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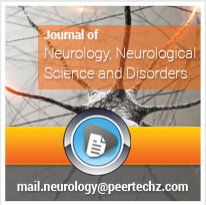

Clinical Group

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Review Article

Cytoprotection in Multiple Sclerosis and Ischemic Stroke with C-Phycocyanin and Phycocyanobilin

Abstract

Cytoprotection in human diseases can be achieved by avoiding and ameliorating tissue damage or by restoring the homeostatic balance either as a local or a systemic defense response. Multiple Sclerosis (MS) and Ischemic Stroke (IS) although being different central nervous system diseases, have common pathogenic aspects such as a deregulated inflammatory response, a toxic redox imbalance and a prominent neuronal dysfunction. C-Phycocyanin (C-PC), the main biliprotein of the *Spirulina platensis* cyanobacteria, and its associated chromophore named Phycocyanobilin (PCB), has shown strong antioxidant, anti-inflammatory and immunomodulatory properties. In this review, we describe the main experimental findings of our group supporting the medical application of C-PC/PCB as effective disease-modifying therapies for MS and IS. We demonstrated that C-PC induced regulatory T cells and protected both mice and rats against the progression of experimental autoimmune encephalomyelitis. Both compounds exerted beneficial actions in several models of IS, either *in vitro* or *in vivo*. We also addressed the hypothesis of possible combinations of C-PC/PCB with already approved treatments for MS, such as beta IFN, to improve the effectiveness, lower the cost and achieve patient relief or recovery. The safety and tolerability of these compounds are also stressed. The gathered evidence supports the implementation of clinical trials to demonstrate the potential therapeutic effect of C-PC/PCB against these diseases.

Abbreviations

C-PC: C-Phycocyanin; PCB: Phycocyanobilin; MS: Multiple Sclerosis; IS: Ischemic Stroke; CNS: Central Nervous System; EAE: Experimental Autoimmune Encephalomyelitis; IFN: interferon

Introduction

According to the World Health Organization, Multiple Sclerosis (MS) is the most common neurological disorder in young adults of Caucasian origin [1]. A recent update on the global impact of MS has shown its higher prevalence in economically developed regions such as North America, Europe and Australia, with more than 60 per 100 000 inhabitants with this disease [2]. Neurological deficits in MS patients have two pathogenic branches: acute inflammatory demyelination and axonal degeneration, the latter being the main cause of irreversible neurological disability. The disability caused by inflammatory demyelination clinically dominates the early Relapsing Remitting-MS stages and is reversible. However, for undetermined reasons, natural remyelination often fails in MS patients. In this sense, enhancing remyelination may be a therapeutic goal to prevent disability. Unfortunately, no such treatment is currently available.

Cerebrovascular diseases are responsible for a high proportion of deaths and disabilities throughout the world, and their incidence is expected to rise dramatically over the coming years with the increase of an aging population, chronic hypertension, obesity and other associated risk factors. Data from the World Health Organization indicated that 15 million people worldwide suffer from stroke each year. Of these, more than 5 million die, which accounts for the 10% of total deaths, and another 5 million are permanently disabled [3]. Ischemic Stroke (IS), caused by the interruption of the brain blood supply by the blocking of blood flow through the arteries, accounts for the majority of clinical cerebrovascular cases [4]. The pathogenesis of IS include, in the acute phase, processes such as excitotoxicity, oxidative stress, inflammation and disruption to the blood brain barrier [5]. Compounds able to block these pathogenic processes may potentially protect the brain against ischemia, but despite the large number of preclinically proved neuroprotectants, clinical translation has been challenging [6].

C-Phycocyanin (C-PC), the main biliprotein of the cyanobacteria *Spirulina platensis*, and its associated chromophore

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named Phycocyanobilin (PCB), exhibit an array of biological properties such as antioxidant and anti-inflammatory characteristics, in addition to immunomodulatory actions [7,8]. In this review, we aim to present results from our group and from other authors demonstrating the beneficial actions of C-PC and PCB in experimental models of MS and IS, which support their potential medical application for these diseases.

C-Phycocyanin and Phycocyanobilin as possible cytoprotective treatments for Multiple Sclerosis and Ischemic Stroke

For more than a decade our group has been exploring through different experimental approaches the pharmacological properties of C-PC and PCB, including their neuroprotective and neurorestorative activities. These are linked-but not restricted- to their conventional anti-oxidant, free radical scavenging and anti-inflammatory properties [9-12], such as the selective COX-2 enzyme inhibition [13,14], but also to the modulation of the expression of several genes linked to other biological processes [15]. In the anterior cerebral cortex of rats subjected to a global acute brain hypoperfusion, we have observed that a total of 93 genes were upregulated and 97 genes were down-regulated due to the therapeutic treatment of PCB. A Gene Ontology analysis showed that these genes were linked to biological processes such as the regulation of acute inflammatory response, the cellular extravasation, the positive regulation of phagocytosis and the cellular response to molecules of bacterial origin [15]. Furthermore, PCB significantly induced the expression of genes associated to neurophysiological functions such as Mal (myelinogenesis), Bcl-2a1 (anti-apoptosis) and Baiap2 (dendritic spine morphogenesis) [15].

We have mostly monitored C-PC/PCB activity toward Central Nervous System (CNS) disorders, and in particular, in MS and IS, which are included among its most prevalent neurodegenerative diseases. Their actions, however, are not exclusively restricted to neurological disorders, as exemplified by previous studies reporting C-PC/PCB cytoprotective properties at least against hepatotoxicity [16,17], diabetic nephropathy [18] and atherosclerosis [19].

Administered by the oral route, C-PC can render, by digestive proteolysis, PCB-bound peptides and free PCB [20], the latter being responsible for most of the pharmacological actions of C-PC, including the C-PC/PCB neuroprotective properties [21,22]. PCB may also be obtained by extraction methods [23], chemical synthesis [24] and recombinant DNA procedures [25,26]. For their preclinical evaluation, we have used widely recognized cell and animal models, particularly the experimental autoimmune encephalomyelitis (EAE) MS model [27], in different animal species (mice and rats). We have shown that C-PC/PCB exert CNS protective effects on cell lines, such as PC-12 and SH-SY5Y, on neuronal lines under excitotoxic or oxidative insults, on isolated rat brain mitochondria exposed to neurotoxic agents, on focal retinal ischemia/reperfusion injury in rats [28], and on acute global brain ischemia injury in gerbils [29].

C-PC and PCB are major components of *Spirulina platensis*, their natural source, and therefore they share the GRAS (Generally Recognized As Safe) condition granted by the US Food and Drug Administration (FDA) [30], which support their safety for clinical trials. In this sense, a recent clinical study showed that the daily consumption of a *Spirulina platensis* extract dose accounting for approximately 1 g C-PC for 2 weeks is tolerable and safe, regarding blood and liver markers, in connection with a rapid and robust relief from chronic pain of the patient at rest and when physically active [31].

On the other hand, previous studies suggested that activated microglia, with the combined activities of the inducible nitric oxide synthase (iNOS) and the NADPH oxidase enzymes, could release the highly cytotoxic oxidant superoxide radical anion and peroxynitrite, which are then able to produce brain tissue injury and mediate the pathogenesis of neurodegenerative disorders [32]. It has been reported that PCB, absorbed through the oral route, acts as a potent inhibitor of the expression of NADPH oxidase in the kidney [18]. Thus, it is a plausible idea that PCB may also reach the brain and inhibits this enzyme locally and therefore positively influences microglial and neuronal functioning.

Within the former scenario, our team proposed a new focus of neuroprotection aiming to reestablish the effector/regulator balance of the immune response once it has been disrupted, a situation that arises in human autoimmune diseases such as MS. Using the EAE rat model of MS, and peripheral blood mononuclear cells from patients of this disease, we have shown the ability of C-PC to induce regulatory T cells, to prevent and promote remyelination and to stop or reverse axonal loss [33]. The oral route can be a competitive advantage for the development of effective therapies for MS, offering the patients a far more convenient administration route, whether applied alone or combined with other active ingredients such as interferons (IFN) [34]. Doses, costs and side effects of beta IFN, widely used for MS [35] treatment, could be reduced by combining it with C-PC/PCB.

The work outlined above was significantly improved with our recent study showing the neuroregenerative effects of C-PC and beta IFN in a C57BL/6 mouse model of MS [36], where beta IFN (2000 IU, s.c.) was compared to C-PC (2, 4 or 8 mg/kg i.p.) once a day or every other day, respectively, starting at disease onset (11 to 15 days post-induction). Both compounds were assessed in CNS tissues according to their microarray overall gene expression profile (Illumina Mouse WG-6V2 BeadChip) and the qPCR expression of particular genes (Fast SYBR Green RTPCR Master Mix). Oxidative stress parameters (malondialdehyde, peroxidation potential, catalase/superoxide dismutase ratio and reduced glutathione) were also tested. Histological and immunohistochemistry (anti-Mac-3, anti-CD3 and anti-APP) assessments were also carried out in spinal cord post-EAE induction. We identified genes related to remyelination and gliogenesis processes. The microarray evaluation indicated that C-PC modulates mainly processes involved with the immune and inflammatory responses. The differential gene expression profile of C-PC and beta IFN

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evidenced both common and specific process modulation activities (Table 1).

This implies that in a combined therapy both components modulate genes linked to shared activities, while each component separately modulates, in a different way, genes linked to particular processes. Our previous reports on the C-PC/PCB anti-inflammatory and neuroprotective properties in different CNS animal models, have also found immunohistochemical confirmation in this study. We showed that C-PC decreased the inflammatory infiltrates, the axonal loss and the demyelination in the spinal cord, consistent with the animal´s clinical improvement. By using Real Time PCR, we observed that C-PC reduce the IL-17 mRNA levels in the brain, correlated with a down-regulating effect on IL-17 protein levels in serum, which is known to be the main MS effector cytokine [37]. Our results also showed that both C-PC and IFN-beta reduced the oxidative stress typical of EAE mice and tackled, in the same way, the expression of a common gene subset. However, they also influence the differential expression of another subset of genes linked to the modulation of remyelination, gliogenesis and axon-glia processes, preferentially expressed by C-PC as identified by microarray analysis [36].

In another set of experiments using a model of penumbra tissue in cerebral ischemia induced by the permanent bilateral common carotid arteries occlusion in rats [38], we reported that important immune and inflammatory genes were positively modulated by the treatment with PCB. These genes include IFN-γ, IL-6, CD74, Foxp3, TGF-β, CCL12, IL-4, IL-17A, C/EBPβ, CXCL2, ICAM-1, IL-1β, and TNF-α [15]. As several of these cytokines and chemokines participate in the deleterious inflammatory reactions after ischemic stroke [39], our data suggest that PCB may diminish their harmful impact on the ischemic brain tissue and thus contributing to neuroprotection.

Collectively, these results evidenced the beneficial activity of C-PC/PCB within the EAE and ischemic model settings, which is also indicative of their regulatory capacity on these biological processes. Notably, the regulatory T cells phenotype induction/activation by C-PC in the EAE model and PBMC from MS patients is a step forward toward the clinical setting. The therapeutic actions of approved MS treatments such as beta IFN could be intensified and diversified by combining it with C-PC/PCB, aimed at rebalancing the immune response of the recipient by providing common and mutually complementary gene activities. For example, these combined therapies would benefit from the regulatory T cells restorative activity of the biliprotein active component. Moreover, the presence of C-PC/PCB in the digestive tract and in a common mucosal immune system also enables their influence on the microbiome, the mucosal immunity, increasing their range of interactions. Additionally, personalized medicine that matches treatments with patients and their immune re-education that ensures tolerance to self and non-dangerous antigens could further support clinical trials and the potential of treatment success [40,41].

Table 1: Specific and shared biological processes modulated by the treatments with IFN-beta and C-PC in the brains of EAE mice assessed by microarray (Illumina Mouse WG-6_V2) [15].

Biological processes	IFN-beta	IFN-beta and C-PC	C-PC
Neurological processes	Glial cell differentiation Synapse organization Regulation of axonogenesis	Neuron development Neuron differentiation Neurotransmitter biosynthetic process Regulation of synaptic transmission	Glial cell development Synaptic vesicle secretion Neurotransmitter secretion
Apoptosis		Negative regulation of cell death	
Immune processes	Regulation of macrophage differentiation T cell activation T cell differentiation		
Signaling			Positive regulation of MAP kinase activity Activation of protein kinase C activity by G-protein coupled receptor protein signaling pathway
Redox			Oxidation-reduction Cell redox homeostasis

Conclusion

A novel proposal for C-PC/PCB cytoprotective activity has been introduced taking into account important findings of our group in MS and IS cell and animal models. Prominent findings include the activation of regulatory T cells, which represents a new therapeutic concept for human autoimmune diseases and also for other frequent pathologies. The differential modulation by C-PC/PCB of gene expression involved in the regulation of signal transduction, protein transport, synaptic transmission, immune processes, apoptosis, remyelination and gliogenesis have also been identified. Immunohistochemical changes and cytokine level rearrangement evidenced C-PC improvements in the CNS tissue in relevant MS and IS animal models. Combined applications of C-PC/PCB with other active therapeutic compounds such as beta IFN for MS have also been suggested.

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