | 6.5 | 7.6, 7.1 | 6.4 | 7.4 | 6.3 | 7.3 |
| 5-$HT_{1B}$ | 7.8 | 8.3 | 8.7, 8.1 | 6.9, 8.1, 7.7 | 8.0 | 8.0 | 8.6 |
| 5-$HT_{1D}$ | 8.5 | 9.2 | 8.3, 8.4 | 7.9, 8.6 | 8.9 | 8.0 | 8.4 |
| 5-$ht_{1E}$ | 5.8 | 7.7 | 7.7 | 6.8 | 7.3 | – | < 6.0 |
| 5-$ht_{1F}$ | 7.9, 7.9 | 7.2, 7.5 | 8.2 | 6.8 | 8.0 | – | 7.0 |
| 5-$HT_{2A}$ | < 5.0 | < 5.5 | < 5.5 | < 5.5 | < 5.5 | – | < 5.3 |
| 5-$HT_{2B}$ | 6.9 | 7.2 | – | 6.6 | – | – | – |
| 5-$HT_{2C}$ | < 5.0[a] | 4.1[c] | < 5.5 | < 5.5 | < 5.5 | – | < 5.3 |
| 5-$HT_3$[d] | < 5.0 | < 5.5 | < 5.5 | < 5.5 | < 5.5 | – | < 6.0 |
| 5-$HT_4$[c] | < 5.0 | < 5.5 | < 5.5 | < 5.5 | < 5.5 | – | – |
| 5-$ht_{5A}$ | 5.5, < 5.5[b] | 6.4 | 5.5[b] | 5.3[b] | 5.8[b] | – | – |
| 5-$ht_6$ | < 5.5 | < 5.5 | < 5.5 | < 5.5 | 6.3 | – | – |
| 5-$HT_7$ | 5.9 | 7.0 | < 5.5 | 5.7 | 6.7 | < 6.5 | 6.70 |

[a] Pig; [b] Rat; [c] Guinea pig; [d] Mouse

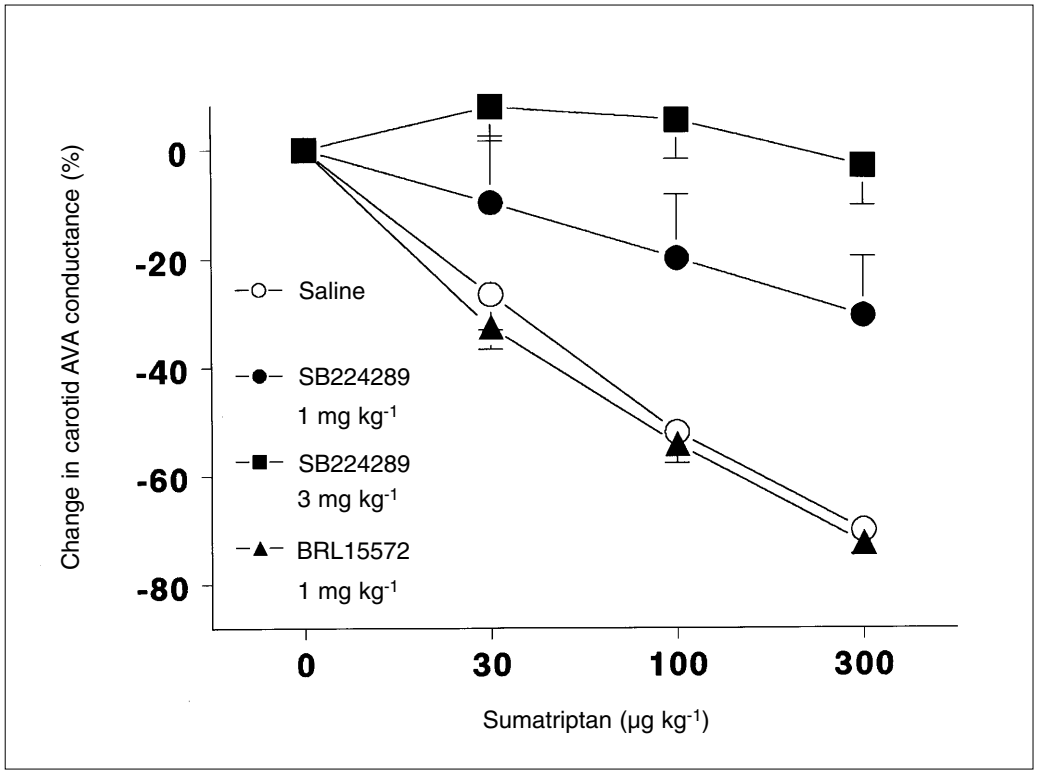


**Fig. 2** Effect (% change from baseline values) of intravenous sumatriptan on carotid arteriovenous anastomotic (AVA) conductance in anaesthetised pigs treated with saline, SB224289 (5-$HT_{1B}$ receptor antagonist) or BRL15572 (5-$HT_{1D}$ receptor antagonist). Data are means and SEM. (Modified from [12])

increases internal carotid and middle cerebral artery blood flow velocities in migraine patients [7, 8]. Investigations in anaesthetised animals show that sumatriptan as well as other triptans exclusively decrease the arteriovenous anastomotic fraction of carotid blood flow [5, 6]. The role of 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors in the sumatriptan-induced constriction of porcine carotid arteriovenous anastomoses has been investigated by using SB224289 and BRL15572, which have a selective antagonist activity at cloned human 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors, respectively [9–11]. SB224289, but not BRL15572 antagonises the effects of sumatriptan (Fig. 2) [12]. Despite the fact that our recent investigation revealed that BRL15572, has a low affinity for the porcine 5-$HT_{1D}$ receptor in contrast to the human 5-$HT_{1D}$ receptor [13], it is obvious that the 5-$HT_{1B}$ receptor mediates carotid vasoconstrictor response.

A number of isolated blood vessels from several species contracts in response to triptans, but the contractile effect is more marked on cranial vessels. There is ample evidence that this effect is mediated by the 5-$HT_{1B}$ receptor and not by 5-$HT_{1D}$ or 5-$ht_{1F}$ receptors [14–16].

*Inhibition of the trigeminovascular system*

Triptans interfere with the trigeminovascular system, at both the peripheral and central levels. Thus, they inhibit plasma protein extravasation, calcitonin gene-related peptide (CGRP) release and dural vasodilatation following trigeminal ganglion stimulation; they also inhibit neuronal activity in trigeminal nucleus caudalis following stimulation of sagittal sinus or dural vessels (reviewed in [5]). Unlike more lipophilic triptans, sumatriptan does not enter the central nervous system and, therefore, fails to affect c-fos mRNA expression in the trigeminal nucleus caudalis following trigeminal ganglion stimulation in rats [17]. In view of excellent therapeutic action of sumatriptan (see subsequent section), one can question whether central trigeminal inhibition is predictive of antimigraine potential.

## Pharmacokinetics of triptans

The pharmacokinetic characteristics of triptans are presented in Table 2. Subcutaneous sumatriptan (6 mg) is quickly absorbed with a $t_{max}$ of approximately 10 min and an average bioavailability of 96%. After oral administration of therapeutic doses (100 mg) of sumatriptan, the $t_{max}$ is substantially delayed (1.5 h) and, more importantly, the bioavailability is rather low (~14%). Intranasal or rectal administration of sumatriptan does not seem to improve these parameters much. The oral bioavailability of newer triptans is much improved. This can be partly attributed to the more lipophilic

**Table 2** Pharmacokinetic parameters for triptans (Modified from [5, 6])

| Drug | Dose (mg) and route of administration | $T_{max}$ (h) | $C_{max}$ (ng $ml^{-1}$) | Bioavailability (%) | $T_{1/2}$ (h) | AUC (ng h $ml^{-1}$) | Active metabolites | Plasma protein binding (%) | $CL_R$ (ml $min^{-1}$) | Log $D_{pH7.4}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Sumatriptan | 6 s.c. | 0.17 | 72 | 96 | 2 | 90 | No | 14–21 | 220 | -1.5 |
| | 100 p.o. | 1.5 | 54 | 14 | 2 | 158 | – | – | 260 | – |
| | 20 i.n. | 1.5 | 13 | 15.8 | 1.8 | 48 | – | – | 210 | – |
| | 25 rectal | 1.5 | 27 | 19.2 | 1.8 | 78 | – | – | 200 | – |
| Zolmitriptan | 2.5 p.o. | 1.5 | 3.3, 3.8[a] | 39 | 2.3, 2.6[a] | 18, 21[a] | Yes | 25 | 193 | -1.0 |
| | 5 p.o. | 1.5 | 10 | 46 | 3.0 | 42 | – | – | 193 | – |
| Naratriptan | 2.5 p.o. | 2.0 | 12.6 | 74 | 5.5 | 98 | No | 20 | 220 | -0.2 |
| Rizatriptan | 10 p.o. | 1.0 | 19.8 | 40 | 2.0 | 50 | Yes | 14 | 414 | -0.7 |
| Eletriptan | 40 p.o. | 1.8 | 82 | 50 | – | – | Yes | 85 | 597 | +0.5 |
| | 80 p.o. | 1.4 | 246 | 50 | 6.3 | 1661 | – | – | – | – |
| Almotriptan | 12.5 p.o. | 2.5 | 49.5 | 80 | 3.1 | 266 | – | – | – | – |
| | 25 p.o. | 2.7 | 64 | 69 | 3.6 | 443 | – | – | – | – |
| Frovatriptan | 2.5 p.o. | 3.0 | 4.2, 7.0[a] | 29.6 | 25.7 | 94 | – | 15[b] | – | – |
| | 40 p.o. | 5.0 | 24.7, 53.4[a] | 17.5 | 29.7 | 881 | – | – | – | – |
| | 0.8 i.v. | – | 18.6, 24.4[a] | 100 | 23.6 | 104 | – | – | 132 | – |

[a]Values for men and women, respectively; [b]Besides plasma protein binding, about 60% of frovatriptan is bound to red blood cells.
*AUC*, area under curve; $CL_R$, renal clearance; *Log* $D_{pH7.4}$, measure of lipophilicity with increasing numbers indicating greater lipid solubility; *s.c.*, subcutaneous; *p.o.*, per os; *i.n.*, intranasal; *i.v.*, intravenous

nature of these drugs. Interestingly, the $t_{max}$ after oral administration of zolmitriptan, naratriptan, eletriptan, almotriptan and frovatriptan is not much better, for some even worse, than that of sumatriptan, whereas rizatriptan seems to reach its peak plasma levels quicker compared to sumatriptan. The unbound $C_{max}$ values ($C_{max}$ corrected for plasma protein binding) of newer triptans are lower than that of sumatriptan. This is apparently due to two main factors: lower therapeutic concentrations are needed as these drugs have a higher affinity at 5-$HT_{1B/1D}$ receptors and these drugs have been better titrated, thus reducing therapeutic penalty.

With the exception of rizatriptan, the newer triptans are degraded slower than sumatriptan. Especially frovatriptan has a plasma half-life of 26–30 h, but it is uncertain that headache recurrence is lower with frovatriptan, and low sub-therapeutic concentrations of a drug may not be related to its effects on recurrence. In contrast to sumatriptan and naratriptan, active metabolites have been reported for zolmitriptan, rizatriptan and eletriptan. It is not known whether and, if so, to what extent the metabolites contribute towards therapeutic activity.

## Success of triptans

### Excellent therapeutic option

The advent of sumatriptan, followed by other triptans, has provided an excellent therapeutic option for migraine patients. As depicted in Fig. 3, the mean therapeutic gain for headache relief achieved with triptans is high; 6 mg subcu-

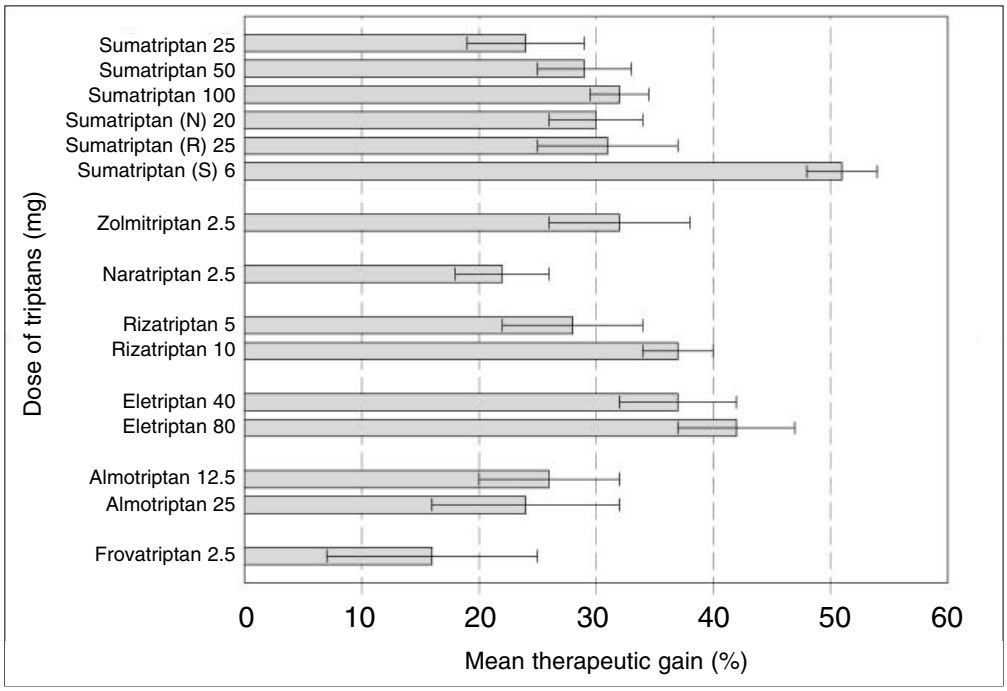


**Fig. 3** Mean therapeutic gain (proportion of patients responding to active drug minus proportion of patients responding to placebo) and 95% confidence intervals for different doses of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan and frovatriptan. All triptans were administered orally, except sumatriptan for which nasal (N), rectal (R) and subcutaneous (S) routes were also employed. Note that the therapeutic gain was determined with most certainty for 100 mg sumatriptan, 6 mg subcutaneous sumatriptan and 10 mg rizatriptan (approximately, 4500, 3000 and 3500 patients, respectively). (Modified from [5, 6])

taneous sumatriptan is the most effective. This analysis indicates that 80 mg eletriptan concerning headache relief at 2 hours is superior to 100 mg sumatriptan, and that 2.5 mg naratriptan and 2.5 mg frovatriptan are inferior to 100 mg sumatriptan. All other triptans or doses of oral triptans seem roughly equivalent to 50–100 mg sumatriptan. Intranasal and rectal sumatriptan seem equivalent to oral sumatriptan [5, 6].

## Awareness for migraine in patients, clinicians and researchers

The availability of triptans has undoubtedly heightened awareness for migraine in patients, clinicians and researchers alike. There is much more understanding for the disease today than before the triptan era. Obviously, the market for antimigraine drugs has expanded as never before and this has resulted in serious drug development programmes being undertaken by pharmaceutical companies. The results are already there in terms of the growing number of triptans available to physicians and consumers.

## Better understanding of the pathophysiology of migraine

The increased awareness in migraine and the availability of triptans as analytical tools have indirectly helped our understanding of migraine. It is now generally believed that migraine is a channelopathy (probably genetically determined) [18], which triggers a central ‘generator’ to initiate an attack along the process depicted in Fig. 4 (explained in De Vries et al. [19]). Triptans (and ergot alkaloids) abort migraine attack primarily via constriction of dilated cranial extracerebral blood vessels. Although the triptans reduce neuropeptide release and plasma protein extravasation across dural vessels [20, 21] and inhibit impulse transmission centrally within the trigeminovascular system [22, 23], the contribution of neuronal effects in the therapeutic action is yet uncertain. Nonetheless, the increasing number of novel experimental models for migraine [19] may lead to the development of antimigraine drugs that are devoid of vasocontrictor action (Fig. 4). Some attempts have indeed failed [24]. However, in view of the possible involvement of CGRP in migraine pathophysiology [25–28], antagonism of CGRP receptors is an interesting approach for discovering a cardiovascular-safe antimigraine drug. Doods et al. [29] have

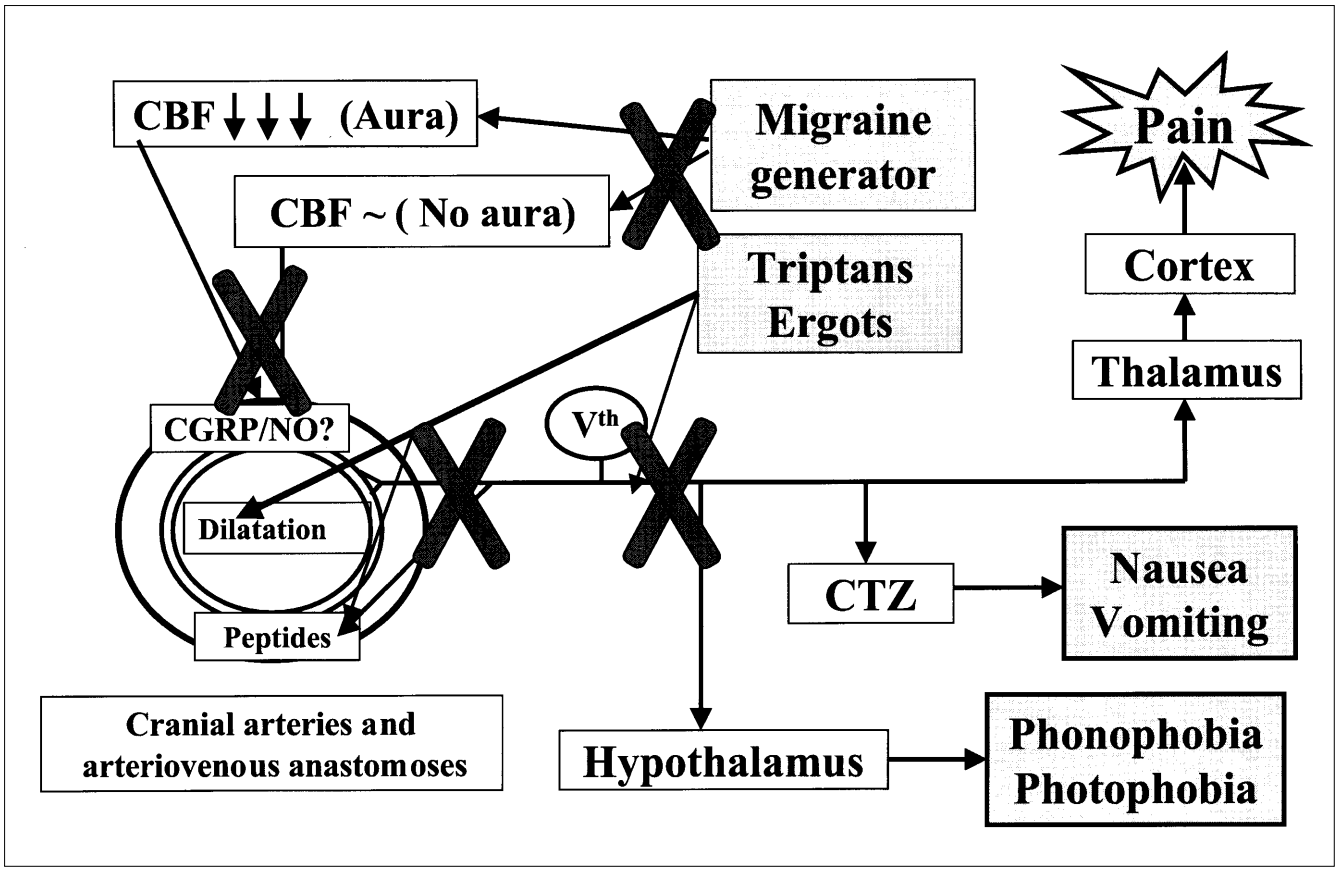


**Fig. 4** Putative changes in migraine and the therapeutic targets of acutely acting antimigraine drugs. These drugs are believed to owe their antimigraine efficacy mainly to constriction of dilated cranial blood vessels, but other factors, such as the inhibition of trigeminally induced cranial vasodilatation, plasma protein extravasation and central neuronal activity, may be involved to some extent. Only lipophilic, brain-penetrating triptans (not sumatriptan) exert central trigeminal inhibitory effects. *Crosses* depict that future antimigraine drugs 'beyond triptans' may act by the mechanism indicated and whereby cranial vasoconstriction may not be a necessary factor. *CBF*, cerebral blood flow; *CTZ*, chemoreceptor trigger zone; *Vth*, fifth cranial nerve; *CGRP/NO*, calcitonin gene-related peptide/nitric oxide

recently described a dipeptide compound, BIBN4096BS, which is a potent and selective CGRP receptor antagonist. BIBN4096BS is presently under clinical investigation and the results of the phase IIa trials are awaited with great interest.

## Failure of triptans

### Triptan-resistant patients

A minority of patients does not respond to oral triptans. The non-responders are much less with parenteral sumatriptan. The exact reason for triptan-resistance is not known, but genetic variability in the receptors may be one aspect.

### Slow headache relief and high headache recurrence

In some patients, the headache relief may not be quick enough and in others after initial relief the headache may reappear. Although the exact causes for slow headache relief and high headache recurrence are not known, a relatively long $t_{max}$ for oral triptans in combination with short $t_{1/2}$ may be involved in specific patients.

### Chest symptoms and coronary artery constriction

There is obviously a concern about the contractile effect of triptans on the human coronary artery (reviewed by

MaassenVanDenBrink et al. [30]). However, this effect of triptans is fortunately much weaker than that on human cerebral vessels [5, 6]. As exemplified in Figs. 5 and 6, based on the concentration response curves in isolated human blood vessels, the predicted contraction in patients following a therapeutic dose of sumatriptan and eletriptan is much more in the middle menigeal artery than in the coronary artery or saphenous vein [31]. Therefore, the triptans are not expected to cause myocardial ischaemia in migraine patients *without* any coronary artery affliction. However, these drugs must remain contraindicated in patients *with* stenosed or hyperreactive coronary arteries [30, 31].

## Conclusions

Overall, despite some shortcomings, the triptans represent an excellent option in the therapy of migraine.

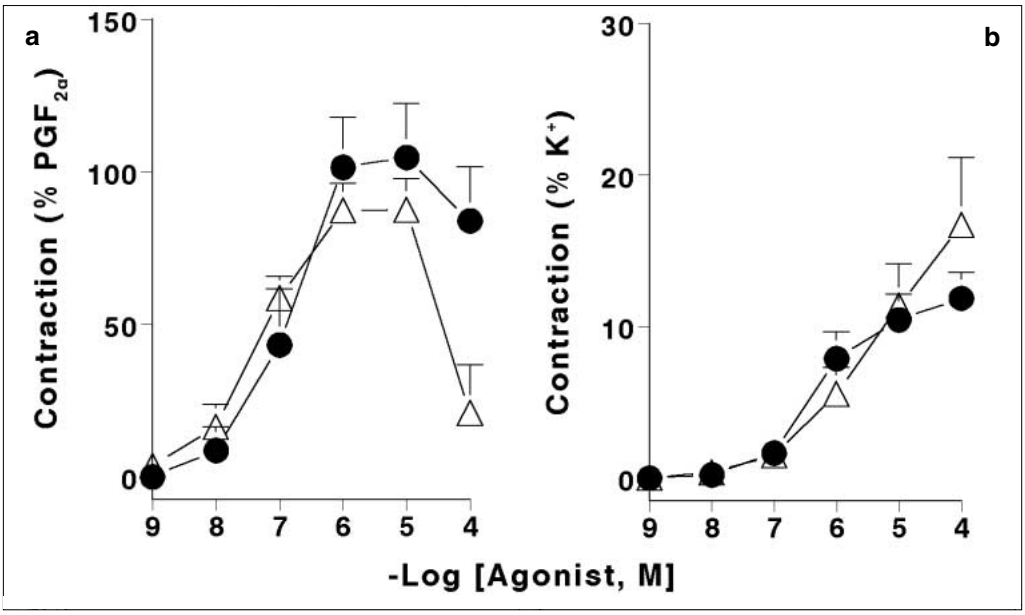


**Fig. 5a, b** Concentration response curves for sumatriptan and eletriptan. **a** Human middle menigeal artery. **b** Human coronary artery. ●, Sumatriptan; △, Eletriptan

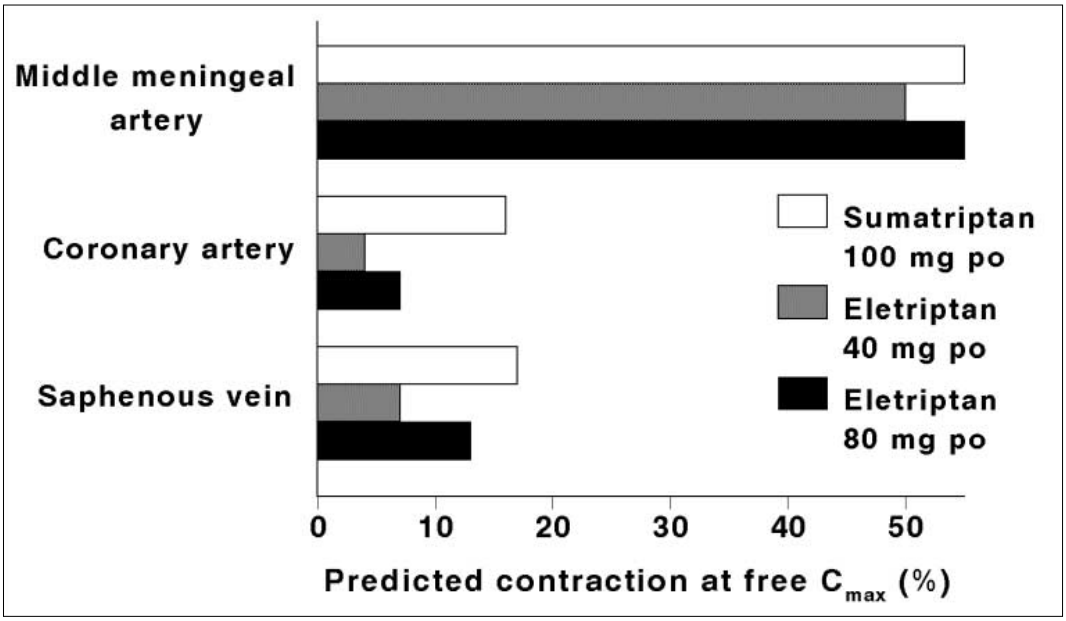


**Fig. 6** Predicted contraction, based on respective concentration response curves, of the middle meningeal artery (percent of contraction to 1 μM $PGF_{2\alpha}$), coronary artery and saphenous vein (both percent of contraction to 100 mM KCl) at reported free $C_{max}$ concentration in patients following oral therapeutic doses of sumatriptan (100 mg) and eletriptan (40 and 80 mg). (Modified from [31])

## References


1. Saxena PR, De Vries P, Villalón CM (1998) 5-$HT_1$-like receptors: a time to bid goodbye. Trends Pharmacol Sci 19:311–316
2. De Vries P, Villalón CM, Saxena PR (1999) Pharmacology of triptans. Emerg Drugs 4:107–125
3. Humphrey PPA, Feniuk W (1991) Mode of action of the anti-migraine drug sumatriptan. Trends Pharmacol Sci 12:444–446
4. Perry CN, Markham A (1998) Sumatriptan. An updated review of its use in migraine. Drugs 55:889–922
5. Saxena PR, Tfelt-Hansen P (2000) Triptans, 5-$HT_{1B/1D}$ receptor agonists in the acute treatment of migraine. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, pp 411–438
6. Tfelt-Hansen P, De Vries P, Saxena PR (2000) Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. Drugs 60:1259–1287
7. Friberg L, Olesen J, Iversen HK, Sperling B (1991) Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. Lancet 338:13–17
8. Caekebeke JF, Ferrari MD, Zwetsloot CP, Jansen J, Saxena PR (1992) Antimigraine drug sumatriptan increases blood flow velocity in large cerebral arteries during migraine attacks. Neurology 42:1522–1526
9. Schlicker E, Fink K, Molderings GJ, Price GW, Duckworth M, Gaster L, Middlemiss DN, Zentner J, Likungu J, Göthert M (1997) Effects of selective h5-$HT_{1B}$ (SB-216641) and h5-$HT_{1D}$ (BRL-15572) receptor ligands on guinea-pig and human 5-HT auto- and heteroreceptors. Naunyn-Schmiedeberg's Arch Pharmacol 356:321–327
10. Selkirk JV, Scott C, Ho M, Burton MJ, Watson J, Gaster LM, Collin L, Jones BJ, Middlemiss DN, Price GW (1998) SB-224289 – a novel selective (human) 5-$HT_{1B}$ receptor antagonist with negative intrinsic activity. Br J Pharmacol 125:202–208
11. Gaster LM, Blaney FE, Davies S, Duckworth DM, Ham P, Jenkins S, Jennings AJ, Joiner GF, King FD, Mulholland KR, Wyman PA, Hagan JJ, Hatcher J, Jones BJ, Middlemiss DN, Price GW, Riley G, Roberts C, Routledge C, Selkirk J, Slade PD (1998) The selective 5-$HT_{1B}$ receptor inverse agonist 1'-methyl-5-[[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine] (SB-224289) potently blocks terminal 5-HT autoreceptor function both in vitro and in vivo. J Med Chem 41:1218–1235
12. De Vries P, Willems EW, Heiligers JPC, Villalón CM, Saxena PR (1999) Investigation of the role of 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors in the sumatriptan-induced constriction of porcine carotid arteriovenous anastomoses. Br J Pharmacol 127:405–412
13. Bhalla P, Sharma HS, Wurch T, Pauwels PJ, Saxena PR (2000) Molecular cloning, sequence analysis and pharmacological properties of the porcine 5-$HT_{1D}$ receptor. Br J Pharmacol 131:949–957
14. Bouchelet I, Case B, Olivier A, Hamel E (2000) No contractile effect for 5-$HT_{1D}$ and 5-$HT_{1F}$ receptor antagonists in human and bovine cerebral arteries: similarity with human coronary artery. Br J Pharmacol 129:501–508
15. Cohen ML, Schenck K (2000) Contractile responses to sumatriptan and ergotamine in the rabbit saphenous vein: effect of selective 5-$HT_{1F}$ receptor agonists and $PGF_{2\alpha}$. Br J Pharmacol 131:562–568
16. Van Den Broek RWM, MaassenVanDenBrink A, De Vries R, Bogers AJJC, Stegmann AP, Avezaat CJ, Saxena PR (2000) Pharmacological analysis of contractile effects of eletriptan and sumatriptan on human isolated blood vessels. Eur J Pharmacol 407:165–173
17. Shepheard SL, Williamson DJ, Williams J, Hill RG, Hargreaves RJ (1995) Comparison of the effects of sumatriptan and the $NK_1$ antagonist CP-99,994 on plasma extravasation in dura mater and c-fos mRNA expression in trigeminal nucleus caudalis of rats. Neuropharmacology 34:255–261
18. Ophoff RA, Terwindt GM, Frants RR, Ferrari MD (1998) P/Q-type Ca2+ channel defects in migraine, ataxia and epilepsy. Trends Pharmacol Sci 19:121–127
19. De Vries P, Villalón CM, Saxena PR (1999) Pharmacological aspects of experimental headache models in relation to acute antimigraine therapy. Eur J Pharmacol 375:61–74
20. Moskowitz MA (1992) Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. Trends Pharmacol Sci 13:307–311
21. Moskowitz MA (1993) Neurogenic inflammation in the pathophysiology and treatment of migraine. Neurology 43:S16–20
22. Goadsby PJ (1997) Current concepts of the pathophysiology of migraine. Neurol Clin 15:27–42
23. Goadsby PJ, Zagami AS, Lambert GA (1991) Neural processing of craniovascular pain: a synthesis of the central structures involved in migraine. Headache 31:365–371
24. Dahlöf C, Saxena PR (2000) Novel compounds in development for treatment of acute migraine. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, pp 439–443

25. Hargreaves RJ, Shepheard SL (1999) Pathophysiology of migraine – new insights. Can J Neurol Sci 26:S12–S19
26. Knight YE, Edvinsson L, Goadsby PJ (1999) Blockade of calcitonin gene-related peptide release after superior sagittal sinus stimulation in cat: a comparison of avitriptan and CP122,288. Neuropeptides 33:41–46
27. Ashina M, Bendtsen L, Jensen R, Schifter S, Olesen J (2000) Evidence for increased plasma levels of calcitonin gene-related peptide in migraine outside of attacks. Pain 86:133–138
28. Olivar T, Razzaque Z, Nwagwu M, Longmore J (2000) Neurogenic vasodilation in rabbit basilar isolated artery: involvement of calcitonin-gene related peptide. Eur J Pharmacol 395:61–68
29. Doods H, Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, Eberlein W (2000) Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol 129:420–423
30. MaassenVanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR (1998) Coronary side-effect potential of current and prospective antimigraine drugs. Circulation 98:25–30
31. MaassenVanDenBrink A, Van Den Broek RWM, De Vries R, Bogers AJ, Avezaat CJ, Saxena PR (2000) Craniovascular selectivity of eletriptan and sumatriptan in human isolated blood vessels. Neurology 55:1524–1530