Glial cells and pharmacological targets in Sandhoff disease

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Sandhoff disease (SD) is a genetic disorder caused by a mutation in the beta-hexosaminidase B (*HEXB*) gene in humans. This results in the massive accumulation of GM2 gangliosides in the nervous system, causing progressive neurodegeneration. The symptoms of SD include muscle weakness, seizures, and mental illness; along with loss of muscle coordination, vision, and hearing. In the most severe form, the onset begins during early infancy, and death usually occurs within 2-5 years of age. The established animal model, *Hexb*-deficient ($Hexb^{-/-}$) mouse, shows abnormalities that resemble the severe phenotype found in human infants. We have previously reported that activated microglia causes astrogliosis in $Hexb^{-/-}$ mouse at the early stage of development that can be ameliorated via immunosuppression. Moreover, within the cerebral cortices of $Hexb^{-/-}$ mouse, reactive astrocytes were found to express adenosine A_{2A} receptors in later inflammatory phases. Inhibiting this receptor with istradefylline decreases the number of activated microglial cells and inflammatory cytokines/chemokines. Thus, we underline the importance of the astrocytic A_{2A} receptor as a sensor, in regulating microglial activation in the late phase of inflammation.