ATP AS A SIGNALLING MOLECULE IN TRIGEMINAL PAIN

Stefania Ceruti[1], Marta Fumagalli[1], Giovanni Villa[1], Claudia Verderio[2], Maria P. Abbracchio[1]

[1]Department of Pharmacological Sciences – University of Milan – Milan, Italy
[2]CNR Institute of Neuroscience, Milan, Italy

Migraine is a common, highly incapacitating, and life-long disease affecting more than 10% of population (Pietrobon, 2005). Despite the availability of new pharmacological approaches, a significant percentage of migraineurs is insensitive to therapy, suggesting that yet-unidentified molecular pathways are involved. ATP represents a likely candidate signalling molecule in migraine pain, in agreement with its key role as an algogenic transmitter in chronic and acute pain situations through the activation of specific membrane receptors (the P2 receptors; Burnstock, 2006). Since it is now recognized that migraine pain primarily depends on the activation of sensitive afferent fibers from trigeminal ganglia (TG) innervating meningeal blood vessels, we have evaluated the presence and function of P2 purinoceptors (with a special focus on metabotropic P2Y receptors) in mixed neuron-glia primary cultures from mouse TG. Immunocytochemistry revealed that about 10% of cells were neurons, with the great majority (94.5%) being small/medium size sensitive neurons, and only the 5% belonging to the large size neuron subgroup. Moreover, over the 75% of the total cell population were satellite glial cells (SGCs) which surrounded and wrapped neurons, therefore maintaining to some extent the anatomical organization that is observed in TG in vivo. Concerning the presence and function of P2 receptors, ionotropic $P2X_2/P2X_3$ receptors were only functionally expressed by neurons in agreement with literature data. All the P2Y receptors cloned from rodent tissue were detected by RT-PCR (i.e., $P2Y_{1,2,4,6,12,13,14}$). Single cell calcium imaging experiments demonstrated that 8.5±3.9% of neurons and 78±5% of SGCs responded to ADP and 2MeADP application, suggesting the presence of functional $P2Y_1$ and $P2Y_{12,13}$ subtypes (as also confirmed by selective antagonists). Moreover, 83±4% of SGCs and 13±4.1% of neurons responded to UTP (i.e., through the $P2Y_2/P2Y_4$ subtypes), while only 21±7% of SGCs and no neurons were sensitive to UDP (acting on the $P2Y_6$ receptor). Finally, a 24-hour exposure to a known pro-algogenic substance (bradykinin) significantly enhanced P2Y-mediated calcium responses in SGCs, while downregulating the number of neurons responding to a $P2X_3$ agonist. Taken together, our results demonstrate that in mouse TG P2Y receptors contribute to ATP-mediated calcium signalling. Additional studies on the interactions between purinergic signalling and known pro-algogenic pathways in neurons and SGCs might therefore help identifying new potential targets for the development of effective anti-migraine therapies.

Burnstock G. (2006) Pharmacol. Ther. 110: 433-454; Pietrobon D. (2005) Neuroscientist 11: 373-386.