The role of glutamate in trigeminal nociception and migraine pathogenesis

On the analogy of dorsal root and dorsal horn spinal nociceptive neurons, a broad range of glutamate receptors are expressed on the surface of the trigeminal ganglia and also the caudal trigeminal nucleus. The findings that trigeminal stimulation induces glutamate release within the caudal trigeminal nucleus, accompanied by an increased expression of neuronal activity marker FOS, and that this increase in FOS can be mitigated by glutamate receptor inhibitors clearly demonstrate the mediatory role of glutamate in the transmission between the first- and second-order nociceptive neurons within the caudal trigeminal nucleus.

Alterations in glutamate homeostasis have been reported in individuals with migraine. Reports concerning plasma levels are rather inconclusive. Platelet and cerebrospinal fluid (CSF) glutamate levels have more consequently been found elevated during both intervals and attacks. The predominant findings of elevated glutamate levels in individuals with migraine suggest that altered glutamate homeostasis might contribute to the pathogenesis of migraine-type headaches, with particular regard to migraine with aura, where the elevations are more pronounced and more frequently reported.

To date, mutations of three genes have been associated with familial migraine, all of them leading to an increased susceptibility to cortical spreading depression via an enhanced synaptic glutamate release (CACNA1A; alpha-1 subunit of the neuronal voltage-gated Ca2+ channels Ca(V)2.1), a reduced extent of synaptic glutamate and K+ removal (ATP1A2; alpha-2 subunit of the Na+, K+ ATPase) or an elevated extracellular K+ level (SCNA1A; alpha-1 subunit of the neuronal voltage-gated Na+ channels Na(V)1.1). Recent genome-wide association studies also revealed the association of common migraine with MTDH/AEG-1 (metadherin/astrocyte elevated gene-1) and LRP1 (low density lipoprotein-related protein 1), which are involved in the regulation of synaptic glutamate uptake and transmitter-dependent postsynaptic glutamate signalling, respectively.

Both the elicitation and the propagation of cortical spreading depression are known to develop in consequence of glutamatergic mechanisms, and particularly through the activation of NMDA (N-methyl-D-aspartate) receptors, since NMDA receptor blockers inhibit cortical spreading depression, whereas non-NMDA receptor blockers do not. Moreover, glutamate has been found to be released to the cortical interstitium during cortical spreading depression under both ex vivo and in vivo conditions. The findings of two recent studies indicate direct connections between cortical spreading depression and the activation of meningeal nociceptors and central trigeminovascular neurons, which tends to confirm the early observations of Moskowitz et al. and Ivanov et al. The stimulation of trigeminal afferents leads to the development of extended mechanical and thermal cutaneous allodynia and hyperalgesia, a phenomenon due to the central sensitization of trigeminal and thalamic nociceptive neurons mediated at least in part by NMDA receptors. The activities of brainstem migraine generators, including the nucleus raphe magnus, the periaqueductal gray, the locus coeruleus and the dorsal raphe nucleus, are also related to glutamate-mediated neurotransmission. These data collectively indicate the contribution of glutamate to the development of the main pathophysiological hallmarks of migraine, including cortical spreading depression, trigeminovascular activation, central sensitization of the higher-order sensory neurons, and activation of brainstem migraine generator nuclei.
Correspondingly, glutamate receptor antagonists have proved efficacious against aura in familial hemiplegic migraine, and also against attacks in common migraine. Furthermore, topiramate, a well-known glutamate antagonist, has been found effective as prophylactic therapy in a randomized clinical trial. Interestingly, however, all effective prophylactic therapies have recently been demonstrated to decrease plasma glutamate levels in migraineurs. These data suggest that glutamate takes part in the initiation of migraine attacks, and that plasma glutamate level may serve as biomarker for therapy responsiveness.