METABOTROPIC GLUTAMATE RECEPTORS BEYOND THE REGULATION OF SYNAPTIC PLASTICITY: A ROLE IN THE PROLIFERATION AND DIFFERENTIATION OF STEM/PROGENITOR CELLS

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Metabotropic glutamate receptors (mGluRs) are classically considered as "synaptic" receptors, activated by glutamate released from the pre-synaptic terminal. However, recent evidence show the expression of individual mGlu receptors in progenitor cells at differentiation stages that precede synapses formation, and even in cells that do not belong to the Central Nervous System. We will review our recent data on the role of mGluRs in the regulation of proliferation and differentiation of both embryonic as well as neural stem/progenitor cells. Embryonic stem (ES) cells are pluripotent cells isolated from the pre-implantation embryo that can be propagated in vitro as self-renewal cells in the presence of the cytokine LIF, or can be induced to differentiate in virtually all type of somatic cell. When cultured in the presence of LIF, ES cells selectively express mGlu5 receptors, the activation of which support, in collaboration with LIF, the undifferentiated state of ES cells. mGlu5 receptors on ES cells are activated by glutamate that is produced and released in large amounts by cultured ES cells. Pharmacological blockade or knock down of mGlu5 receptors, in the presence of LIF, induces the differentiation of ES cells into mesoderm and endoderm lineages. Differentiation of ES cells, induced by LIF withdrawal and formation of embryoid bodies (EBs), leads to a time-dependent decrease in the expression of mGlu5 receptors and the "de novo" appearance of mGlu4. Cultured EBs differentiate in cells of the three germ layers. Pharmacological activation of mGlu4 receptors modulate differentiation of EBs in a context-dependent manner, favouring neuronal differentiation only in the presence of neuronal cues, as retinoic acid or chemically defined media supplemented with pro-neural factors. When ES cells are induced to differentiate directly into cells of the neural lineage, skipping the formation of EB, the expression of mGlu5 receptors is retained through all the differentiation procedure. In this context, the pharmacological blockade of mGlu5 receptors favours neuronal differentiation, increasing the number of both nestin$^+$ and Glutamic Acid Decarboxylase 65/67$^+$ cells. Neural progenitor cells isolated from the subventricular zone of 4-5 PND-old mice and cultured as undifferentiated neurospheres, in the presence of mitogens, express mGlu3 and mGlu5 receptors, the activation of which maintain cell proliferation and survival. Activation of mGlu3 receptors on neurospheres induced to differentiate into glial cells alters differentiation into mature astrocytes and favours the appearance in culture of proliferating progenitors similar to the GFAP$^+$ progenitor cells detected in zones of active neurogenesis in the adult brain.