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Meeting abstract

The role of $P2X_7$ ATP receptors in the nervous system: potential implications in inflammatory and depression-like diseases

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Background

The $P2X_7$ 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 $P2X_7$ receptor can modulate the maturation and release of the proinflammatory cytokine, interleukin-1β (IL-1β). IL-1β 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-1β production were quantified in the hippocampi of rodents, using an ELISA kit. In order to identify genes involved in LPS-induced changes in $P2X_7$ receptor knock-out (KO) and wild-type (WT) mouse amygdala we performed whole mouse genome microarray analysis of mRNA extracted after six hours of intaperitoneal LPS injection.

Results

We showed that *in vivo* LPS challenge elevated IL-1β levels in the rodent hippocampus. Antagonists of P2X receptors inhibited LPS-induced IL-1β levels with a pharmacological profile similar to that of $P2X_7$ receptors and their inhibitory effect was attenuated in the absence of $P2X_7$ receptors. In WT mice, LPS overexpressed mRNA encoding $P2X_4$ and $P2X_7$ receptors in the hippocampus and also caused a remarkable increase in the levels of IL-1β in the blood serum. The hippocampal increase of IL-1β was substantially alleviated when contamination by circulating blood cells was excluded by transcardial perfusion, indicating the peripheral origin of hippocampal IL-1β 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 $P2X_7$ receptors indicating that the deletion of $P2X_7$ receptors causes genome-wide alterations of gene expression including depression-related genes in mouse amygdale ($GABA_A$, $GABA_C$ receptors, AMPA and $NMDA_{2B}$ ionotropic and $mGlu_5$, $mGlu_7$ metabotropic glutamate receptors were downregulated in KO mice).

Conclusion

These results point to the key role of the endogenous activation of $P2X_7$ receptors in the level of IL-1β 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.