

Cell cycle regulation by sn-1 diacylglycerol lipase (DAGL) in neural stem cells

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An emerging concept in the field of stem cell biology is that the brain endocannabinoid signalling system directs the cell fate specification of neural stem cells (NSC) in the central nervous system (CNS). Neurospheres containing nestin- and sn-1 diacylglycerol lipase (DAGL)-positive NSC expressed both CB1 and CB2 receptors whose activation modulates neurosphere formation and precursor cell proliferation (Molina-Holgado et al., 2007). In addition, oligodendrocyte progenitor cells (OPC) expressed DAGL and DAGL enzymes responsible for the synthesis and degradation of 2-AG. The inhibition of DAGL activity with RHC-80267, a specific pharmacological inhibitor, or disruption of 2-AG synthesis using specific siRNAs against DAG Lipases impairs oligodendrocyte progenitor differentiation (Gomez et al., 2010). Here we show that the pharmacological blockade of the DAGL activity has a key role in regulating the proliferative activity of NSC. For this purpose, we have researched the effects of RHC-80267 (5mM, t=24h) in the cell cycle regulation in NSC. Cultures of NSC (n=3) were prepared from the cortex of embryonic day 16 (ED16) C57BL6 mice (wild type, WT). After exposure to RHC-80267, gene expression levels in NSC from WT were determined by microarray analysis (Gene Chip mouse genome 430A 2.0 array, Affymetrix). Microarray-based gene expression analysis of NSC from WT mice identified a set of novel candidate genes (192 genes), being up regulated or down regulated relative to the functionality of DAGL (NSC RHC-80267 treated vs. NSC control: 3 fold change; pValue: 2.224E-04; Min FDR: 1.4767557) in WT neural stem cells. These genes are specifically involved in the development of neurogenesis. The most significant changes, after blockade of the DAGL, were observed in the following genes: TH1, Radical fringe, CREB1, SIAT8B, Notch, NOTCH2, Neurogenin 2, EGR1, CNTF, HOXA2, Myelin basic protein, EGR2 (Krox20), MEF2C and Hedgehog. In addition, our results indicate that DAGL blockade induced a down regulated expression of several genes involved in NSC positive regulation of cell proliferation (Cyclin D1, Cyclin A and c-Fos). Overall, our data suggest a novel role of endocannabinoids in NSC proliferation and oligodendrocyte differentiation such that constitutive release of 2-AG activates cannabinoid receptors in an autocrine/paracrine way in OPCs, which might have important implications for brain self-repair.

- Molina-Holgado F et al. Eur J Neurosci. 25:629, 2007.
- Gomez O et al. Glia 58:1913, 2010.

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