The relationship between gamma-aminobutyric acid (GABA) and migraine headache has been suggested by several areas of research. More than 25 years ago GABA levels in cerebrospinal fluid were shown to be elevated only during migraine attacks as compared with tension-type headache. Furthermore, GABAergic compounds such as valproate, baclofen, and propofol have been shown to have antimigraine activity. Valproate and propofol act at GABA_A receptors and baclofen is a brain-penetrant compound that acts at GABA_B receptors. GABA is a major inhibitory amino acid in the central nervous system, and both GABA_A and GABA_B receptors have been implicated in the modulation of pain. GABA receptors are found in the central nervous system and glutamic acid decarboxylase, which is responsible for GABA synthesis, has been found in the cat trigeminal nucleus caudalis.

This study characterized GABA receptors on cells in craniovascular nociceptive pathways by recording the responses of L-glutamate-driven cells in the trigeminal nucleus caudalis of the cat. These cells also responded to electrical stimulation of the superior sagittal sinus (SSS) and to GABA agonists and antagonists. Through microiontophoresis, GABA agonists and antagonists were applied directly onto the neurons, and their responses recorded with a tungsten wire electrode. Specifically, the following compounds were tested: GABA, muscimol (GABA_A receptor agonist), baclofen (GABA_B receptor agonist), N-methylated bicuculline (GABA_A receptor antagonist), and 2-hydroxysaclofen (GABA_A receptor antagonist). N-methylated bicuculline was used because of its higher potency and solubility as compared with bicuculline. Similarly, 2-hydroxysaclofen was used instead of the archetypical GABA_B receptor antagonist, phaclofen, because it is more potent, soluble, and selective than phaclofen.

Some cells responding to supramaximal electrical stimulation of the SSS were also activated by microiontophoretically applied L-glutamate. Dose-dependent inhibition of these cells was found after the application of either GABA (n = 32) or muscimol (n = 18) or both, but not controls. The inhibition by GABA was reversed by N-methylated bicuculline, but not by 2-hydroxysaclofen in all cells tested (n = 20 and n = 12, respectively). N-methylated bicuculline also was able to reverse muscimol inhibition (n = 18). Baclofen inhibition of L-glutamate activation (n = 5) could be reversed by 2-hydroxysaclofen. However, the number of cells in which this occurred was small (n = 3) and the affected cells were characterized as having low threshold mechanoreceptor/wide dynamic range input.

GABA appears to modulate nociceptive input to the trigeminocervical complex, primarily through GABA_A receptors. GABA_A receptors may, therefore, be a potential therapeutic target for the treatment of primary headache disorders.

REFERENCES


PROCEEDINGS

GABA_A RECEPTORS APPEAR TO MODULATE NOCICEPTIVE NEUROTRANSMISSION IN THE TRIGEMINOCERVICAL COMPLEX

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