project in the quintothalamic tract and, after decussating in the brainstem, synapse on neurons in the thalamus. Important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus.

Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene–related peptide (CGRP), at vascular terminals of the trigeminal nerve and within the trigeminal nucleus. CGRP receptor antagonists, *gepants*, have now been shown to be effective in the acute and preventive treatment of migraine, and four monoclonal antibodies to CGRP, or its receptor, have been shown to be effective in migraine prevention. Centrally, the second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus for further processing. Additionally, there are projections to the periaqueductal gray and hypothalamus, from which reciprocal descending systems have established antinociceptive effects. Other brainstem regions likely to be involved in descending modulation of trigeminal pain include the nucleus locus coeruleus in the pons and the rostroventromedial medulla.

Pharmacologic and other data point to the involvement of the neurotransmitter 5-hydroxytryptamine (5-HT; also known as *serotonin*) in migraine. In the late 1950s, methysergide was found to antagonize certain peripheral actions of 5-HT and was introduced, based on its anti-inflammation properties, as a migraine preventive. The *triptans* were designed to stimulate selectively subpopulations of 5-HT receptors; at least 14 different 5-HT receptors exist in humans. The triptans are potent agonists of 5-HT_{1B} and 5-HT_{1D} receptors, and some are active at the 5-HT_{1F} receptor; the latter's exclusive agonists are called *ditans*. Triptans arrest nerve signaling in the nociceptive pathways of the trigeminovascular system, at least in the trigeminal nucleus caudalis and trigeminal sensory thalamus, in addition to promoting cranial vasoconstriction, whereas *ditans*, now shown conclusively to be effective in acute migraine, act only at neural and not vascular targets. A range of other neural targets are currently under investigation for the acute and preventive management of migraine.