Review Article

Phosphodiesterase 7B1 as Therapeutic Target for Treatment of Cognitive Dysfunctions in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune, chronic degenerative neuroinflammatory disorder affecting younger age groups of the United States of America and Europe. MS prevalence studies in India have shown that India is no longer a low-risk zone. Many studies have shown the seriousness of cognitive impairments (CIs) and its types caused in MS. In this review, the pathological basis for CI in various stages of MS was reviewed and revealed to provide a basis for the treatment. Role of phosphodiesterase 7B1 (PDE7B1) inhibitors in treating CI related to MS were also stated in this review. The literature for this review was collected from PubMed and Embase.

Keywords: Chronic degenerative neuroinflammatory disease, cognitive dysfunction, demyelinating disorder, memory, multiple sclerosis, phosphodiesterase 7B1

Introduction

Cognitive impairment (CI) in multiple sclerosis (MS) was considered as heterogeneous. However, there are studies which have stated the pathological basis for deviation of cognitive functions in MS, contributing to factors such as defects in neural conductions in brain,[1] deviation of biochemical components, and up-regulation of cyclic adenosine monophosphate (AMP)-specific phosphodiesterases (PDE).[2-5] Furthermore, this was considered as an early symptom unnoticed in MS.[6] This review also stated many PDE7 inhibitors stated in different disease conditions and showed that they could be potential for treatment of CI's in MS. The role of PDE7B in CI's of MS patients was reviewed using the literature from PubMed and Embase.

Multiple Sclerosis

MS is a chronic neuroinflammatory and autoimmune disorder affecting the central nervous system.[7] This disease incidence varies from onset at 18 years, progressing up to 40 years, rare after 50 years of age and more prevalent in the USA and European countries.[8-11] In the USA, it was reported that 250000–350000 people were suffering from MS and in European countries, the prevalence rate was 83 for every 1 lakh population. In India, the prevalence of MS was reported as 8.3 for every 1 lakh population.[12] Many studies reported the higher incidence rate in female population than male.[13,14] The etiology included genetic and environmental factors.[11-15] Genetic factors were reported to be associated with risk of MS. DRβ1 allele 15.01 of human leukocyte antigen gene located on Chromosome 6 was considered responsible for MS.[16,17] Another factor included was familial recurrence which was reported to have 20% risk. An inverse relation was observed with a degree of consanguinity ranging from 2.77% to 0.88%.[18] MS risk was 24%–34% in monozygotic twins and 2%–3% in dizygotic twins.[19] The environmental factors include the Epstein–Barr virus, infectious mononucleosis,[20] Vitamin D,[21] smoking,[22] commensal gut flora,[23] childhood and adolescence,[24] vascular comorbidities,[25] and gestational environmental influences like month of birth.[26] Smoking was reported to cause MS and also to aggravate the disease progression. Most of the disease risk was associated with the Epstein–Barr virus and infectious mononucleosis. It was reported that in the northern hemisphere, the births in May were more prone to MS than in November.

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The pathological features of MS include initiation of inflammation in white matter resulting finally in axon loss. This features characteristic "focal plaques" which are inflammatory lesions in the white matter due to demyelination. This further progresses to a range of axonal loss and later results in gliosis. Inflammatory processes include the crossing of the blood-brain barrier by autoreactive T cells, secretion of cytokines, antibody induction by plasma cells which results in damage of tissue within the plaque.[27] The axonal injury which is secondary event caused due to myelin damage in this disease process was described in two models. "Outside-in" model states axonal injury might be caused due to lesion arising from myelin. "Inside-out" model states that secondary myelin injury might be triggered by primary axonal injury.[28] This results in diffuse atrophy of gray and white matter as disease progresses. In further progression, the plaques are rare. The preexisting plaques consist of activated microglia at their border causing low-grade inflammation. Because of this slow and gradual expansion of plaque and secondary demyelination occurs.[27] Lucchinetti *et al*. reported that cerebral cortex was also affected in MS.[29] Clinical features of MS include optic neuritis, cerebellar symptoms, sensory deficits exhibited mostly by relapsing type or initial stages. The progressive type may show spinal symptoms such as spasticity, ataxic gait, paresis, and corticospinal dysfunctions.[9] This dysfunction or disability in MS is measured by the expanded disability status scale (EDSS).[30] Based on disease progression and clinical course, the patients were grouped under the following categories. They are relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS). RRMS is the initial stage of the disease including 85% of the MS patients and changes to SPMS including 75% on progression. Forty percent of the patients gradually progress to PPMS. 15% of patients were reported to be in PRMS type from the onset of MS.[9,31] A study reported that an EDSS score of 6 is attained by 7 years and 12.5 years in PPMS and SPMS category patients, respectively.[30] The diagnosis of MS includes magnetic resonance imaging of the central nervous system, cerebrospinal fluid examination with clinical correlation.[32]

Cognitive Impairment in Multiple Sclerosis

CI symptoms were considered as the earliest symptoms in the initial stages of MS.[6] Cognitive dysfunctions in MS patients were considered as heterogeneous type. A study revealed MS as a causal factor for CI.[33] Cross-sectional studies showed CI in 45%–60% MS patients and among these 20%–30% had severe dementia in their final stages.[34] Memory, executive function, processing speed, information processing, efficient verbal fluency, visuospatial analysis, and attention are the cognitive functions impaired in MS patients. Processing speed impairment and memory impairment are the most commonly affected cognitive functions in MS. Processing speed is the amount of work done in a given time and memory is the amount of information learned and recalled.[35] These cognitive functions were evaluated in MS patients by cognitive batteries. The most commonly used are the brief visuospatial memory test-revised (BVMT-R), California verbal learning test–II (CVLT-II) and symbol digit modalities test (SDMT). SDMT was considered as most sensitive test in MS patients.[36] 40%–65% of MS patients showed impairment in memory function, but some reported that encoding and storage capacity is not breached.[37] Benedict *et al.* reported that 30%–55% of MS patients showed memory impairment (using BVMT-R, CVLT-II).[38] Acquisition of new knowledge was found as a difficult task in MS patients.[33] Speed of information processing was found to be affected in 20%–30% of MS cases and this was considered as key deficit which had an impact in work environment. The reason for this slowed down of information processing was contributed to impaired conduction property of demyelinating neurons.[39] Attention function impairment was reported in 25% of MS patients.[40] Benedict *et al.* reported that 28%–52% of MS patients showed impairment in processing speed (using SDMT).[38] Studies related cognitive deficits in MS to changes in thalamic nuclei[41-44] and hippocampus.[45-47]

Phosphodiesterase 7 and Cognitive Impairment in Multiple Sclerosis

PDE7 is cyclic adenosine monophosphate (cAMP) specific hydrolysing enzyme. This enzyme exists in two isoforms, namely, PDE7A and PDE7B. These two isoforms exists in various transcripts. PDE7A exists as PDE7A1, PDE7A2, PDE7A3 and PDE7B exists as PDE7B1, PDE7B2, and PDE7B3.[48] Dopaminergic D_1 receptors was considered to activate PDE7B1 enzymes further playing a major role in cAMP/protein kinase A (PKA)/cAMP response element binding protein (CREB) pathway regulation, particularly in the striatum. This was reported to affect cognition.[49] Activation of PDE7B1 causes decrease in levels of cAMP which may have a deteriorating effect. cAMP was considered to have a protective effect on demyelinating neurons. Furthermore, increased striatal dopamine levels were reported in MS.[50] This increased dopamine levels were reported to increase pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin 10 through D_1 receptors.[51]

D_1 receptor pathway in the corticostriatal circuit

Dopaminergic receptor D_1, play an important role in motor control.[52] Furthermore, D_1 regulates long-term memory by triggering G-proteins. Gαs/olf subunit of G-protein activates the C2 site of adenylate cyclase. This causes binding of C1 and C2 resulting in the synthesis of cAMP from adenosine triphosphate.[53,54] cAMP activates guanine nucleotide exchange factors (GEFs). This turns on Ras-proximate 1 which induces mitogen-activated protein kinase (MAPK) signaling.[55-57] MAPK causes phosphorylation of CREB which finally triggers the translational and transcription factors resulting in formation of long-term memory.[58,59] Phosphorylation of CREB is also triggered directly by PKA. This mechanism of long-term potentiation of memory is found, not only in hippocampus

but also seen in the striatum and frontal cortex.[60-65] PDE7B1, majorly localized in the striatum of the brain is a known hydrolyzing enzyme specific to the cAMP. PDE7B1 reduces the levels of cAMP, thus reducing its physiological effects. Inhibition of PDE7B1 may elevate the levels of the cAMP in the striatum of the brain [Figure 1].

Role of Phosphodiesterase 7B1 Inhibitors in Cognitive Impairment

PDE7B1 inhibition was represented for the treatment of airway inflammatory diseases. IBFB-211913 is a new PDE7 inhibitor under development for treatment of asthma, autoimmune diseases, and psoriasis.[66,67]

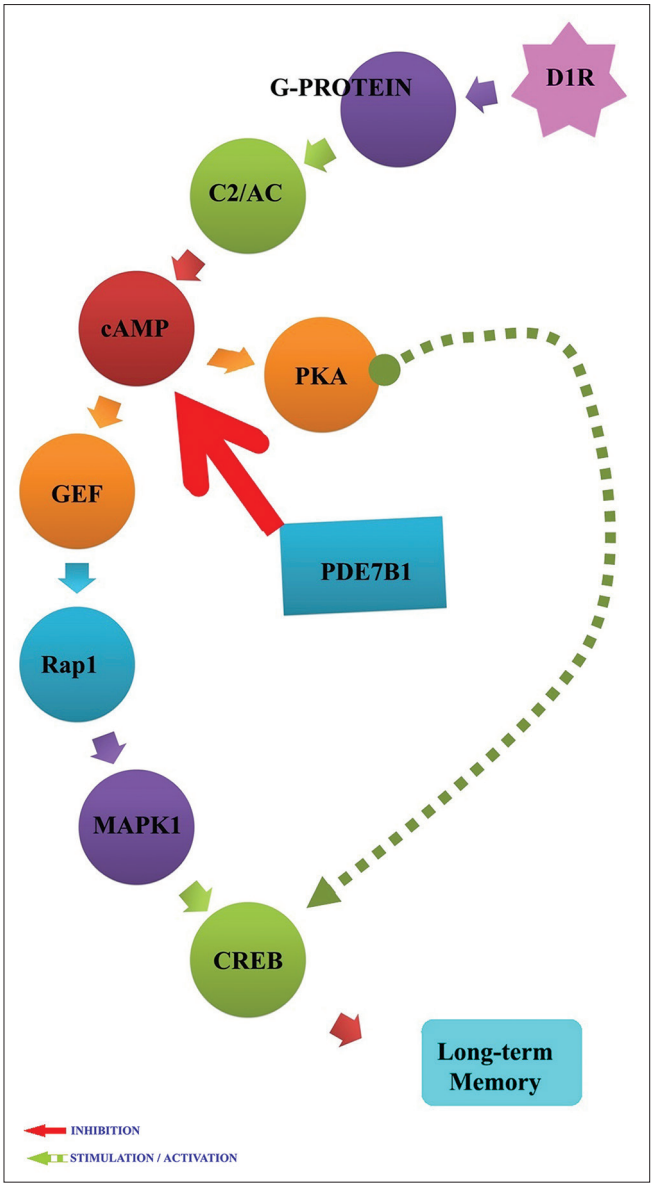

Figure 1: D1R/cyclic adenosine monophosphate/cyclic adenosine monophosphate response element binding pathway. C2/AC: C2 sub-unit of Adenylyl cyclase, cAMP: Cyclic Adenosine monophosphate, GEF: Guanine nucleotide exchange factors, Rap1: Ras-proximate 1, MAPK1: Mitogen-activated protein kinase 1, CREB: CAMP response element binding protein, PKA: Protein kinase A, PDE7B1: Phosphodiesterase 7B1

Increasing the levels of cAMP and decreasing the increased expression of cAMP-specific PDE could be potential combination effect in treatment of MS-related CI. PDE7 inhibitors have shown protective effects in similar pathological events. So a scope for its beneficial importance in treatment of MS and its related CI could be given. S14, 5-imino-1,2,4-thiadiazole (VP1.15) were two PDE inhibitors proved to enhance cAMP levels in spinal cord injury mice model[68] while VP1.15, quinazoline (TC3.6) showed remyelinating effects in an *in vitro* study with oligodendrocyte precursor cells.[69] Enhanced Foxp3 levels was also reported with TC3.6, proving its neuroprotective effects.[70] VP1.15 was reported to enhance early attention processing.[71] A small molecule PDE7 inhibitor with heterocyclic structure (S14) was proved to antagonize microglial activation. This PDE inhibitor also showed improvement in cognitive functions.[72,73] Till now, the PDE7 inhibitors available in the market are isoxazole derivative compounds, benzo(thio)pyranoimidazolone derivatives.[74] Many other PDE7 inhibitors were shown to have a neuroprotective effects in MS condition but did not reveal about the effects on CI's.[75-77]

Conclusion

In this review, MS was shown to have a significant role in developing cognitive dysfunctions due to its effects in hippocampus and corticostriatal regions in brain. PDE7B1 was shown to be an important interventional site for the treatment of CI's in MS. Exploring and producing effective PDE7B1 inhibitors for the treatment CI in MS and studies revealing their effectiveness in preclinical and clinical research are required as 65% of MS patients were shown to have CI's.

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Conflicts of interest

There are no conflicts of interest.

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