**Introduction**

In Japan it is estimated that about 8.4% of the population experiences migraine, but many go undiagnosed and undertreated. As treatment drugs, ergotamine agents and analgesic drugs have been employed for a long time for headache attacks. Studies of the pathophysiology of migraine, on the other hand, have reported transmitters such as serotonin, catecholamine, and neuropeptides play an important role in migraine. Especially the use of sumatriptan, a serotonin (5-hydroxytryptamine (5-HT) receptor agonist developed by Humphrey et al., started approximately 10 years ago in overseas countries. The drug is effective in 50 to 70% of migraine patients during the headache phase. Because of these facts, the relationship between serotonin and migraine has regained attention. Ever since various drugs that have a similar chemical
MIGRAINE

Some kind of stimulation acts on the axons in the trigeminal nerves, which are found around the dural vessels, and vasoactive neuropeptides (substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), etc.) are released and cause neurogenic inflammation (vasodilatation, leakage of plasma protein, and mast cell degranulation). Because of this, both anterograde and retrograde conduction occur in the trigeminal nerves. Anterograde conduction reaches the trigeminal nuclei, and is then transmitted to the thalamus and cerebral cortex. This message is felt as pain. Retrograde conduction, on the other hand, further activates a release of vasoactive neuropeptides on the periphery of the trigeminal nerves. It has been demonstrated that sumatriptan acts on 5-HT\textsubscript{1B} receptors, which are found in the intracranial vascular smooth muscle, to constrict the vessels, and it also inhibits a release of neuropeptides by binding to 5-HT\textsubscript{1D} receptors, which are found in the trigeminal nerves around the blood vessels.

(Figure modified from Moskowitz and Goadsby)

Pain

Upper central nerves

Unknown stimuli

Anterograde conduction

Activation of trigeminal sensory fibers

Release of neuropeptides

Caudal trigeminal nuclei

Activation of automatic nerves

Nausea/vomiting

Transmission of pain

Retrograde conduction

Vasodilatation and extravasation induced by neuropeptides

Mast cells

Neurokinin A, Substance P, CGRP, 5-HT\textsubscript{1B} receptors, 5-HT\textsubscript{1D} receptors, Sumatriptan

Fig. 1 Mechanism of the development of migraine via the trigeminovascular system

Some kind of stimulation acts on the axons in the trigeminal nerves, which are found around the dural vessels, and vasoactive neuropeptides (substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), etc.) are released and cause neurogenic inflammation (vasodilatation, leakage of plasma protein, and mast cell degranulation). Because of this, both anterograde and retrograde conduction occur in the trigeminal nerves. Anterograde conduction reaches the trigeminal nuclei, and is then transmitted to the thalamus and cerebral cortex. This message is felt as pain. Retrograde conduction, on the other hand, further activates a release of vasoactive neuropeptides on the periphery of the trigeminal nerves. It has been demonstrated that sumatriptan acts on 5-HT\textsubscript{1B} receptors, which are found in the intracranial vascular smooth muscle, to constrict the vessels, and it also inhibits a release of neuropeptides by binding to 5-HT\textsubscript{1D} receptors, which are found in the trigeminal nerves around the blood vessels.

(Figure modified from Moskowitz and Goadsby)
found around the dural vessels, and vasoactive neuropeptides (substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), etc.) are released. These in turn cause neurogenic inflammation (vasodilatation, leakage of plasma protein, and mast cell degranulation). This causes both anterograde and retrograde conduction in the trigeminal nerves.

According to this theory, anterograde conduction reaches the trigeminal nuclei, and is then transmitted to the thalamus and cerebral cortex. This message is felt as pain. Retrograde conduction, on the other hand, further activates a release of vasoactive neuropeptides on the periphery of the trigeminal nerves. In addition, it is demonstrated that sumatriptan acts on 5-HT\textsubscript{1B} receptors in the intracranial vascular smooth muscle to constrict the vessels, and it also inhibits the release of neuropeptides by binding to 5-HT\textsubscript{1D} receptors which are found in the trigeminal nerves around the blood vessels.

Furthermore, Moskowitz presented an article in which this unknown stimulation is considered as the cortical spreading depression found during an aura. This theory seems to be an organic combination of the traditional vascular and neuronal theories.

**Relationship between Migraine and Serotonin**

Since 1959 when Sicuteri *et al.* measured the serotonin metabolite 5HIAA in the urine of patients with migraine and discovered that its level is higher than that of healthy individuals, the relationship between migraine and serotonin has become a fascinating topic. When the level of platelet serotonin was measured in migraine patients, it was revealed that the level decreased to about 40% during a headache attack. In addition, when reserpine, which acts to release serotonin from platelets, is administered, a migraine-like headache is produced. It was proved that this headache is improved by the intravenous administration of serotonin. However, because serotonin also has systemic effects, various side effects are produced; and serotonin has therefore not come into practical use.

Thereafter serotonin agonists that selectively act on the cerebral blood vessels were developed. A serotonin 5-HT\textsubscript{1B/D} receptor agonist, sumatriptan (Fig. 2), developed by Humphrey *et al.*\textsuperscript{2}) was effective in 50 to 70% of the migraine patients during the headache phase. It has been discovered that sumatriptan acts on...
5-HT\textsubscript{1B} receptors, which are found in the intracranial vascular smooth muscle, to constrict the vessels, and it also inhibits the release of neuropeptides by binding to 5-HT\textsubscript{1D} receptors which are found in the trigeminal nerves around the blood vessels (Fig. 1). Furthermore, the possibility that sumatriptan acts on 5-HT\textsubscript{1F} receptors, which are found in the trigeminal nerve cells, to inhibit a migraine attack has been considered.

Ergotamine agents, which have traditionally been used, also act on these serotonin receptors, and constrict the cerebral vessels. However, as shown in Table 1, since these agents act not only on serotonin receptors but also on adrenaline and dopamine receptors, they cause various side effects.

### Sumatriptan

Twenty placebo-controlled trials of the subcutaneous administration of sumatriptan, a serotonin 5-HT\textsubscript{1B/1D} receptor agonist, have been performed. In all these trials sumatriptan manifested significantly superior effects on migraine to placebo. In other words, the remission rate of headache by subcutaneous injections of 6 mg of sumatriptan is 65 to 80% and of that of 3 mg subcutaneous injections is 57 to 75%; both showing a superior effect to that of placebo. The incidence of adverse reactions at that time was significantly higher in the subcutaneous sumatriptan group than in the placebo group. Injection site pain/redness and chest discomfort were recognized as adverse reactions. Furthermore, 20 placebo-controlled double-blind trials of the effect of oral administration of sumatriptan were conducted. In all these trials the sumatriptan administration groups showed a significantly superior effect to the placebo groups.

In Japan, sumatriptan injection (3 mg) has been available since April 2000, while an oral agent (sumatriptan 50 mg tablet) has been available since August 2001. Also, a nasal spray will be approved in the future. Sumatriptan 6 mg injection, 25, 50, and 100 mg tablets, nasal spray and suppositories are utilized around the world. With the injection the bioavailability is 96% and a therapeutic range is reached in 10 minutes, while with the tablet, the bioavailability is only 14% and a therapeutic range is reached after 30 to 90 minutes. The elimination half-life in the blood is approximately 2 hours.

In addition, it has been proven that sumatriptan is also effective against concomitant symptoms such as nausea, vomiting, and phonophobia/photophobia which accompany migraine attacks. However, administration of sumatriptan during the aura is not very effective. It is more effective to administer the drug during the headache phase. Nevertheless, in approximately 1/3 of the patients in whom sumatriptan was effective, there was a problem with recurrence of the headache 24 to 48 hours after administration.

Sumatriptan is contraindicated in patients with ischemic heart diseases and/or epilepsy, inadequately controlled hypertension or hepatic dysfunction, and in patients who had taken ergotamine agents within 24 hours, or who are taking monoamine oxidase (MAO) inhibitors.

### Second Generation Agents of the Triptan Family

Since the success of sumatriptan, various triptan agents have been developed by improving the weak points of sumatriptan (the elimination half-life in the blood is short, crossing of the blood-brain barrier is weak, and the metabolites do not have an inhibiting action on migraine). From 1997 to 1998, zolmitriptan, naratriptan and rizatriptan were approved in various countries. Thereafter, almotriptan, eletriptan, and frovatriptan have been developed (Fig. 3). Compared with sumatriptan, in these second generation agents of the triptan family, the bioavailability is higher (45 to 75%), the time it takes for the blood concentration to reach the therapeutic range is short (30 to 60 minutes), the elimination half-life in the blood is longer, and because of their high liposolu-
bility, they can cross the blood-brain barrier to act on the central nerves.

Recently it was reported that naratriptan was effective in over 40% of the migraine patients in whom sumatriptan treatment failed. The efficacy of zolmitriptan was 73% and that of rizatriptan was 81% in migraine patients in whom sumatriptan was not effective. As a result, it was revealed that even if one agent of the triptan family is not effective, it is worthwhile to try other triptan agents.

In 2001 Ferrari et al.9) carried out a meta-analysis of 53 clinical trials on seven triptans involving 24,089 patients and presented the following results: the mean improvement rate of headache at two hours after taking 100 mg of sumatriptan is 59%. By using this data as the standard, the improvement rate of each triptan agent was examined. As a result, it was revealed that even if one agent of the triptan family is not effective, it is worthwhile to try other triptan agents.

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Prophylactic Therapy for Migraine

Prophylactic therapy for migraine should be considered when the frequency of migraine is high, when treatment of the acute phase is insufficient, when treatment during the acute phase is contraindicated or is impossible due to adverse reactions, or when abuse of the acute phase treatment is observed. Traditionally propranolol, a β-adrenergic blocking agent, and amitriptyline, an antidepressant, were considered effective prophylactic agents and they have thus been employed.

Flunarizine, an effective calcium channel blocker, was employed lately, but it has been taken off the market in Japan due to adverse reactions. Thereafter, lomerizine was developed in Japan. In a placebo-controlled double-blind development study11) it was revealed that, compared with placebo, lomerizine significantly reduces the frequency and degree of headaches. Currently, it is widely utilized on the clinical scene.

Conclusion

Since the development of sumatriptan in Europe and the United States the treatment of migraine has changed. In the guidelines for migraine headache set out in the Report of the Quality Standards Subcommittee of the American Academy of Neurology in 2000,12) triptan agents are also regarded as the first choice drugs for migraine.

Since April 2000 the subcutaneous sumatriptan injection has been available in Japan. From August 2001 orally administered sumatriptan and zolmitriptan have also been available, and eletriptan was approved in July 2002.
Consequently, the treatment of migraine has drastically changed in Japan. In the guidelines for treatment of chronic headache, the Japanese Society of Neurology (http://www.neurology-jp.org/guideline/headache/index.html) also placed triptan agents as the most effective drugs for the treatment of migraine and cluster headache, also from an EBM perspective.

REFERENCES


