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The Functions of ATP Receptors in Pain Signaling and Drug Development

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Neuropathic pain is a highly debilitating chronic pain that occurs after nerve injury and is resistant to currently available treatments. We have shown that activating P2X4R upregulated in spinal microglia after nerve injury contributes to neuropathic pain (Nature, 2003), and the stimulation of P2X4Rs causes release of brain-derived neurotrophic factor (BDNF) evoking a collapse of their transmembrane anion gradient and the subsequent neuronal hyper-excitability (Nature, 2005). These receptors are expressed in activated microglia in response to peripheral nerve injury, but the mechanisms underlying activation of microglia following nerve injury remains to be determined. We recently found that a single intrathecal administration of IFN-γ to normal animals produces a long-lasting tactile allodynic behavior and activation of microglia in the spinal cord (PNAS, 2009). The expression of IFN-γ receptor mRNA in the spinal cord is localized predominantly in microglia. IFN-γ evoked P2X4 up-regulation in microglia. Furthermore, IFN-γ receptor-deficient mice (ifngr-/-) exhibited a striking reduction in nerve injury-induced tactile allodynia and in the increase in microglial cells with hypertrophic morphology. Activated spinal microglia also express $P2Y_{12}R$. It was demonstrated that intrathecally administered P2Y12 receptor antagonists or antisense oligonucleotide for P2Y12 receptors significantly suppressed development of neuropathic pain after spinal nerve injury. A crucial finding was established using P2Y12-knockout mice. Genetic ablation of P2Y12 receptors failed to produce tactile allodynia. Strategic advances in targeting P2Y12 receptors were considered because of its restricted expression in the CNS. Several lines of evidence revealed that P2Y12 receptor expression is specifically observed in brain and spinal cord resident microglia but is not observed in fms- or CD11b-positive peripheral macrophages in spleen (Haynes et al., 2006; Kobayashi et al., 2006; Pausch et al., 2004; Sasaki et al., 2003). In line with these facts, we could consider that P2Y12 receptor inhibition results from P2Y12 receptor-gated signal modulation in the CNS. These ATP receptors may have great potential for medicines against neuropathic pain.