Preclinical Neuropharmacology of Naratriptan

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ABSTRACT

The basic CNS neuropharmacology of naratriptan is reviewed here. Naratriptan is a second-generation triptan antimigraine drug, developed at a time when CNS activity was thought not to be relevant to its therapeutic effect in migraine. It was, however, developed to be a more lipid-soluble, more readily absorbed and less readily metabolized variant on preexisting triptans and these variations conferred on it a higher CNS profile. Naratriptan is a 5-HT<sub>1B/1D</sub> receptor agonist with a highly selective action on migraine pain and nausea, without significant effect on other pain or even other trigeminal pain. Probable sites of therapeutic action of naratriptan include any or all of: the cranial vasculature; the peripheral terminations of trigeminovascular sensory nerves; the first-order synapses of the trigeminovascular sensory system; the descending pain control system; and the nuclei of the thalamus. Naratriptan may prevent painful dilatation of intracranial vessels or reverse such painful dilatation. Naratriptan can prevent the release of sensory peptides and inhibit painful neurogenic vasodilatation of intracranial blood vessels. At the first order synapse of the trigeminal sensory system, naratriptan can selectively suppress neurotransmission from sensory fibers from dural and vascular tissue, while sparing transmission from other trigeminal fibers, probably through inhibition of neuropeptide transmitter release. In the periaqueductal gray matter and in the nucleus raphe magnus, naratriptan selectively activates inhibitory neurons which project to the trigeminal nucleus and spinal cord and which exert inhibitory influences on trigeminovascular sensory input. Naratriptan has also a therapeutic effect on the nausea of migraine, possibly exerting its action at the level of the nucleus tractus solitarius via the same mechanisms by which it inhibits trigeminovascular nociceptive input. The incidence of naratriptan-induced adverse effects in the CNS is low and it is not an analgesic for pain other than that of vascular headache. In patients receiving selective serotonin uptake inhibitors (SSRIs) naratriptan may cause serotonin syn-
drome-like behavioral side effects. The mechanism of action involved in the production of behavioral and other CNS side effects of naratriptan is unknown.