Serotonin, sumatriptan, and the management of migraine

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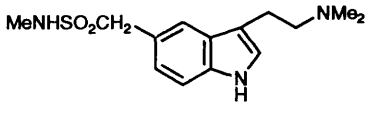
1 Introduction

Migraine has long been recognized as a common highly distressing disorder that can cause severe disruption of normal daily life since no reliable treatment has been available. Many of the drugs currently in use are only partially effective and possess limiting side-effects. However, a significant advance has recently been made with the development at Glaxo of *agonists* at a novel serotonin vascular 5-HT_1 receptor for the acute treatment of migraine. The purpose of this article is to describe the history of events leading to the discovery of sumatriptan (Imigran®) (**1**), the first drug of this kind to be introduced into medicine.



1 sumatriptan

*Italicized terms are defined in the glossary.

2 The nature of migraine

The main characteristic symptom of a migraine attack is of a one-sided headache, throbbing and intense, often accompanied by nausea, vomiting, and sensitivity to light and sound. Attacks usually last 4–72 hours and are separated by symptom-free intervals between episodes.[1] There may be *prodromal symptoms* several hours before the attack in the form of mood changes or altered behaviour. About 15% of migraineurs experience an aura up to an hour before the onset of headache. Most commonly this is a visual disturbance such as a pattern of scintillating lights or a blind spot. Sensory disturbances can also occur and occasionally difficulties with speech. After the attack the sufferer is usually tired and drained of energy.

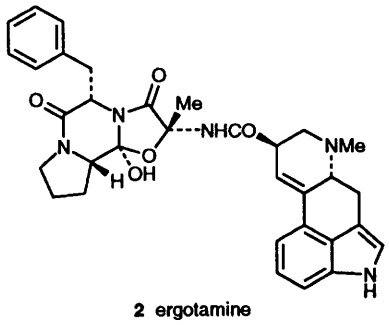
Migraine is estimated to affect about 8% of the adult population[2] but this is most probably an underestimate since only a minority of sufferers seek medical attention.

In most cases it is not known what precipitates an attack although some sufferers can clearly identify specific trigger factors. These may be dietary (certain foods or drinks), hormonal (often associated with oral contraceptives), environmental, or related to stress.

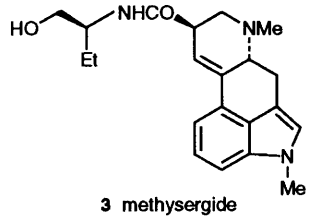
3 Management of migraine

Self-medication with non-prescription products containing analgesics such as aspirin or paracetamol has usually been the mainstay of therapy for many migraine sufferers but these medicines are often ineffective and may give rise to damage of the gastrointestinal tract on chronic use. Other drugs available only on prescription mostly give variable results but a few specific anti-migraine agents are considered to be efficacious. These include the ergot alkaloid ergotamine (**2**) and a synthetic analogue, methysergide (**3**).

Ergotamine was originally isolated from a parasitic fungus that grows on rye and other grains and has been in clinical use for many years.[3] It is a potent vasoconstrictor agent and has a number of side-effects associated with its non-specific actions at 5-hydroxytryptamine (**4**), dopamine (**7**), and *α-adrenoceptors*.[4] These include vomiting, nausea, and, most importantly, peripheral *vasoconstriction*, so the dose has to be monitored closely. Ergotamine is



2 ergotamine

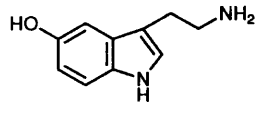


3 methysergide

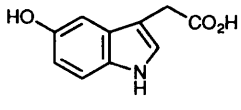
effective in treating the acute phase of migraine but the outcome is variable because it is poorly absorbed from the gastrointestinal (GI) tract. Methysergide, however, is only effective as a *prophylactic agent* but it too has side-effects which can be serious on continuous long term use.

4 5-Hydroxytryptamine, a possible pathological mediator in migraine

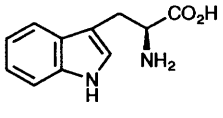
There is a wealth of clinical evidence, albeit circumstantial, linking the neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) (**4**) with the pathophysiology of migraine but the aetiology of the disease is still not fully understood. 5-HT is biosynthesized in mammals from dietary tryptophan (**6**) mainly in tissues where it is stored. Most of it is found in enterochromaffin cells of the GI tract but some is present in the brain and in blood platelets. However, platelets have no capacity to synthesize 5-HT and can only acquire it by uptake of the 5-HT released into the blood from enterochromaffin cells. It has been found that platelet levels of 5-HT fall by up to 45% at the onset of migraine[5] and an increase in the urinary excretion of the main metabolite 5-hydroxyindole acetic acid (5-HIAA) (**5**) has been observed.[6] For many years it was thought that 5-HT released from platelets caused cerebral *vasoconstriction* and that this gave rise to the *prodromal symptoms*. The low blood levels of 5-HT were then thought to lead to *vasodilatation* of *extracranial* blood vessels and headache.[7]



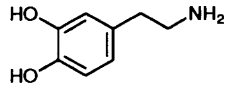
4 5-HT



5 5-HIAA

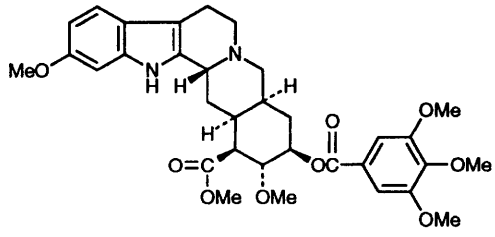


6 L-tryptophan



7 dopamine

Interestingly, reserpine (**8**), an amine-releasing agent used in hypertension, will precipitate a migraine headache in migraineurs but not normal subjects, by lowering plasma levels of 5-HT.[8,9]



8 reserpine

Undoubtedly though the most compelling evidence implicating 5-HT in migraine was the key observation that administering 5-HT itself intravenously would alleviate either a spontaneous or reserpine-induced attack.[8,9] However, 5-HT is unsuitable to be formulated as a drug because it is not well absorbed orally, is rapidly metabolized, and has undesirable side-effects, in particular vasoconstriction, arising from its interactions with the various subtypes of 5-HT receptors. It is significant that many of the drugs used to treat migraine, including ergotamine and methysergide, interact in some way with 5-HT receptors.[10]

Nevertheless it is also known that a wide range of vasoconstrictor agents acting by different mechanisms will also abort migraine attacks.[7]

5 Selective vasoconstriction as a novel mechanism to treat migraine

It was in 1972 that work was initiated at Glaxo to satisfy what was then recognized as an unmet medical need: a safe efficacious agent for the treatment of migraine. Early ideas focused on serotonin in the light of the evidence implicating it in the disease and the knowledge that many antimigraine drugs interact with 5-HT receptors. This led us to undertake a systematic study to characterize and classify vascular 5-HT receptors. Nevertheless, we took the view that regardless of the mediator involved a selective vasoconstrictor agent was required that could alleviate the pain arising from *vasodilatation* of pain sensitive blood vessels in the head, particularly *extracranial* vessels.

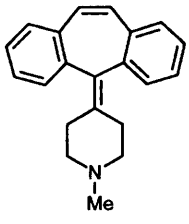
We recognized that pointers to how this could be achieved were already in the literature and related to the properties of the *prophylactic agent* methysergide. Originally this drug was introduced into migraine therapy on the basis of its antagonist activity at 5-HT 'D' (now called 5-HT_2) receptors but later work cast doubt on whether this accounted for its efficacy. Firstly, a comparative trial of several 5-HT_2 receptor *antagonists* as migraine *prophylactic agents* showed that methysergide was clearly the most effective drug in its class even though it was no more potent as a 5-HT_2 receptor antagonist compared to any of the other compounds,[11] so indicating that some additional action accounted for its efficacy.

Secondly, Saxena showed that methysergide given intravenously elicited a selective, dose-dependent *vasoconstriction* of the *carotid arterial bed* in the anaesthetized dog with little effect on heart rate and blood pressure and he suggested that this action rather than its 5-HT_2 receptor antagonist activity might account for its anti-migraine properties.[12] Saxena also found that 5-HT elicited the same vasoconstrictor action as methysergide in the dog and showed it could not be blocked by any of the available 5-HT *antagonists*.[13]

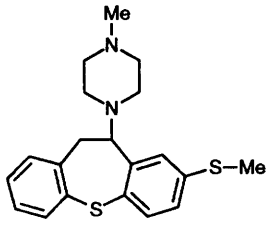
We concluded that methysergide might be producing its therapeutic effects by acting as an *agonist* or *partial agonist* at a previously uncharacterized 5-HT receptor mediating smooth muscle contraction of the cranial vasculature.

6 Identification of a novel vascular 5-HT_1 receptor

5-Hydroxytryptamine mediates its many functional responses by interacting with membrane bound receptors on smooth muscle and neurones and a number of different 5-HT receptors exist. To date, seven different classes of 5-HT receptor have been described.[14] In 1972, however, only two receptor types were known, the D receptor (later called 5-HT_2) which is found in most blood vessels where it mediates *vasoconstriction*, and the neuronally located M receptor (now called 5-HT_3) that seems to modulate the release of *neurotransmitters* from a variety of neurones. The failure of selective 5-HT_2 *antagonists* such as a cyproheptadine (**9**) to block the vasoconstrictor activity of methysergide or 5-HT in the *carotid arterial bed* of the dog excluded the involvement of this receptor and encouraged us to investigate isolated blood vessels throughout the vasculature. Large conductance vessels such as the lingual and external carotid arteries contained only 5-HT_2 receptors but fortuitously the dog saphenous vein (DSV), a peripheral vein isolated from the leg, was found to contract in a dose dependent manner to 5-HT and methysergide.[15,16] Neither response was affected by 5-HT_2 or 5-HT_3 *antagonists* but both were selectively inhibited by methiothepin (**10**),[17] an *antagonist* with affinity for 5-HT_1 receptors.



9 cyproheptadine



10 methiothepin

We failed to demonstate the existence of the DSV receptor on isolated blood vessels from the extracranial circulation by *in vitro* experiments[16] but attributed this to the presence of these receptors only on resistance vessels which were too small to be studied using isolated tissue techniques. Indirect evidence for their presence on carotid blood vessels came from the obervation that methiothepin, but not cyproheptadine, selectively antagonized the dose related carotid *vasoconstriction* produced by methysergide in the anaesthetized dog.

We concluded therefore that the novel 5-HT receptor found in the carotid circulation of the dog was identical to that on the dog saphenous vein and was later termed a 5-HT_1-like receptor[14] as it was pharmacologically similar to certain 5-HT_1 radioligand binding sites found in brain tissue.

7 Medicinal chemistry strategy

The identification of the DSV receptor in the dog carotid vasculature defined for us the objective for a chemical programme, namely a potent selective full *agonist* at this receptor suitable for oral administration with which to evaluate this novel mechanism for the treatment of migraine. Most of the undesirable effects of 5-HT are mediated through 5-HT_2 (vasoconstriction, bronchoconstriction, platelet aggregation) and 5-HT_3 (neuronal activation) receptors so it was essential compounds were selective for the DSV receptor. We felt that a full agonist was required to be efficacious in the acute phase since methysergide acts only prophylactically and is a *partial agonist* at this receptor.[16]

Methysergide and 5-HT were obvious prototype molecules for initiating chemistry but we were anxious to avoid the potential side-effect problems of ergot derivatives associated with their affinity for dopamine and *α-adrenoceptors*, so our preference was to modify 5-HT. Our strategy was to carry out systematic changes to the molecule to define the structural features required for potency and selectivity, and then apply this knowledge to the design of novel structures that incorporate the additional properties required of a drug for migraine, that of rapid absorption from the GI tract and an extended duration of action.

8 Biological tests

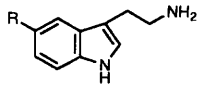
We employed isolated tissue preparations for *in vitro* functional assays to evaluate new compounds for their potency relative to 5-HT at the DSV receptor and the other 5-HT subtypes that had been identified at this time. Contraction of the dog saphenous vein provided a robust preparation to test for activity at the receptor conferring putative antimigraine activity. Contraction of the rabbit isolated aorta (RA) and depolarization of the rat vagus nerve were employed to measure 5-HT_2 and 5-HT_3 agonist activity, respectively. In the following tables the functional *in vitro* activity of compounds at the various 5-HT receptors are expressed as equipotent molar ratios (EPMR) with 5-HT = 1.

There are no animal models of migraine but *in vivo* activity was determined in the anaesthetized dog by measuring blood flow changes in the carotid artery using an electromagnetic flow probe. Reduction in flow gave a measure of *vasoconstriction* in the *carotid arterial bed.*

9 Structural modification of 5-hydroxytryptamine

The 5-hydroxyl group was regarded as a key structural element for affinity at 5-HT receptors so early work focused on systematic replacement of this with other functional groups to define the properties required for activity and selectivity at the DSV receptor.

Table 1 Relative agonist activities of selected 5-substituted tryptamines



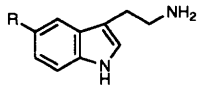
EPMR (5-HT = 1)

R	5-HT_1-like (DSV)	5-HT_2 (RA)
H	171	48
Cl	58	33
MeO	10	2
NO_2	45	70
Me	14	8
$HOCH_2$	39	14
MeCO	5	7
11, H_2NCO	0.4	26

Table 1 illustrates a series of 5-substituted tryptamines that were synthesized, showing that replacing the hyroxyl with a hydrogen atom or other substituents usually resulted in a loss of activity at the DSV receptor and failed to impart selectivity over 5-HT_2 receptors. The one exception, however, was 5-carboxamidotryptamine (**11**) (5-CT) which was found to be twice as potent as a DSV 5-HT_1-like agonist[18,19] and 25 times less potent as a 5-HT_2 agonist compared to 5-HT. Such a compound we predicted would produce selective *vasoconstriction* of the *carotid arterial bed* in the anaesthetized dog with little effect on blood pressure but much to our surprise 5-CT caused *vasodilatation* of the carotid circulation and a profound fall in blood pressure. Further investigation of the action of 5-CT on isolated blood vessels *in vitro* showed that it possessed agonist activity at another previously unreported 5-HT receptor mediating vascular relaxation[20] and accounted for the hypotensive effect in the dog.[21] A convenient isolated preparation containing this receptor was found to be the cat saphenous vein (CSV) which was shown to be relaxed by 5-HT and much more potently by 5-CT.[20] This provided us with an additional functional assay with which to evaluate compounds. The receptor, like the DSV receptor was characterized as 5-HT_1-like since it was antagonized by methiothepin but was unaffected by 5-HT_2 or 5-HT_3 antagonists. It was therefore apparent that compounds needed to be selective for the DSV receptor with respect to 5-HT_2, the 5-HT_3 as well as the 5-HT_1-like receptor mediating vasodilatation. However, modification of the hydroxyl group generally reduced agonist activity at the 5-HT_3 receptor to such an extent that routine screening for this was considered unnecessary.

5-CT was an important lead to us, being so potent an agonist at the DSV 5-HT_1-like receptor. Attempts to optimize potency and selectivity by alkylating the carboxamide function afforded compounds that possessed some selectivity for the DSV receptor compared to the CSV receptor but only at the loss of potency. Alkylation of the amino group in the side-chain reduced activity at all the receptor types examined with no clear trends in selectivity.

Table 2 Relative agonist activities of selected analogues of 5-carboxamidotryptamine



R	5-HT_1-like (DSV)	5-HT_1-like (CSV)	5-HT_2 (RA)
H_2NCO	0.4	0.02	26
H_2NSO_2	36	85	261
$MeSO_2$	8	60	49
MeSO	16	27	22
MeCO	5	NT	7
12, H_2NCOCH_2	9	201	> 1696
13, $MeNHCOCH_2$	4	> 100	> 1000

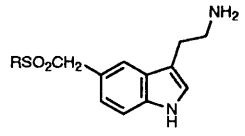
The data summarized in **Table 2** showed that replacing the carboxamide group with other electron-withdrawing hydrophilic substituents imparted marginal selectivity but not sufficient to justify further elaboration. Quite unexpectedly, however, the homologated carboxamide **12** provided us with a significant new lead devoid of activity at 5-HT_2 receptors and 20 fold selective over the CSV 5-HT_1-like relaxant receptor. Further analogues were synthesized from which AH 25086 (**13**) emerged as the most active and selective, being four-fold less potent than 5-HT at the DSV 5-HT_1-like receptor and essentially inactive at the other 5-HT receptors that were tested, in particular at the CSV 5-HT_1 receptor.[22,23] In contrast to 5-CT, AH 25086 elicited the predicted vasoconstrictor action on the carotid vasculature in the anaesthetized dog after intravenous administration with little effect on heart rate or blood pressure.[24] AH 25086 met the required activity criteria *in vitro* and *in vivo* to test the hypothesis that a DSV 5-HT_1-like agonist would alleviate the migraine headache, so safety and tolerability studies were carried out in human volunteers, followed by a pilot study in patients.[25,26] The clinical evaluation established for the first time the principle that such an agent given by intravenous injection was effective in resolving the headache and alleviating the other symptoms of an acute migraine attack.

10 Lead development of AH 25086

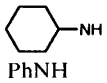
Although AH 25086 was an effective antimigraine agent by the intravenous route it was unsuitable for oral administration so we continued to search for alternative drug candidates. One approach that was particularly attractive was to elaborate the homologated sulfonamide **14** which displayed similar selectivity to the corresponding carboxamide[27] **12**.

Modification of the sulfonamide residue established that the *N*-methylsulfonamide **15** had optimum potency at the DSV receptor and the more bulky lipophilic substituents reduced activity (*cf.* **Table 3**). None of the compounds showed significant affinity for 5-HT_2 receptors. Substituting a methyl group in either the 1- or 2-position of the indole nucleus or β-position in the side-chain abolished activity at the DSV receptor, suggesting that these positions were subject to steric effects. However, anticipating the primary amino group would be vulnerable to metabolism and therefore limit the duration of action in this series we carried out a systematic substitution of the amino group to inhibit this process.

Table 3 Relative agonist activities of selected 5-alkylaminosulfonylmethyl tryptamines

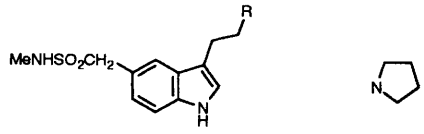


(NT = not tested)

R	5-HT_1, like (DSV)	5-HT_1-like (CSV)	5-HT_2 (RA)
14, H_2N	16	>79	>94
15, MeNH	8.8	1470	>294
EtNH	19	NT	973
Pr^iNH	48	NT	645
	57	NT	>419
PhNH	78	NT	>316
	15	NT	300
H_2N (2-methyl)	>2000	NT	>436
MeNH (1-methyl)	984	NT	>655
MeNH (β-methyl)	>811	NT	>381

We chose to modify the *N*-methylsulfonamidomethyl tryptamine **15** which had the most favourable activity profile to establish structure–activity relationships. Only small alkyl and dialkylamino substituents were accommodated without a major loss of activity at the DSV receptor (*cf.* **Table 4**). The one compound that stood out as being potent and selective as well as having other desirable properties of an antimigraine drug, such as being rapidly absorbed from the GI tract and having a good duration of action, was the dimethylamino derivative **1**, later to be known as sumatriptan. The compound was first synthesized in 1984, seven years after the chemistry programme was initiated, and was one of several hundred tryptamine derivatives synthesized by this time.

Table 4 Relative agonist activities of *N*-substituted 5-methylaminosulfonylmethyl tryptamines



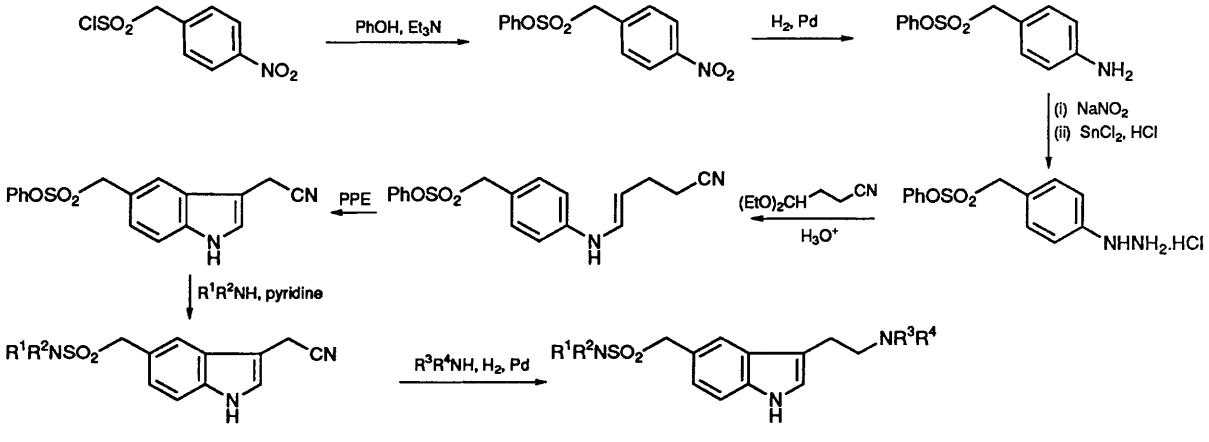
R	5-HT_1-like (DSV)	5-HT_1-like (CSV)	5-HT_2 (RA)
15, NH_2	8.8	>79	>94
NHMe	5.3	NT	>342
$NHPr^i$	633	NT	>132
1, NMe_2	4.6	>100	>1000
	100	NT	>87

Many of the compounds listed in **Tables 3 and 4** were synthesized by the general route shown in **Scheme 1**.

11 The pharmacology of sumatriptan

In vitro tests showed that sumatriptan was highly selective for the DSV 5-HT_1-like receptor and was essentially devoid of activity at 5-HT_2, 5-HT_3, 5-HT_4, dopaminergic, and *α-adrenoceptors.*[23] Hence it produced a selective constriction of the *carotid vasculature* in the anaesthetized dog[28] with little effect on heart rate and blood pressure, in marked contrast to ergotamine which through stimulation of other receptors produced a significant increase in blood pressure at doses that markedly reduced carotid blood flow.[29] Sumatriptan was rapidly absorbed from the GI tract of the dog and had a good duration of action.

Further *haemodynamic* experiments in the anaesthetized cat established that the *vasoconstrictor* activity was confined to the carotid arterial vasculature



Scheme 1

and there was no impairment of the blood supply to major organs, including the liver, kidney, heart, and brain.[30,31] The vasoconstrictor activity was furthermore shown to be selective within the carotid vasculature being localized to AVAs (arteriovenous anastomoses or shunt vessels).[30] These vessels perform the function of diverting oxygenated blood from the capillaries to the venous circulation but although constricted by sumatriptan the blood flow to the brain or extracerebral capillary beds remains unchanged. However, it is not known how relevant this is to the antimigraine activity of sumatriptan since experiments of this type cannot be carried out in man.

12 Results of clinical trials with sumatriptan

Sumatriptan was found to be well tolerated in volunteers[32] and clinically effective in migraine.[33-35] Extensive clinical trials established it to be a specific antimigraine agent highly effective by subcutaneous or oral administration.[36] In these studies over 7000 patients were treated involving over 35 000 migraine attacks. Relief of symptoms was achieved in 86% of patients within 2 hours following a single 6mg subcutaneous dose, and in 75% after 4 hours following a single 100mg oral dose, compared to 37% in the group treated with placebo. The relief of headache is rapid and begins to occur 10 minutes after an injection or 30 minutes after a tablet. The drug is well tolerated but produces a few adverse events that are mostly mild and transient. These include feelings of pressure or heaviness, warmth, and tingling. There was a clear patient preference for sumatriptan over ergotamine on the grounds of efficacy and side-effect liability. Following these studies sumatriptan was introduced as a novel therapy for the acute treatment of migraine[37] in 1991.

13 Mode of action of sumatriptan

Sumatriptan was originally conceived on a vascular hypothesis and the basis of its action may indeed be to contract painful abnormally distended and inflamed blood vessels of the cranial vasculature during a migraine headache. The most likely source of the pain is in the arterial blood vessels in the *meninges* which are amongst the few blood vessels in the head known to be pain sensitive. Thus, it has been shown that sumatriptan potently constricts blood vessels within the perfused *dura mater* isolated from cadavers.[40] However, these vessels are innervated by a dense network of sensory nerves which in migraine may release neuropeptide transmitters such as substance P and CGRP (calcitonin gene-related peptide) from nerve endings, leading to increased vascular permeability in the blood vessel wall, followed by protein extravasation, and oedema.[38] There is evidence, at least in animal models, that sumatriptan can attenuate neurogenic inflammation in the *dura* by inhibiting release of these vasodilator neuropeptides.[39]

However, whether the primary site of action is at 5-HT_1-like receptors on the blood vessel wall or on the sensory neurones that innervate them is still a matter of debate though both mechanisms may be important to the action of the drug.

14 Conclusions

This case history of sumatriptan illustrates how it is possible to design a useful therapeutic agent by mimicking the beneficial actions and minimizing the undesirable ones of a neurotransmitter believed to be important in a disease without fully understanding the underlying pathophysiology. The introduction of sumatriptan has stimulated much new research into the aetiology of migraine and studies of its action are suggesting new avenues for future new drugs. More importantly, clinical studies have shown sumatriptan is a significant advance on previous therapies for the acute treatment of migraine and the accompanying symptoms and is providing the patient with a much improved quality of life.

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16 Glossary of terms

α-Adrenoceptors. Receptors stimulated by noradrenaline and other sympathomimetic amines that mediate vasoconstriction.
Agonist. A drug which binds to a receptor and activates it, producing a pharmacological response (*e.g.* contraction, relaxation, secretion, *etc.*).
Antagonist. A drug that binds to a receptor and doesn't activate it but attenuates the effect of an agonist by limiting its access to the receptor.
Carotid arterial bed (or carotid vasculature). This is the network of blood vessels supplied by the carotid artery. There is a carotid artery on both the right and left side of the neck and they each divide into two main branches, the internal carotid, supplying the brain and parts of the head, and the external carotid, which sends branches to the face, neck, and scalp.
Cranial. Relating to the skull.
Extravasation. Escape of fluid from a vessel into the surrounding tissue.
Haemodynamic. Relating to blood flow.
Meninges. The three membranes that line the skull and cover the brain and spinal cord. The outermost layer is a tough fibrous membrane known as the *dura mater.* Also called *dura.*
Neurotransmitter. A natural agonist which on being released from nerves (neurones) by nerve stimulation elicits a pharmacological response.
Partial agonist. An agonist, which no matter how high a concentration is applied, is unable to produce maximal activation of the receptors.
Prophylactic agent. A drug that provides preventative treatment.
Prodromal symptoms. Premonitory symptoms of a migraine attack experienced several hours before the aura and headache (*e.g.* yawning, craving for special foods, depression, *etc.*).
Vasoconstriction. Contraction of blood vessels.
Vasodilatation. Increase in the calibre of blood vessels.