Identification and characterization of select oxysterols as ligands for Gpr17

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Abstract

Abstract Background and Purpose: Gpr17 is an orphan receptor involved in the process of myelination due to its ability to inhibit the maturation of oligodendrocyte progenitor cells into myelinating oligodendrocytes. Despite multiple claims that the biological ligand has been identified, it remains an orphan receptor. Experimental Approach: Seventy-seven oxysterols were screened in a cell-free [35S]- GTPgS binding assay using membranes from cells expressing Gpr17. The positive hits were characterised using cAMP, IP1, and calcium mobilisation assays, with results confirmed in rat primary oligodendrocytes. Rat and pig brain extracts were separated by HPLC chromatography and endogenous activator(s) were identified in receptor activation assays. Gene expression studies of Gpr17 and Cyp46a1, the enzymes responsible for the conversion of cholesterol into specific oxysterols, were performed using quantitative real time PCR. Key Results: Eight oxysterols were able to stimulate Gpr17 activity, including the brain cholesterol, 24(S)-hydroxycholesterol. A specific brain fraction from rat and pig extracts containing 24S-HC activates Gpr17 in vitro assays. Expression of Gpr17 during mouse brain development correlates with the expression of Cyp46a1 and the levels of 24S-HC itself. Other active oxysterols have low brain concentrations below effective ranges. Conclusions and Implications: Oxysterols, including but not limited to 24S-HC, could be physiological activators for Gpr17 and thus potentially regulate OPC differentiation and myelination through activation of the receptor.

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