Editorial Commentary

**Sumatriptan relaxes isolated porcine ophthalmic artery**

The paper by MB Vincent et al. in this issue represents a further piece of investigation on the mechanism of action of sumatriptan. It focuses on the efficacy of the drug in aborting cluster headache (CH) attacks, a clinical condition for which sumatriptan is highly effective and now represents the treatment of choice. The authors have chosen porcine ophthalmic artery (POA) for evaluating the vascular effects of sumatriptan, since CH is characterized by marked oculovascular abnormalities. Therefore, the in vitro experimental model results in a reliable method for characterizing the activity of sumatriptan on ocular vessels. The drug was tested on CGRP- and VIP-induced POA relaxation, the results indicating that the drug is unable to inhibit CGRP-induced relaxation. Activation of peripheral trigeminal fibers has been proposed as a possible pathogenetic mechanism for migraine and CH attacks. Such depolarization induces vasodilatation and plasma protein leakage (neurogenic inflammation) through the release of vasodilator and permeability promoting peptides (CGRP and SP). Based on previous findings and on the data reported in this paper, sumatriptan seems not to act via a vasoconstrictor mechanism. A neuronal, prejunctional mechanism via autoreceptors on trigeminal fibers appears more likely. The authors also report that sumatriptan inhibits VIP-induced relaxation. The discussion on this finding is focused on the possible secondary activation of parasympathetic fibers releasing VIP during CH attacks. Relaxation induced by VIP is known to be endothelium-independent and to act via cyclic AMP. Sumatriptan inhibits cyclic AMP accumulation in canine saphenous vein. These pharmacological properties may well explain why sumatriptan inhibits VIP-induced relaxation. The paper by MB Vincent et al. offers an interesting model for further studies on the relevance of autonomic responses during CH attacks and on different mechanisms of action of sumatriptan on such a complex clinical condition.

M Gabriella Buzzi

**Sumatriptan and vasoconstriction**

The data concerning norepinephrine (NE) amplified vasoconstriction after the local (hand vein) or systemic (subcutaneous) administration of sumatriptan (provided by Panconesi and colleagues in this issue) appear worthy of note, since (i) increased NE-induced vasoconstriction is demonstrated 1 h after the systemic administration of sumatriptan and (ii) the "clinical" doses of sumatriptan used are shown to be incapable of inducing vasoconstriction if given alone. Previous studies regarding drugs such as NE and monamine-oxidase inhibitors (imipramine, paraglyline) indicate that these drugs strongly potentiate NE and 5HT vasoconstriction (1), but display poor symptomatic and prophylactic activity in migraine. On the other hand, 5HT itself, which the present study demonstrates is 500-1000 times more effective than sumatriptan in contracting vein as well as in potentiating NE-induced vasoconstriction, does not produce the major therapeutic effects in acute migraine attacks which characterize sumatriptan. By considering the poor acute therapeutic action of both noradrenergic compounds and 5HT and their strong vasoconstrictive action it seems that the activity of 5HT agonist drugs such as sumatriptan may be independent of vasoconstriction. The sumatriptan potentiation of NE-induced vasoconstriction observed in Panconesi's study, and the already demonstrated NE potentiation of ergotamine vasoconstriction are two noteworthy phenomena in that they both suggest: (i) greater attention should be paid to possible dynamic interaction between 5HT agonist and NE, which may be especially important when occurring in specific brain regions, and (ii) since small amounts of sumatriptan enter the brain in animals (2), a 5HT/NE interpotentiation may play a role particularly in "circumventricular structures", where the blood brain barrier is largely fenestrated (3) and analgesic pathways are present. The vasoconstriction test used in this work, which was introduced 29 years ago (4) and stimulated much research, has proved again to be a good model for our understanding the action of serotonergic drugs in migraine subjects.

References


Maria Nicolodi

**Genetics of migraine**

Genetic analysis by modern techniques has led to the classification of the molecular basis for an ever-increasing number of