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Invalidation of 5-HT_{2B} receptors on microglia impairs microglia processes motility

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Context: Microglia interacts with synapses and contribute to synaptic plasticity, nevertheless we don't know yet how this interaction is regulated. Previous results of the laboratory showed that 5-HT_{2B} receptor is the main serotonin (5-HT) receptor expressed in microglia in culture. This receptor is also expressed in some dopaminergic and serotonergic neurons. Moreover, we showed that a local application of 5-HT on acute brain slices induces an attraction of microglial processes. This attraction could serve to guide microglial processes towards synaptic remodeling areas. We observed that in mice lacking 5-HT_{2B} receptor expression (Htr2b^{-/-}-mice), this attraction was lost. So, this receptor is required, but as Htr2b gene is expressed in different cell types, further experiments are required to understand the mechanism and signaling pathways involved.

Objectives: We aim at determining whether the effect of 5-HT on the outgrowth of microglial processes is direct or not, and at deciphering the signaling pathways involved. Indeed, it has been shown that the 5-HT_{2B} receptor is coupled to a Gq protein in transfected cells but we don't know yet its coupling in microglia in vivo.

Results: We first tested the response of microglia to serotonin in brain slices from mice with invalidation of Htr2b gene in microglia only (Cx3cr1creERT2^{+/+};Htr2b^{fl/fl}), and observed that the effect of serotonin on directional motility was abolished. We checked that the response of microglia processes to ATP was normal, indicating that the lack of response to serotonin is not due to a general loss of microglial morphological plasticity in these mice. Thus, the effect of 5-HT on microglia motility directly requires microglial 5-HT_{2B} receptors. However, as the microglial response toward 5-HT is similar to the response to ATP, we investigated a potential role of the purinergic system. Surprisingly, by using antagonists of purinergic receptors, the microglia processes attraction toward a local application of 5-HT is abolished.

Discussion: Our results show that the morphological effect of 5-HT on microglia is direct, through the microglial 5-HT_{2B} receptor. Nevertheless, this mechanism also involves the purinergic signaling pathway. To better understand how the 5-HT and ATP signaling pathways both contribute to microglial processes attraction toward 5-HT, we are investigating which purinergic receptor is involved in this mechanism. We will then investigate whether these two receptors dimerize together in order to lead to microglial response to 5-HT. Nevertheless, it is necessary not to exclude a potential role of ATP released by astrocytes as an indirect response to the local application of 5-HT.

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