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"Disease modifying nutricals" for multiple sclerosis

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ABSTRACT

The association between vitamin D and multiple sclerosis has (re)-opened new interest in nutrition and natural compounds in the prevention and treatment of this neuroinflammatory disease. The dietary amount and type of fat, probiotics and biologicals, salmon proteoglycans, phytoestrogens and protease inhibitor of soy, sodium chloride and trace elements, and fat soluble vitamins including D, A and E were all considered as disease-modifying nutraceuticals. Studies in experimental autoimmune encephalomyelitis mice suggest that poly-unsaturated fatty acids and their 'inflammation-resolving' metabolites and the gut microflora may reduce auto-aggressive immune cells and reduce progression or risk of relapse, and infection with whipworm eggs may positively change the gut–brain communication. Encouraged by the recent interest in multiple sclerosis–nutrition nature's pharmacy has been searched for novel compounds with anti-inflammatory, immune-modifying and antioxidative properties, the most interesting being the scorpion toxins that inhibit specific potassium channels of T cells and antioxidative compounds including the green tea flavonoid epigallocatechin-3-gallate, curcumin and the mustard oil glycoside from e.g. broccoli and sulforaphane. They mostly also inhibit pro-inflammatory signaling through NF-κB or toll-like receptors and stabilize the blood brain barrier. Disease modifying functions may also complement analgesic and anti-spastic effects of cannabis, its constituents, and of 'endocannabinoid enhancing' drugs or nutricals like inhibitors of fatty acid amide hydrolase. Nutricals will not solve multiple sclerosis therapeutic challenges but possibly support pharmacological interventions or unearth novel structures.

Contents

Abbreviations: 4-AP, 4-aminopyridine; APC, antigen presenting cell; ApoE, apolipoprotein E; ATRA, all-trans-retinoic acid; BBB, blood brain barrier; BBI, Bowman–Birk inhibitor; CB1/2, cannabinoid receptor; CBD, cannabidiol; CNS, central nervous system; DC, dendritic cell; DHA, docosahexanoic acid; EAE, experimental autoimmune encephalomyelitis; EDSS, expanded disability status scale; EGCG, epigallocatechin-3-gallate; EPA, eicosapentaenoic acid; FAAH, fatty acid amide hydrolase; IFN, interferon; IKK, inhibitor kappa B kinase; JAK, Janus kinase; K^+, potassium; Kca, calcium-activated potassium channel; Kir, potassium inward rectifier channel; Kv, voltage activated potassium channel; LDLR, low-density lipoprotein receptor; MBP, myelin basic protein; MMP, matrix metalloproteinase; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; MyD88, myeloid differentiation primary response gene 88; NaCl, sodium chloride; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOS, nitric oxide synthase; NOX, NADPH oxidase; NQO, NADPH quinone oxidoreductase; Nrf2, nuclear factor (erythroid-derived 2) related factor-2; PLP, proteolipid protein; PP, primary progressive; PPAR, peroxisome proliferator activated receptor; PR, progressive relapsing; PUFA, polyunsaturated fatty acid; RAR, retinoic acid receptor; ROR, RAR-related orphan receptor; ROS, reactive oxygen species; RR, relapsing remitting; RXR, retinoid X receptor; Shk, stichodactyla toxin; SP, secondary progressive; STAT, signal transducer and activator of transcription; Th, T helper cell; THC, tetrahydrocannabinol; TIMP, tissue inhibitor of metalloproteinase; TLR, toll-like receptor; TNFα, tumor necrosis factor-α; Treg, regulatory T cell; TREK1, TWIK-related potassium channel-1; TSO, *Trichuris suis* ova; VDR, vitamin D receptor

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1. Introduction

1.1. Multiple sclerosis and experimental autoimmune encephalomyelitis mouse models

MS is an inflammatory autoimmune disorder of brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons. Initially, inflammation is transient and remyelination occurs but is mostly not durable. Hence, in the most frequent relapsing remitting MS (RRMS) the early course of disease is characterized by episodes of neurological dysfunction that usually recover. But over time the pathological changes are dominated by widespread microglial activation associated with extensive and chronic neurodegeneration, and the relapsing course may eventually turn into a secondary progressive disease (SPMS), the clinical correlate of which is progressive accumulation of disability (Compston & Coles, 2008). Available treatments reduce the number of relapses and hence delay the progression of disability, but some patients show a primary progressive course (PPMS) with a steady increase of demyelination and loss of neurologic functions. In some patients further complications occur with aggravating acute attacks (progressive-relapsing PRMS) (Goodin et al., 2002) and so far no drug is able to change the course of the progressive disease. With an overall incidence of about 3.6 cases per 100,000 person-years in women and about 2.0 in men (Alonso & Hernán, 2008), MS is the most frequent cause of neurological disability in young adults.

The course of EAE in animals is also heterogeneous with higher susceptibility in females than males and can be induced in various species, including mice, rats, guinea pigs, rabbits and non-human primates, either by active immunization with myelin antigens, infection with Theiler viruses or by adoptive transfer of activated autoreactive T cells. Few mouse strains carrying myelin-specific transgenic T cell receptor variants, develop EAE or isolated optic neuritis spontaneously (Pollinger et al., 2009; Simmons et al., 2013) and like humans, rodents develop diverse courses of EAE, mainly RR-EAE and PP-EAE, depending on the genetic background and induction protocol, thus reflecting the complexity and heterogeneity of the human disease. But still, EAE mimics only part of the human pathophysiology limiting the translational predictability of clinical efficacy of investigational therapeutics (Simmons et al., 2013).

1.2. Risk factors and current multiple sclerosis therapeutics

MS is triggered by environmental factors in individuals with complex genetic risk profiles (Frohman et al., 2006; Compston & Coles, 2008). The latitude gradient of the MS incidence with higher numbers in the north compared to equator regions is disappearing in recent years, but still, place of birth is a risk factor (Alonso & Hernán, 2008). Environmental risk factors may be immune challenges such as infections with Epstein–Barr virus (Ascherio & Munger, 2007; Levin et al., 2010), low maternal exposure to ultraviolet radiation in the first trimester (Staples et al., 2010), cigarette smoke (Riise et al., 2003) and stressful life events (Mohr et al., 2004). Malnutrition and obesity at the age of 18 to 20 years may also increase the risk (Munger et al., 2009; von Geldern & Mowry, 2012) whereas cohort studies and case–control studies provide some evidence for protective effects of vitamin D (Munger et al., 2006; Simpson et al., 2010).

Irrespective of the intensive research therapeutic options for MS are still quite limited. Acute attacks are controlled with intravenous glucocorticoids but they provide no long-term benefit (Goodin et al., 2002) and research focuses on disease modifying treatments, which mainly reduce the relapse frequency in RRMS. The first have been interferon beta-1a and 1b (IFNβ-1a/b) (Goodin et al., 2002; Ruggieri et al., 2007). Natalizumab is a humanized monoclonal antibody directed against α_4-integrin, which interferes with T cell attachment and passage of the blood brain barrier (BBB) (McCormack, 2013). Further monoclonals with therapeutic efficacy are rituximab and alemtuzumab, which are directed against CD20 and CD52 respectively, with rituximab primarily targeting B cells and alemtuzumab also strongly targeting T cells (Ontaneda et al., 2012). Mitoxantrone is a type II topoisomerase inhibitor and blocks DNA synthesis (Ontaneda et al., 2012). These drugs are considered second line treatments due to toxicity. Particularly, natalizumab may cause progressive multifocal leucoencephalopathy that is rare but potentially fatal (Ontaneda et al., 2012). For teriflunomide, the active metabolite of leflunomide, and an inhibitor of de novo pyrimidine synthesis, clinical trials support an overall good safety profile (Ontaneda et al., 2012) (current therapeutics summarized in Fig. 1).

Since 2010 the first oral disease modifying drug fingolimod is available for the treatment of RRMS (Ontaneda et al., 2012). It is a derivative of myriocin, a metabolite of the fungus *Isaria sinclarii* which is pathogenic for insects, and as analogue of sphingosine it acts as an agonist of sphingosine-1-phosphate receptors with complex effects on immune cells, glia, BBB and neurons. The predominant effect is believed to be an inhibition of T cell egress from the lymph nodes and hence, inhibition of central nervous system (CNS) invasion (Brinkmann et al., 2010), but neuroprotection and enhancement of remyelination likely contribute to the favorable outcome. Another drug derived from a natural compound, dimethyl fumarate was recently approved for the treatment of RRMS. It has been used previously for the treatment of psoriarsis with however, moderate efficacy for the skin disease. In EAE models it mildly reduced clinical scores in late phases of EAE in C57BL/6 mice, which were ascribed to an increase of Nrf2-dependent (nuclear factor (erythroid-derived 2) related factor-2) upregulations of antioxidative genes (Linker et al., 2011). Compared with fingolimod its efficacy in preclinical models was rather low, but clinical trials revealed a surprisingly strong reduction of active magnetic resonance imaging (MRI) lesions and reduction of the relapse rate (Hutchinson et al., 2014).

Despite recent success with fingolimod and dimethyl fumarate there is still a high clinical need for novel disease modifying drugs particularly for the treatment of primary or SPMS and the natural sources of these drugs encourage the search for drug candidates among effective compositions of traditional medicines. The observed environmental and nutritional risk factors and the recent studies with vitamin D further suggest that nutricals and herbal mixtures may be supportive in primary and secondary prevention. The present review summarizes preclinical and clinical experiences with specified nutrients and neutraceuticals including supplements with inflammation resolving lipids, vitamins and trace elements. The second part focuses on preclinical studies in EAE models with novel compounds of natural sources including herbs, vegetable, roots and animal toxins. Despite the restrictions of the EAE models, these studies may point to novel targets and may uncover novel lead structures.

2. Fats and lipids

2.1. Polyunsaturated fatty acids

2.1.1. Neuroprotection with polyunsaturated fatty acids

Cardiovascular and epidemiological colon cancer research encourages low consumption of saturated fatty acids in favor of polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids including alpha-linoleic acid. Some initial studies also raised the hope that omega-3 and omega-6 fatty acids may be beneficial in human MS, because PUFAs have some neuroprotective effects, possibly mediated through activation of two-pore mechanosensitive potassium channels, like TWIK-related potassium channel-1 (TREK1), which is widely expressed by neurons (Heurteaux et al., 2004) and endothelial cells of the BBB (Bittner et al., 2013). TREK1 deficient mice showed increased susceptibility to epileptic seizures (Heurteaux et al., 2004) and the TREK1 agonist alpha-linoleic acid protected wildtype mice but not TREK1 knockouts against kainic acid evoked epileptic seizures and neuronal death (Lauritzen et al., 2000). PUFAs were also suggested to strengthen

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