CALCIUM-REGULATED GLUTAMATE EXOCYTOSIS FROM ASTROCYTES: A TWO-FACETED ROLE IN NORMAL AND PATHOLOGICAL NEURON-GLIA COMMUNICATION

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Astrocytes often ensheath synapses with fine processes expressing receptors for neurotransmitters and other mediators. Such astrocyte receptors are in the position to sense neuronal activity and translate it into intracellular calcium ([Ca2+]i) elevations which, in turn, start local or long-range glial communication, notably by glutamate release. Stimulation of G protein-coupled receptors such as purinergic receptor P2Y1 (Domercq et et al., JBC, 2006) or the chemokine stromal cell-derived factor-1 receptor CXCR4, trigger Ca2+-dependent glutamate exocytosis in astrocytes. Such process peculiarly implicates TNFa and prostaglandin E2 (PGE2) as necessary, sequential intermediates. TNFa and PGE2 act as autocrine/paracrine factors amplifying intracellular [Ca2+]i rises responsible for glutamate release. In hippocampal slices, PGE2-evoked glutamate release from astrocytes elicits [Ca2+]i responses in neighbouring neurons, thereby providing a modulatory input to the ongoing activity. In pathological conditions this pathway may become neurotoxic. Thus, when glial cells are “reactive” (e.g. during inflammation) and microglia migrates in apposition to astrocytes, CXCR4 stimulation is followed by a significantly higher TNFa production and, as a consequence, by potentiated astrocyte glutamate release, which triggers neuronal apoptosis (Bezzi et al., Nature Neurosci., 2001). This CXCR4-dependent intercellular death cascade can be activated by the HIV-1 coat glycoprotein, gp120IIIB and play a role in the pathogenesis of AIDS dementia. Agents interfering with it provide neuroprotection both in vitro and in vivo.