Immune and nervous systems after initiation of experimental allergic encephalomyelitis and activation of remyelination in rats – Nataliia O. Melnyk- National O.O. Bogomolets medical university, Ukraine

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Abstract

In experimental research was investigate morphological changers in organs of central nervous system (CNS) – spinal cord, cerebrum and cerebellum and in organs of immune system– thymus and spleen after initiation of experimental allergic encephalomyelitis (EAE) in rats. Process of remyelination was induce after injections of Rebif® (interferon beta-1a) and laser therapy in condition of experimental model (EAE). Was observe changers of demyelination and remyelination in nerve fibers and reactions in neurons of central nervous system (CNS) on 21 days and 39 days after initiation of EAE. Also, was study reactions in thymus and in spleen on 21 days and 39 days after initiation of EAE. Histological sections of thymus and spleen was stain hematoxylin – eosin and azure II-eosin. Histological sections of the spinal cord, cerebrum and cerebellum was stain by cresyl violet and toluidine blue (by Nissl). By methods of electron microscopy and morphometry was investigate demyelination and remyelination in nervous fibers. After initiation of EAE reactive changers in thymus was include – formation of small nodules in cortical part of lobules, decrease amount of lymphocytes in cortex of lobules in early period on 21 days. In late period – 39 days after initiation EAE and influence of Rebif® (interferon beta-1a) and laser therapy by 2 weeks was observe similar changers - increase amount of lymphocytes in cortex. Reactive changers in spleen after remyelination was include increase amount of lymphoblasts and white pulp in parenchyma. After influence of Rebif® (interferon beta-1a) by 2 weeks, we observed process of remyelination. We observed the percentage of neurons with unmodified, moderate and severe structural changes, changers of myelinated and unmyelinated nervous fibers. Similar changers was observe after laser therapy, however, in not all cases. Myelinated nerve fibers was regenerate and the percentage of normal neurons in the brain and spinal cord was increased, the amounts of neurons with severe and destructive changes were reduce in late period of EAE (39 days), after influence of Rebif® (interferon beta-1a) and laser therapy. Our investigation formed characteristics of demyelination process in EAE condition and reactive changers in the central and peripheral organs of immune system. Microglia are intrinsic immune cells in the central nervous system (CNS). The under controlled microglia activation plays important roles in inflammatory demyelination diseases, such as multiple sclerosis (MS). However, the means to modulate microglia activation as a therapeutic modality and the underlying mechanisms remain elusive. Here we show that administration of 18β-glycyrrhetinic acid (GRA), by using both preventive and therapeutic treatment protocols, significantly suppresses disease severity of experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice. The treatment effect of GRA on EAE is attributed to its regulatory effect on microglia. GRA-modulated microglia significantly decreased pro-inflammatory profile in the CNS through suppression of MAPK signal pathway. The ameliorated CNS pro-inflammatory profile prevented the recruitment of encephalitogenic T cells into the CNS, which alleviated inflammation-induced demyelination. In addition, GRA treatment promoted remyelination in the CNS of EAE mice. The induced remyelination can be mediated by the overcome of inflammation-induced blockade of brain-derived neurotrophic factor expression in microglia, as well as enhancing oligodendrocyte precursor cell proliferation. Collectively, our results demonstrate that GRA-modulated microglia suppresses EAE through inhibiting microglia activation-mediated CNS inflammation and promoting neuroprotective effect of microglia, which represents a potential therapeutic strategy for MS and maybe other neuroinflammatory diseases associated with microglia activation. Microglia are central nervous system (CNS)-specific macrophages that viewed as the major immunocompetent element in the CNS in charge of sensing any brain-damaging event. Increasing studies suggest that activation of microglia is a hallmark of inflammatory demyelinating diseases such as multiple sclerosis (MS) and the animal model, experimental autoimmune encephalomyelitis (EAE). In MS and EAE, microglia exhibit uncontrolled activation, produce pro-inflammatory mediators, which recruit encephalitogenic T cells into the CNS and play a leading role in oligodendrocyte death and demyelination. However, when microglia activation is properly modulated, they can promote CNS remyelination through increased neurotrophic factor production, which is in accordance with our recent results. Therefore, the development of new therapeutic approaches designed to modulate activation of microglia, while preserving their neuroprotective effects, would suppress EAE pathogenesis and be great beneficial for MS therapy.

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To this end, we employed such an approach to identify novel therapeutic compounds for EAE and to characterize the underlying regulatory mechanisms. We recently find that 18β-glycyrrhetinic acid (GRA), a chemically defined compound, shows a potent inhibitory effect on the inflammatory activation of liver-resident macrophages, Kupffer cells. In addition, GRA exhibits neuroprotective effects, which prompted us to examine whether GRA has potential regulatory effects on modulation of CNS-resident macrophages, microglia in EAE. Our data indicate that GRA effectively suppresses EAE disease severity and the treatment effect is attributed to GRA-modulated microglia, which reduce the recruitment of encephalitogenic T cells in the CNS, as well as promote oligodendrocyte precursor cell (OPC)-mediated CNS remyelination. To investigate the mechanisms by which *in vivo* administration of GRA attenuated disease severity of EAE, day 15 splenocytes were isolated from GRA-treated and control EAE mice and characterized for *ex vivo* T cell reactivity and cytokine profile in response to MOG challenge. The results revealed that the proliferation of MOG-reactive T cells derived from GRA-treated mice was similar to that of controls. In addition, there was no significant difference in the amounts of cytokines (IFN-γ, IL-4, IL-10 and IL-17) released by T cells obtained upon MOG stimulation of GRA-treated or control EAE mice. Moreover, GRA treatment did not alter the proportion and quantity of T helper (Th) 1 cells, Th17 and regulatory T cells (Treg) in EAE mice. Recent studies report that granulocyte-macrophage colony-stimulating factor (GM-CSF) in the encephalitogenicity of T cells is involved in EAE development. As expected, GRA treatment did not alter the proportion and quantity of GM-CSF$^+$ T cells in accordance to IFN-γ$^+$ and IL-17$^+$ T cells in EAE mice.

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