Cytokines receptors as modulators of the excitatory synapse: focus on Interelukin-1 receptor type I

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Pro-inflammatory cytokines have been acknowledged as potential triggers of functional changes leading to cognitive decline, memory impairment as well as increased susceptibility to neurodegenerative and psychiatric disorders. These changes rise from the disruption of the delicate balance between the production of inflammatory mediators by immune cells and the ability of neurons to sense them through the expression of specific receptors.
Interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) receptors and many others are expressed on neurons and involved in various functions ranging from neurotransmission to cell survival. Indeed, pro-inflammatory cytokines exert a direct functional interaction with specific neurotransmitter systems. We have recently described a dynamic and functional interaction between the IL-1ß signalling system (IL-1 receptor type I and accessory proteins) and the NMDA receptor (NMDAR) complex; TNF-α similarly modulates the AMPA receptor (AMPAR). Intriguingly, NMDARs and AMPARs are critically involved in numerous cognitive and functional processes as well as synaptic plasticity, and these events can also be modulated by IL-1ß through IL-1RI. In particular, we have found that IL-1RI receptors co-localise with, and bind NMDARs in a specific and highly organised compartment of the glutamatergic synapse: the postsynaptic density. Moreover, IL-1RI interactions with NMDARs and its localisation at the synaptic membranes can be dynamically modulated in primary hippocampal neurons. Here we discuss the hypothesis that the expression and distribution of cytokine receptors might contribute to shape the molecular structure of the synapse and define a neuronal 'immunophenotype'. In this scenario, neurons might allow the immune response to be integrated with specific functions, such as neurotransmission and synaptic plasticity, by translating the immune response into behaviour.