Involvement of Sphingosine 1 Phosphate receptor on the Blood Brain Barrier properties upon inflammatory stimuli?

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The blood brain barrier (BBB) maintains the proper environment and facilitates the central nervous system (CNS) functions. The principal cellular constituents are endothelial cells, astrocytes and perycites, and they all interact to increase its barrier's properties. Several CNS affections involve the BBB either primarily or as a consequence of the disease. In multiple sclerosis (MS), for instance, leaky BBB together with demyelinated multifocal lesions are the typical hallmarks. Several pharmacological approaches have been developed to modify the course of MS, and recently the immune modulator fingolimod has been introduced in the treatment of relapsing forms of the pathology. The drug is structurally similar to the bioactive sphingosine 1 phosphate (S1P), and is able to interact with the same receptors. Acting as a functional S1P1 antagonist it prevents the egress of leukocytes from the lymph nodes, thus reducing the rate of relapses. As its biological counterpart, fingolimod can exert several activity on endothelial cells and astrocytes, both expressing S1P receptors. Here we investigated whether key BBB properties are modified by S1P receptors modulation, addressing in particular the role exerted by the immunomodulator fingolimod. For this purpose, we used an *in vitro* co-culture model that allowed us to investigate the effects of S1P receptors modulation on endothelial cells and astrocytes. The effects of S1P and fingolimod were investigated either on endothelial cells and astrocytes independently or in a more physiological condition in which the two cell types could interact. Modulation of S1P receptors, and specifically modulation of S1P1, rescued endothelial cells from death upon cytokine challenge, either directly, or indirectly through stimulation of astrocytes. When astrocytes were exposed to S1P modulators they released trophic factors able to prevent endothelial cells death induced by cytokines exposure. Upon the other factors, we identified in granulocytes and macrophages colony growing factor (GM-CSF) the one mostly involved in these effects. Modifications in the barrier properties induced by S1P1 receptor signaling were finally investigated in a *in vitro* BBB model incorporating shear stress; once again, the modulation of the receptor increased barrier properties, thus reducing leukocytes migration. The data here reported point out the possibility that fingolimod, already in use for the treatment of relapsing remitting forms of MS, acting at the BBB, can further reduce the access of leukocytes in the CNS, reinforcing barrier properties upon cytokines stimuli.