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### **The role of P2X<sub>7</sub> ATP receptors in the nervous system: potential implications in inflammatory and depression-like diseases**

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#### **Background**

The P2X<sub>7</sub> receptor is a ligand-gated ion channel expressed in neuronal, glial and immune cells and is implicated in a wide range of pathological conditions, including ischemia, and inflammation. The P2X<sub>7</sub> receptor can modulate the maturation and release of the proinflammatory cytokine, interleukin-1 $\beta$  (IL-1 $\beta$ ). IL-1 $\beta$  is suggested to be involved in the pathophysiology of depression and sickness behaviour, elicited by peripherally administered bacterial lipopolysaccharide (LPS).

#### **Methods**

The levels of IL-1 $\beta$  production were quantified in the hippocampi of rodents, using an ELISA kit. In order to identify genes involved in LPS-induced changes in P2X<sub>7</sub> receptor knock-out (KO) and wild-type (WT) mouse amygdala we performed whole mouse genome microarray analysis of mRNA extracted after six hours of intraperitoneal LPS injection.

#### **Results**

We showed that *in vivo* LPS challenge elevated IL-1 $\beta$  levels in the rodent hippocampus. Antagonists of P2X receptors inhibited LPS-induced IL-1 $\beta$  levels with a pharmacological profile similar to that of P2X<sub>7</sub> receptors and their inhibitory effect was attenuated in the absence of P2X<sub>7</sub> receptors. In WT mice, LPS overexpressed mRNA encoding P2X<sub>4</sub> and P2X<sub>7</sub> receptors in the hippocampus and also caused a remarkable increase in the levels of IL-1 $\beta$  in the blood serum. The hippocampal increase of IL-1 $\beta$  was substantially alleviated when contamination by circulating blood cells was excluded by transcardial perfusion, indicating the peripheral origin of hippocampal IL-1 $\beta$  elevation. Six h after i.p. injection of LPS, the expression of 74 transcripts (41 upregulated and 33 downregulated) was significantly altered two-fold or more in mouse amygdala. These genes can be classified according to their biological function as follows: inflammatory response: Il4ra, Ccl21b; depression-associated genes: Slc17a7, Nfatc1, Creb3l3. Our microarray studies have identified 8,165 transcripts that were significantly affected by the deficiency of P2X<sub>7</sub> receptors indicating that the deletion of P2X<sub>7</sub> receptors causes genome-wide alterations of gene expression including depression-related genes in mouse amygdala (GABA<sub>A</sub>, GABA<sub>C</sub> receptors, AMPA and NMDA<sub>2B</sub> ionotropic and mGlu<sub>5</sub>, mGlu<sub>7</sub> metabotropic glutamate receptors were downregulated in KO mice).

#### **Conclusions**

These results point to the key role of the endogenous activation of P2X<sub>7</sub> receptors in the level of IL-1 $\beta$  and in the regulation of individual protein which could be of potential interest for the study of the neurobiological basis underlying psychiatric diseases like depression.