doses of lithium or valproate. Although further investigations are necessary, our results show the neuroprotective effect of lithium and valproate against neural cell death induced by extracellular ATP, probably through a different pathway, and suggest novel uses of these drugs in neurodegenerative diseases.

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Modulation of purinergic signaling by algongens in cultures from trigeminal sensory ganglia

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An increasing number of studies indicate that glial cells, in both sensory ganglia and in the central nervous system, play an important role in the generation and maintenance of pathological pain. In sensory ganglia, satellite glial cells envelop the cell bodies of primary sensory neurons forming a morphological and functional unit, allowing a non-synaptic cell-to-cell communication. Among the various pain mediators that contribute to neuron-to-glia signaling within sensory ganglia (i.e., SP, CGRP, bradykinin), adenine and uracil nucleotides acting via the P2X and P2Y receptors represent a relatively new and interesting class of molecules. It is now widely accepted that the $P2X_3$ channel plays a fundamental role in ATP-mediated painful signals. However, evidence is emerging that P2Y receptors may also participate to pain [1]. We are currently studying the role of these receptors in cell-to-cell communication in trigeminal ganglia, an important station for pain maintenance and integration in various painful situations, including migraine. We have previously reported the presence of functional neuronal $P2X_3$ as well as of ADP-sensitive $P2Y_{1,12,13}$ and UTP-activated $P2Y_2$/$P2Y_4$ receptors in mixed primary trigeminal cultures on both neurons and glia. Moreover, a chronic exposure (i.e., 24 h) to the algogen bradykinin (BK, 100 nM) significantly enhanced the functionality of glial $P2Y_{1,2,4}$ receptor subtypes [2]. Since in our model BK receptors are functional on neurons only, we hypothesized that BK is able to stimulate the neuronal release of a chemical mediator which can, in turn, increase P2Y receptor activity on glial cells. Our results suggest this mediator to be CGRP because (1) this peptide is extracellularly released by BK, (2) exogenously added CGRP fully mimics the BK-mediated potentiation of P2Y receptor function, and (3) the CGRP antagonist CGRP8-37 completely prevents BK-mediated effects. Application of CGRP led to the activation of the ERK 1/2 signaling pathway, which could be then linked to P2Y receptor potentiation. Taken together, our data indicate that P2Y receptors may significantly participate to neuron-to-glia communication in trigeminal ganglia and that they can be modulated by algogens released during chronic pain states. Therefore, we believe that P2Y receptors might represent new potential therapeutic targets for the development of innovative analgesic drugs, especially for migraine.

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