

# The Development of a Highly Selective 5-HT<sub>1</sub> Receptor Agonist, Sumatriptan, for the Treatment of Migraine

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## ABSTRACT

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Sumatriptan is a highly selective 5-HT<sub>1</sub> receptor agonist and an effective treatment for migraine. It causes constriction of cranial blood vessels. In anaesthetised animals, it selectively constricts parts of the carotid vasculature and has been shown to inhibit plasma protein extravasation from blood vessels of the dura mater induced by antidromic stimulation of the trigeminal nerve. This effect may result from a localised vasoconstriction of the meningeal vessels and/or a direct inhibitory effect on adventitial nerve endings. Sumatriptan penetrates the blood brain barrier poorly. These findings are consistent with the view that the locus of action of sumatriptan is at the level of the wall of cranial blood vessels that are distended and edematous during a migraine headache. © 1992 Wiley-Liss, Inc.

**Key words:** sumatriptan, migraine, 5-HT<sub>1</sub> agonists

## INTRODUCTION

One of the continual challenges facing medicinal research is the discovery of safe and effective drugs for the treatment of diseases where existing therapy is unsatisfactory. Migraine is a severely debilitating condition affecting millions of people. The ergot-based derivatives, ergotamine and dihydroergotamine, have long been the mainstay of acute therapy, but their side effect profile, presumably a consequence of their lack of specificity, has limited their clinical usefulness. Recent, extensive clinical studies in severe migraines [Cady et al., 1991;

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Patten, 1991] have established the effectiveness of sumatriptan (3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulfonamide) (GR43175), which heralds it as a major advance in the acute treatment of migraine.

The introduction of any new drug entity into therapeutics undoubtedly stimulates further clinical and preclinical research into further defining the mechanism of action of such compounds, which ultimately may provide us with a better understanding of the pathology of the disease itself. The aim of this review is to outline the basic pharmacology of sumatriptan and to provide a framework for the understanding of the mechanism of its action in treating migraine headaches.

## MIGRAINE PATHOGENESIS

Migraine is an episodic, often unilateral and throbbing headache frequently associated with or preceded by a distinct symptomatology including nausea, photophobia, phonophobia, and gastrointestinal disturbance. Attacks can be triggered by a variety of precipitants. The precise mechanisms involved in the genesis of migraine are not known. In recent years, there has been great controversy as to whether or not the disease is primarily of vascular or neuronal origin [See Edmeads, 1991]. It is, however, not helpful to view the pathological processes in migraine as *either* vascular *or* neurogenic since elements of both theories are likely to be correct. In recent years [Moskowitz, 1984] has focused attention on the importance of the relationship between the trigeminal nerve and the cranial vasculature in head pain. Thus, migrainous headaches may originate and be perpetuated by alterations in the activity of the trigeminovascular system. There is no doubt that many intracranial blood vessels are uniquely pain sensitive and are innervated by a dense perivascular network of sensory nerves [Moskowitz, 1984] that can be activated by distention of the blood vessel wall [Nichols et al., 1990]. Indeed, a recent clinical study [Friberg et al., 1991] provides evidence of dilation of large intracranial arteries during a migraine headache.

Miskowitz and Buzzi [1991] have suggested that migrainous headaches result from a local neurogenically mediated inflammatory response of intracranial vessels, particularly those in the meninges, and argue that the vasodilation is a consequence and not the cause of vascular head pain. Nevertheless, distention of the cranial vasculature will provoke intense pain referred to areas that are innervated by the ophthalmic division of the trigeminal nerve [Nichols et al., 1990]. Such observations now complement the classical observations of Ray and Wolff [1940] who demonstrated a consistent pattern of referred pain in response to faradic stimulation, stretching or dissection of intracranial vessels. Furthermore, Graham and Wolff [1938] demonstrated increased pulsations of the superficial temporal artery during migrainous headache, which were reduced by the vasoconstrictor ergotamine and accompanied by a reduction in headache intensity. Such studies provide us with good evidence for a key role of the cranial vasculature as the source of head pain in migraine without in anyway diminishing the importance of the trigeminal nerve in the pain processing pathway.

## THE DISCOVERY OF SUMATRIPTAN

Of the many substances which have been implicated in migraine, more attention has focused on the potential importance of 5-hydroxytryptamine (5-HT) than any other neurotransmitter substance. However, just as debate over the vascular and neurogenic theories of migraine have continued, so have the arguments for and against an important role of this neurotransmitter substance in migraine pathogenesis. The evidence for an initiating role have recently been reviewed [Humphrey, 1991] and can at best be described as circumstantial. However, the important clinical observation that the slow intravenous infusion of 5-HT could alleviate both reserpine-induced and spontaneous migraine [Kimball et al., 1960; Lance et al., 1967a] and the knowledge that 5-HT was a potent vasoconstrictor of cranial blood vessels

[Toda and Fujita, 1973; Lance et al., 1967b] provided a rational basis for the search for a selective 5-HT agonist, which might selectively constrict cranial blood vessels and which might consequently be effective in the treatment of migraine. The ability of the antimigraine drug methysergide to selectively constrict the carotid vasculature [Saxena, 1974] led us to examine its effects on isolated blood vessels and to conclude that 5-HT could cause contraction of blood vessels by activation of two distinct types of 5-HT receptor [Apperley et al., 1980]. Further studies using more selective agonists and antagonists [Feniuk and Humphrey, 1989] now provide unequivocal evidence to support such a claim. In most peripheral blood vessels 5-HT mediates contraction via activation of 5-HT<sub>2</sub> receptors, whereas contraction of cranial blood vessels, including those of the human basilar artery [Parsons et al., 1989] and human meningeal vessels [Humphrey et al., 1991a], is largely mediated via activation of a subgroup of 5-HT<sub>1</sub> receptors that we have termed *5-HT<sub>1</sub>-like*. Sumatriptan is a selective agonist at this receptor and selectively constricts cranial blood vessels.

### THE PHARMACOLOGY OF SUMATRIPTAN AND THE MECHANISM OF ITS ANTIMIGRAINE ACTION

The animal pharmacology of sumatriptan has been extensively reviewed in recent years [Humphrey et al., 1989; Feniuk et al., 1991; Humphrey et al., 1991b]. Sumatriptan was progressed into clinical development on the basis of its high degree of selectivity for vascular 5-HT<sub>1</sub> receptors that mediate constriction [Humphrey et al., 1988]. These receptors are largely localised on large intracranial blood vessels from a variety of species including man [Connor et al., 1989; Parsons et al., 1989; Humphrey et al., 1990]. The high degree of specificity of sumatriptan for 5-HT<sub>1</sub> receptors has also been confirmed in ligand bindings studies, where it has been shown to have little or no affinity for a wide range of neurotransmitter binding sites [Peroutka and McCarthy, 1989; Van Wijngaarden et al., 1990] which contrasts markedly with that of dihydroergotamine. This selectivity of action in comparison to a variety of ergot derivatives has also been demonstrated functionally both in vitro and in vivo [Feniuk et al., 1989a].

Animal studies in vivo have shown that sumatriptan selectively constricts the carotid arterial circulation [Feniuk et al., 1989b] with little or no effect in a variety of different vascular beds [Feniuk et al., 1989a,b; Perren et al., 1989]. The carotid vasoconstrictor action of sumatriptan appears to be largely restricted to arteriovenous anastomoses or shunts [Perren et al., 1989; Den Boer et al., 1991]. Although the opening of cranial arteriovenous anastomoses has been implicated in migraine [Heyck, 1969], the importance of such a mechanism is not widely accepted although interestingly the meningeal circulation is richly endowed with a network of such vessels [Kerber and Newton, 1973]. The selectivity of sumatriptan's vasoconstrictor action within the carotid circulation is important, since although large cerebral conducting arteries are constricted by sumatriptan, cerebral blood flow is not changed [Perren et al., 1989], a finding that has now been confirmed in man [Friberg et al., 1991].

Since distension of cranial blood vessels activates perivascular nerve fibres which transmit painful sensory information via the trigeminal nerve [Nichols et al., 1990], it seems probable that selective vasoconstriction of cranial vessels could account for sumatriptan's effectiveness in acute migraine therapy. Indeed, the recent clinical findings of Friberg and colleagues [1991] would support such a view. Thus using the combined techniques of transcranial Doppler sonography and single photon emission computerised tomography, they have provided evidence of selective large artery dilatation in migraine on the headache side and showed that sumatriptan abolished the headache and reversed the changes in large artery calibre. Although such studies clearly need to be confirmed they are consistent with, but not definitive proof of, a mechanism of action that primarily involves vasoconstriction.

Nevertheless, it has been known for some time that sumatriptan activates vascular 5-HT<sub>1</sub> receptors that mediate an inhibition of neurotransmitter release on adventitial sympathetic

nerve endings and that these receptors are the same or similar to those 5-HT<sub>1</sub> receptors which mediate vasoconstriction [Watts et al., 1981; Humphrey et al., 1988]. More recently it has now been shown that sumatriptan inhibits the extravasation of plasma protein into the dura mater of rats and guinea pigs, in response to antidromic stimulation of the trigeminal nerve [Buzzi and Moskowitz, 1990; Buzzi et al., 1991a]. It has been suggested that such an action is mediated by an inhibitory effect of sumatriptan on neuropeptide release from peripheral trigeminal nerve endings. The recent finding that sumatriptan inhibits the increase in CGRP output in the sagittal sinus of anaesthetised rats in response to trigeminal nerve stimulation without changing basal output would appear to support such a view [Buzzi et al., 1991b]. Evidence has also been obtained recently of an effect of sumatriptan on the trigeminovascular system in man [Goadsby and Edvinsson, 1991]. Thus, during a migraine headache, CGRP levels in jugular venous blood increase, and these are reversed by sumatriptan at doses that abort the headache. However, although this study provides further evidence for the involvement of the trigeminovascular system in migraine, it does not allow one to define sumatriptan's site of action. An inhibitory effect on trigeminal nerve endings *or* vasoconstriction could explain the inhibitory effect on peptide release. Thus, vasoconstriction could reduce the firing of perivascular afferents and consequently activation of local axonal reflexes by reducing pressure on oedematous pain sensitive vessels within the cranium. Notwithstanding these considerations the only proven observation is that sumatriptan does have a vasoconstrictor action in humans (migraineurs) on those vessels implicated in the pathology of headache [Friberg et al., 1991].

Further clinical studies with sumatriptan will hopefully define the precise locus of its antimigraine action at the level of the cranial vasculature. A generalised analgesic action can be dismissed since in animal studies, extremely high doses of sumatriptan are devoid of analgesic activity in a variety of species [Skingle et al., 1990]. A central action of sumatriptan can also be excluded, since sumatriptan does not readily penetrate the brain [Humphrey et al., 1990; Sleight et al., 1990] and the cerebral vascular intima [Humphrey et al., 1991c]. It is possible that sumatriptan only gains access to those vascular 5-HT<sub>1</sub> receptors where there is no significant blood brain barrier such as the large cerebral conducting arteries and the meningeal vasculature. The results from both clinical and preclinical studies are consistent with the view that the locus of action of sumatriptan is specifically localised within the walls of cranial blood vessels, which are distended and pain-sensitive during a migraine headache. Both vasoconstrictor and local neuronal actions could contribute to its anti-migraine effect.

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