PPARγ agonists as therapeutic agents in demyelinating disorders: study of the protective effects in oligodendrocytes under stress conditions

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Peroxisome proliferator activated receptor-γ (PPARγ) is a nuclear receptor involved in the control of reproduction, metabolism, development and immune response. Several lines of evidence suggest that PPARγ natural and synthetic agonists may control brain inflammation and be of potential therapeutic use in human brain diseases such as demyelinating diseases.

In the present study we sought to investigate the effects of PPARγ on oligodendrocyte cultures in conditions resembling to those found in demyelinating disease.

We have previously shown that natural (15d-PGJ_2) and synthetic (pioglitazone) agonists of PPARγ increase intrinsic cellular mechanisms protecting oligodendrocyte (OL) progenitors (OPs) from oxidative insults and promote their differentiation to OLs. In addition, PPARγ agonists potentiate mitochondrial activities, as the mitochondrial respiratory chain activity and the regulation of cytoplasmic Ca^{2+} waves, which are known to be crucial for OL differentiation.

In the present study, we investigated the effect of PPARγ agonists against conditions found in demyelinating diseases, such as mitochondrial stress and inflammation.

To induce a mitochondrial impairment in OPs we used the complex I inhibitor rotenone. At a concentration not affecting cell viability, rotenone significantly inhibited OL differentiation and caused a diminution of the % of cells showing oscillatory Ca^{2+} transients induced by ADP-mediated P2Y1 receptor activation. In PPARγ agonist–treated OLs the inhibitory effects of rotenone were significantly attenuated, suggesting a protective effect of the agonists against the mitochondrial toxin.

To mimic inflammatory conditions we used TNFα, an inflammatory cytokine known to retard the differentiating program of OPs. As expected, at concentration not affecting cell viability, TNFα significantly inhibited OL differentiation; in parallel, the cytokine induced a significant reduction of mitochondrial membrane potential and caused a reduction of the % of cells showing an ADP-induced oscillatory Ca^{2+} pattern, suggesting an impairment of the mitochondrial functions. The simultaneous treatment with TNFα and PPARγ agonists significantly reverted TNFα effects.

These findings suggest that PPARγ agonists protect OLs and promote myelination through several mechanisms, including those involving mitochondrial functions.

In a clinical perspective, these data contribute to validate the utilization of selected PPARγ agonists to treat demyelinating diseases.