[S1-2] *[4/21/2000 (Fri) 09:50~10:30/Byulkwan Auditorium, Bldg 26]*

Migraine and Antimigraine Drugs

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It has been universally accepted that dilated and engorged cranial blood vessels caused migrainous pain, and that vasoconstriction provided headache relief. Over the past several years, however, accumulating evidence has shifted the emphasis away from the vascular smooth muscle hypothesis and towards mechanisms related to activation of meningeal afferents, neuropeptide release, and neurogenic inflammation.

The trigeminal nerve transmits migraine headache from blood vessels of the dura mater. Triggers of this pain are not well understood, but probably are multiple and largely chemical and develop within the brain parenchyma, the blood vessel wall, and the blood itself. These unknown triggers stimulate the trigeminovascular nerve fibers, causing pain and releasing vasoactive neuropeptides (e.g. substance P, neurokinin A, and calcitonin gene-related peptide) from perivascular nerve fibers. Released neuropeptides activate endothelial cells, mast cells, and platelets, and mediate the neurogenic inflammation including the endothelium-dependent vasodilation and the enhanced permeability. Electric stimulation of trigeminal ganglion or intravenous administration of capsaicin induced neurogenic plasma protein extravasation within the dura mater. This extravasation was markedly attenuated or absent in animals whose perivascular afferent fibers have been destroyed by capsaicin treatment during the neonatal period. Antimigraine drugs such as sumatriptan and dihydroergotamine significantly reduced the neurogenic plasma protein extravasation via prejunctional mechanisms involving 5-HT_{1D} receptors or analogous 5-HT_{1B} receptors in rats. The plasma protein extravasation was also significantly reduced by sodium valproate as well as by NK_1 receptor antagonist.

Introduction of sumatriptan for the treatment of migraine signaled the start of a new era in the management of this common disabling disorder. A range of compounds which were developed for the treatment of migraine and whose structure is based on 5-HT are called triptans as a group. Sumatriptan was the first triptan available in clinical practice. Because there is wide clinical experience and extensive research with sumatriptan, it is considered the standard by which other 5-HT

agonists are compared. Sumatriptan has low bioavailablity and variable absorption rate, and the oral form at the maximum of 100 mg is clinically effective in barely two-thirds of patients. Sumatriptan is contraindicated in patients with a history of cardiovascular disease due to the chest pain caused by coronary artery vasoconstriction. Therefore, the development of the new triptans (zolmitriptan, naratriptan, rizatriptan, eletriptan, frovatriptan, etc) has been aimed at improvement in clinical efficacy and reduction in incidence of adverse effects. It has also stimulated basic research on the possible mechanisms underlying migraine.

Future therapies for acute episodes of migraine include other triptans and agents which do not constrict blood vessels but work via other mechanisms such as inhibiting neurogenic inflammation or preventing vasodilation. These include 5-HT_{1F} agonists, neurosteroids and nitric oxide synthase (NOS) inhibitors.

In conclusion, neurogenic inflammation in dura mater is important not only in the pathophysiology of migraine and related headaches but also to the action of antimigraine drugs, and further, the selective blockade of sensory neuropeptides, both their release and binding, are potential targets for new generation of antimigraine medications.