

# 1 The discovery of sumatriptan and a new class of drug for the acute treatment of migraine

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## Historical background

Successful innovative drug discovery in the pharmaceutical industry depends on several critical factors, which are often overlooked in this age of information overload and anticipation of immediate success from harnessing the new technologies. First, it is important to select an appropriate, prevalent, feasible disease target for which there are no good existing therapeutic agents. Secondly, it is important to have some degree of rational understanding of the disease pathophysiology itself in order to help identify a specific drug target, usually a transmitter receptor protein or enzyme. Thirdly, an adequate amount of biological and chemical resource needs to be allocated to the research discovery process with a commitment to the long term. Without due attention to all three of these points the chance of identifying a drug that may one day be a medicine is drastically reduced. Fortunately, when asked in late 1972 to initiate and lead a migraine project by Sir David Jack, the research and development director of Allen and Hanburys (then a wholly owned subsidiary of Glaxo), these essential criteria were already understood.

As to the first criterion, migraine is unquestionably a common disease, which can be very debilitating and seriously affect people's lives and sense of well being. This was clearly evident in talking to leading clinicians of the day, including Marcia Wilkinson and James Lance, and is dramatically re-enforced today by grateful patients' letters who tell how sumatriptan has changed their lives radically for the better. As to the pathophysiological insights, the basic understanding has been well documented by Harold G. Wolff, who clearly defined the neuroanatomical basis of head pain, showing brain neurons to be insensate and that head pain rather emanates from vascular structures with their dense sensory innervation<sup>1</sup>. For decades the view was widely

held, and is difficult to refute even today, that vasodilator drugs (notably alcohol) cause migraine headaches in migraineurs and that vasoconstrictors (notably ergotamine) can alleviate the pain<sup>2</sup>. In addition, the concept that 5-hydroxytryptamine (5-HT or serotonin) was somehow involved was rigorously investigated by Lance's group, who showed that reserpine caused marked depletion of platelet 5-HT, like that which occurs during an attack, and induces migraine-like symptoms in migraineurs but not in non-migraineurs<sup>3</sup>. This latter fact points to the obvious conclusion that migraineurs are different and have an underlying predisposition, now evinced by modern research on migraine genetics and developing theories of so-called channelopathies and central neuronal sensitization. The fact that our project took some 15 years or more to invent and develop sumatriptan testifies to the dedication and long-term commitment of Glaxo and its scientists.

## **A working hypothesis**

Two independent studies showed experimentally in the clinic that intravenous 5-HT could abort a migraine attack<sup>3,4</sup>. In the Lance study, they also measured the associated increase in plasma concentration of 5-HT, which was small and insufficient to replete platelet stores of 5-HT. Since 5-HT is a basic, non-lipophilic substance, we believed that it would poorly cross the blood-brain barrier and that its likely mechanism of action was vasoconstriction of those cranial vessels distended and inflamed during a migraine attack. Regardless, we argued that we might be able to find a selective agonist that would mimic the desirable effects of 5-HT without mimicking its many undesirable effects. This led us down a long path of research to understand the multiplicity of 5-HT receptor types and their distribution in the trigeminovascular system in particular.

## **Work on isolated cranial blood vessels**

Based on Wolff's clinical observation of a distended temporal artery during a migraine attack<sup>5</sup>, our initial approach was to work on the isolated rabbit ear artery, a well-studied and easily isolatable blood vessel preparation, from the extracranial vasculature. We focused first on the characterization of the 5-HT receptor types involved in vasomotor responses to 5-HT. Early work showed the rabbit ear artery to contain very few, if any, 5-HT receptors but this was not the case in the dog, where 5-HT had been shown to be more potent in contracting cranial than peripheral blood vessels<sup>6,7</sup>. We therefore attempted to determine whether more than one type of 5-HT receptor might be involved in the vasoconstrictor action of 5-HT in the dog, with the working hypothesis that there might be a different type of receptor in cranial blood vessels than in those in the periphery. Parenthetically, we suspected that yet another 5-HT receptor type mediated the vasodilatory effects of 5-HT<sup>8,9</sup> and deliberately set out to avoid making agonists which might activate this receptor, which we now know as the 5-HT<sub>7</sub> receptor.

In our search for a yet to be discovered 5-HT receptor type localized to cranial blood vessels, we were very excited by Saxena's observation that methysergide would selectively constrict the carotid circulation, without affecting blood pressure. Indeed in the femoral artery bed, it actually caused vasodilation, rather than vasoconstriction<sup>10</sup>. This suggested to us that methysergide (an indole containing lysergic acid analogue, chemically related to ergotamine) might be selectively activating a novel 5-HT receptor in the carotid circulation to cause the localized vasoconstriction. This turned out to be the case and intriguingly we were also able to show that even the vasodilation in the femoral bed was mediated by the same receptor, this time located neuronally on sympathetic fibres where it mediated a sympatholytic effect<sup>11,12</sup>. Our interest in methysergide was compounded by the view that it was clinically superior in the prophylaxis of migraine to other 5-HT receptor antagonists<sup>13</sup>.

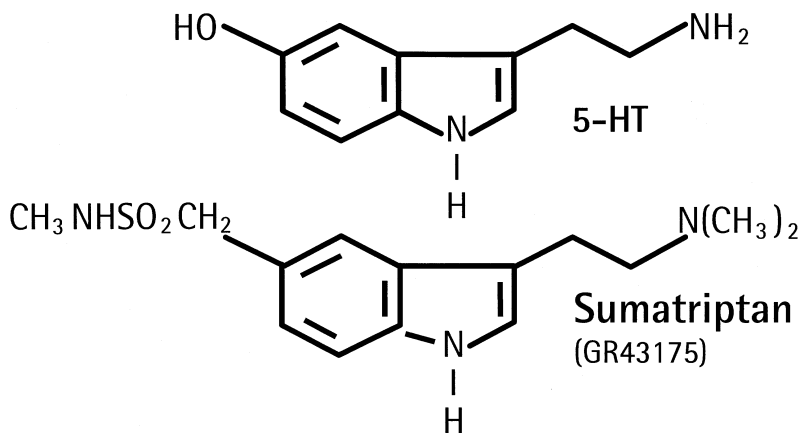
It transpired that methysergide, as a putative selective agonist, was key to our identification of a novel 'carotid' vascular receptor, which paradoxically we were first to find in the canine saphenous vein<sup>14,15</sup>. There we showed that the contractile effects of 5-HT could not be blocked by the then available 5-HT receptor antagonists such as methysergide and cyproheptadine but could be antagonized by methiothepin. Methysergide, but not cyproheptadine, had a particularly interesting profile, since rather than block, methysergide actually mimicked the action of 5-HT in the saphenous vein, albeit that it behaved as a partial rather than a full agonist. Furthermore the contractile effects of methysergide were antagonized by methiothepin at similar concentrations to those required to antagonize the effects of 5-HT. Clearly methysergide and 5-HT both activated a common receptor, now called a 5-HT<sub>1B</sub> receptor, in the canine saphenous vein; but we had to prove that this receptor was also in the carotid circulation to explain the selective carotid vasoconstrictor effects of methysergide<sup>16,17</sup>.

Initial attempts to show this were disappointing as the isolated canine extracranial vessels which we studied from the dog contained only the ubiquitous 5-HT receptor (today called 5-HT<sub>2A</sub>) in peripheral vascular smooth muscle. Only the intermediate auricular artery appeared to contain some of the novel receptor we had identified in a mixed 5-HT receptor population (i.e. 5-HT<sub>2A</sub> and some 5-HT<sub>1B</sub> receptors) to mediate the contractile effects of 5-HT<sup>18</sup>. Later experiments on intracranial vessels showed a very different profile, one just like that in the saphenous vein. Thus 5-HT-induced contraction of isolated basilar artery segments from dog, monkey and man are all resistant to blockade by the classical antagonists (5-HT<sub>2A</sub> receptor blockers) and contain predominantly 5-HT<sub>1B</sub> rather than 5-HT<sub>2A</sub> receptors<sup>19-21</sup>.

## A seminal discovery

In carotid haemodynamic studies in the anaesthetized dog, we showed that close intra-arterial injections of methysergide into the carotid circulation caused vasoconstrictor responses which were not blocked by cyproheptadine but were blocked by methiothepin; this was the same profile we had seen in the canine saphenous vein<sup>16,17</sup>. This led us to the conclusion that we had found a 5-HT receptor, hitherto unknown, and that it was localized to the carotid circulation. This then led to the

initiation of a dedicated chemical programme to look for a selective agonist for the new receptor, not a partial agonist like methysergide and a compound without its other unwanted ergot-like effects. By synthesizing and screening hundreds of analogues of 5-HT on isolated blood vessels, importantly the dog saphenous vein, we ultimately identified GR43175 (sumatriptan; Fig. 1.1)<sup>22</sup>, although not without occasional tangential excursions along the research path. Having found the compound that we were seeking, we were still excited by sumatriptan's remarkably selective profile of action, even though it had been predicted. Thus when injected intravenously it appeared only to constrict the carotid circulation of the anaesthetized dog, without other effects like those produced by either 5-HT itself or the ergots<sup>23,24</sup>. Many studies followed to further examine the vasoconstrictor effects of sumatriptan, including radiolabelled microsphere studies to examine blood flow changes throughout the body of the anaesthetized cat. These studies confirmed the localization of the vasoconstrictor action of sumatriptan to the carotid circulation in contrast to the generalized effect of ergotamine<sup>25,26</sup>. Remarkably vasoconstriction was even localized within the carotid bed to arteriovenous anastomoses without any compromise on cerebral blood flow<sup>26,27</sup>. This provided encouragement that we had indeed identified the receptor in the cranial vasculature that might mediate the beneficial antimigraine effect of 5-HT seen experimentally. Other various studies confirmed the high degree of selectivity of sumatriptan for 5-HT<sub>1</sub> receptors, with little or no effects on other 5-HT receptor types or other non-5-HT receptors<sup>28</sup>. After full toxicological evaluation and testing in volunteers, sumatriptan was evaluated therapeutically during a migraine attack (see ref. 29).



3-[2-(Dimethylamino)ethyl]-N-Methyl-1H-Indole-5-Methane Sulphonamide

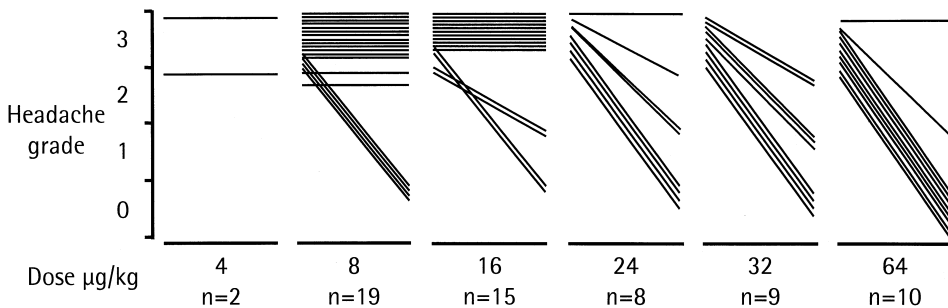
**Fig. 1.1** The basic chemical structure of sumatriptan. Note the remarkable similarity with that of 5-HT; and yet sumatriptan stimulates only 5-HT<sub>1</sub> receptors without effects on 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>6</sub>, or 5-HT<sub>7</sub> receptors<sup>35</sup>.

## A clinical proof of concept study

In an initial non-placebo-controlled study, carried out in parallel in Koenigstein and Munich in Germany, 24 migraine attacks were treated with 2 mg sumatriptan intravenously. Of these 17 attacks (71%), resulted in rapid and complete relief of symptoms, while the remaining seven attacks were associated with partial relief to a 'non-migrainous residual headache' (Fig. 1.2)<sup>30,31</sup>. While these effects were dramatic and not dissimilar to a study in an emergency outpatient setting reported this year, they were not acknowledged as credible until much bigger placebo-controlled studies were reported<sup>32-34</sup>. Scientifically, the most striking observations of the initial clinical study were that first the clinical improvement was so rapid (within 10 min of starting the infusion) and secondly that the dose required (about 30 µg/kg on a dose per weight basis) was almost exactly that predicted from the earlier vasoconstrictor studies in the dog (see ref. 35). Much development activity was to ensue which led to the launch of sumatriptan, a selective 5-HT<sub>1</sub> receptor agonist, in 1991 for clinical use in the acute treatment of migraine.

## Other benefits accrued

Sumatriptan has undoubtedly improved the quality of life of countless migraineurs but in addition other benefits have accrued. Of particular import has been the big impetus it has given to migraine research, with scientists and clinicians all eager to explain exactly how it works—a scientific debate which continues to the benefit of knowledge and the better understanding of the pathophysiology of the disease itself. The essential clinical trials also provided the world's first large-scale placebo-controlled migraine trials and radically changed the image of the disease in the eyes of the public and neurologists alike. The work engendered has also added to the



**Fig. 1.2** The initial proof of concept study with sumatriptan (GR43175) in migraineurs before and after infusion. Note that the relief of symptoms was dose dependent and was rapid, usually being maximal by the end of the infusion (10 min) even though the median duration of symptoms before treatment was 8.5 h<sup>31</sup>. *n*, number of attacks; 0, no headache; 1, mild; 2, moderate; 3, severe.

wealth of knowledge about 5-HT receptors and provided a variety of drug tools for yet more research. It also led to a number of other compounds like sumatriptan, including our own naratriptan<sup>36</sup>, all collectively known as the triptans, which are the topic of this book.

## Acknowledgements

I wish to express my deep gratitude to my friends, especially Wasyl Feniuk, Marion Perren, Helen Connor, and Pam Gaskin for their sustained and important contributions to our research team effort. I would also like to acknowledge my many colleagues within Glaxo involved in the discovery and development of sumatriptan, too numerous to mention here. Others outside the company too have made contributions by their published works, gratuitous help and encouragement, valuable discussions, and intellectual challenge. In particular, I must mention James Lance and Pramod Saxena, who were highly influential in the early critical stages.

## Some reflections on the 'triptan phenomenon'

'I was also instrumental in the naming of the triptans. On being invited to London by Professor Paul Turner, the then chairman of the British Pharmacopoeia sub-committee on drug names, I pointed out that sumatriptan was an agonist (not an antagonist) drug and it worked by mimicking some of the actions of 5-hydroxytryptamine. Hence the primary suffix 'triptan' reflects the action on 'tryptamine' receptors, while 'suma' was chosen as a specific prefix for the 5-sulphonamide group of sumatriptan's chemical structure.'

'Mimicry is the best form of flattery . . .'

'The phenomenon has also substantially contributed directly to the increase in employment opportunities in the pharmaceutical industry today . . .'

## References

1. Wolff, H.G. *Headache and Other Head Pain*. New York: Oxford University Press, 1963.
2. Lance, J.W. The pathogenesis of migraine. In *Mechanism and Management of Headache*, 2nd edn. London: Butterworths, 1973: 113–133.
3. Anthony, M., Hinterberger, H., Lance, J.W. Plasma serotonin in migraine and stress. *Arch Neurol* 1967; **16**: 544–552.
4. Kimball, R.W., Friedman, A.P., Vallejo, E. Effect of serotonin in migraine patients. *Neurol Minneap* 1960; **10**: 107–111.
5. Graham, J.R., Wolff, H.G. Mechanism of migraine headache and action of ergotamine tartrate. *Arch Neurol Psychiatry* 1938; **39**: 737–763.
6. Toda, N., Fujita, Y. Responsiveness of isolated cerebral and peripheral arteries to serotonin, norepinephrine, and transmural electrical stimulation. *Circ Res* 1973; **33**: 98–104.
7. Apperley, E., Humphrey, P.P.A., Levy, G.P. Receptors for 5-hydroxytryptamine and noradrenaline in rabbit isolated ear artery and aorta. *Br J Pharmacol* 1976; **58**: 211–221.

8. Eyre, P. Atypical tryptamine receptors in sheep pulmonary vein. *Br J Pharmacol* 1975; **55**: 329–333.
9. Feniuk, W., Humphrey, P.P.A., Watts, A.D. 5-Hydroxytryptamine-induced relaxation of isolated mammalian smooth muscle. *Eur J Pharmacol* 1983; **96**: 71–78.
10. Saxena, P.R. Selective vasoconstriction in carotid vascular bed by methysergide: possible relevance to its anti-migraine effect. *Eur J Pharmacol* 1974; **27**: 99–105.
11. Feniuk, W., Humphrey, P.P.A., Watts, A.D. Modification of the vasomotor actions of methysergide in the femoral arterial bed of the anaesthetized dog by changes in sympathetic nerve activity. *J Auton Pharmacol* 1981; **1**: 127–132.
12. Watts, A.D., Feniuk, W., Humphrey, P.P.A. A pre-junctional action of 5-hydroxytryptamine and methysergide on noradrenergic nerves in dog isolated saphenous vein. *J Pharm Pharmacol* 1981; **33**: 515–520.
13. Lance, J.W., Anthony, M., Somerville, B. Comparative trial of serotonin antagonists in the management of migraine. *Br Med J* 1970; **1**: 327–330.
14. Apperley, E., Humphrey, P.P.A., Levy, G.P. Two types of excitatory receptor for 5-hydroxytryptamine in dog vasculature? *Br J Pharmacol* 1997; **61**: 465P.
15. Feniuk, W., Humphrey, P.P.A., Perren, M.J., Watts, A.D. A comparison of 5-hydroxytryptamine receptors mediating contraction in rabbit aorta and dog saphenous vein: evidence for different receptor types obtained by use of selective agonists and antagonists. *Br J Pharmacol* 1985; **86**: 697–704.
16. Humphrey, P.P.A., Feniuk, W., Perren, M.J. 5-HT in migraine: evidence from 5-HT<sub>1</sub>-like receptor agonists for a vascular aetiology. In *Migraine: A Spectrum of Ideas* (ed. Sandler, M., Collins, G.M.). Oxford: Oxford University Press, 1990: 147–172.
17. Humphrey, P.P.A., Apperley, E., Feniuk, W., Perren, M.J. A rational approach to identifying a fundamentally new drug for the treatment of migraine. In *Cardiovascular Pharmacology of 5-Hydroxytryptamine* (ed. Saxena, P.R., Wallis, D.I., Wouters, W., Bevan, P.). Dordrecht: Kluwer Academic Publishers, 1990: 417–431.
18. Apperley, E., Feniuk, W., Humphrey, P.P.A., Levy, G.P. Evidence for two types of excitatory receptor for 5-hydroxytryptamine in dog isolated vasculature. *Br J Pharmacol* 1980; **68**: 215–224.
19. Connor, H.E., Feniuk, W., Humphrey, P.P.A. Characterisation of 5-HT receptors mediating contractions of canine and primate basilar artery using GR43175, a selective 5-HT<sub>1</sub>-like receptor agonist. *Br J Pharmacol* 1989; **96**: 379–387.
20. Humphrey, P.P.A., Feniuk, W., Motevalian, M., Parsons, A.A., Whalley, E.T. The vasoconstrictor action of sumatriptan on human isolated dura mater. In *Serotonin: Molecular Biology, Receptors and Functional Effects* (ed. Fozard, J.R., Saxena, P.R.). Basel: Birkhäuser Verlag AG, 1991: 421–429.
21. Parsons, A.A., Whalley, E.T., Feniuk, W., Connor, H.E., Humphrey, P.P.A. 5-HT<sub>1</sub>-like receptors mediate 5-hydroxytryptamine-induced contraction of human isolated basilar artery. *Br J Pharmacol* 1989; **96**: 434–449.
22. Humphrey, P.P.A., Feniuk, W., Perren, M.J., Connor, H.E., Oxford, A.W., Coates, I.H., Butina, D. GR43175, a selective agonist for the 5-HT<sub>1</sub>-like receptor in dog isolated saphenous vein. *Br J Pharmacol* 1988; **94**: 1123–1132.
23. Feniuk, W., Humphrey, P.P.A., Perren, M.J. The selective carotid arterial vasoconstrictor action of GR43175 in anaesthetised dogs. *Br J Pharmacol* 1989; **96**: 83–90.
24. Humphrey, P.P.A., Perren, M.J., Feniuk, W., Oxford, A.W. The pharmacology of the novel 5-HT<sub>1</sub>-like receptor agonist GR43175. *Cephalalgia* 1989; **9** (Suppl. 9): 23–33.
25. Feniuk, W., Humphrey, P.P.A., Perren, M.J. GR43175 does not share the complex pharmacology of the ergots. *Cephalalgia* 1989; **9** (Suppl. 9): 35–39.
26. Perren, M.J., Feniuk, W., Humphrey, P.P.A. The selective closure of feline carotid arteriovenous anastomoses by GR43175. *Cephalalgia* 1989; **9** (Suppl. 9): 41–46.

27. den Boer M.O., Villalon, C.M., Heiligers, J.P.C., Saxena, P.R., Humphrey, P.P.A. The effects of sumatriptan on the carotid circulation of the pig. *Eur J Pharmacol* 1990; **183** (4): 1275–1276.
28. Peroutka, S.J., McCarthy, B.G. Sumatriptan (GR43175) interacts selectively with 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> binding sites. *Eur J Pharmacol* 1989; **163**: 133–136.
29. Humphrey, P.P.A., Feniuk, W., Marriott, A.S., Tanner, R.J.N., Jackson, M.R., Tucker, M.L. Preclinical studies on the anti-migraine drug, sumatriptan. *Eur J Neurol* 1991; **31** (5): 282–290.
30. Doenicke, A., Brand, J., Perrin, V.L. Possible benefit of GR43175, a novel 5-HT<sub>1</sub>-like receptor agonist, for the acute treatment of severe migraine. *Lancet* 1988; **1**: 1309–1311.
31. Perrin, V.L., Farkkila, M., Goasguen, J., Doenicke, A., Brand, J., Tfelt-Hansen, P. Overview of initial clinical studies with intravenous and oral GR43175 in acute migraine. *Cephalalgia* 1989; **9** (S9): 63–72.
32. Cady, R.K., Wendt, J.K., Kirchner, J.R., Sargent, J.D., Rothrock, J.F., Skaggs, H. Jr. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA* 1991; **265**: 2831–2835.
33. Diener, H.C. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicentre, parallel group study. The ASASUMAMIG Study Group. *Cephalalgia* 1999; **19**: 581–588.
34. Ferrari, M.D. and the Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. *N Engl J Med* 1991; **325**: 316–321.
35. Feniuk, W., Humphrey, P.P.A. This volume.
36. Connor, H.E., Feniuk, W., Beattie, D.T., North, P.C., Oxford, A.W., Saynor, D.A., Humphrey, P.P.A. Naratriptan: biological profile in animal models relevant to migraine. *Cephalalgia* 1997; **17**: 145–152.