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Mini Review

Phosphodiesterase as a Drug Target of Alzheimer's Disease

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Abstract

Although amyloid hypothesis is widely accepted, recent findings indicate that the hypothesis may be incorrect, suggesting that Aβ is not a suitable drug target in Alzheimer's disease. Accumulating evidences and new findings suggest that phosphodiesterases is involved in Alzheimer's disease. In this review, I introduce the current state of phosphodiesterases and their inhibitors as for Alzheimer's research.

Keywords: Amyloid; Alzheimer's disease; Phosphodiesterase; Phosphodiesterase inhibitor; Aβ; cAMP; cGMP; Signal transduction; Therapy; Drug

Abbreviations

AD: Alzheimer's Disease; FAD: Familial Alzheimer's Disease; APP: Amyloid Precursor Protein; PDE: Phosphodiesterase; cAMP: Cyclic Adenosine Monophosphate; cGMP: Cyclic Guanosine Monophosphate; PKA: cAMP-dependent Protein Kinase; CREB: cAMP Response Element-Binding Protein; AC: Adenylate Cyclases; sGC: Soluble Guanylyl Cyclase; cGKs: cGMP-dependent Protein Kinases; CNG: Cyclic Nucleotide-gated; HCN: Hyperpolarization-activated Cyclic Nucleotide; CTF: C-terminal Fragments

Introduction

According to the widely accepted amyloid hypothesis, amyloid-β (Aβ) production from amyloid precursor protein (APP) and Aβ amyloid fibril formation are considered the primary causes of Alzheimer's disease (AD). However, Aβ peptides are normal metabolic components, and there is little evidence that Aβ is neurotoxic at *in vivo* concentrations [1]. No significant correlations between the concentration or the brain distribution of neuritic plaques and the degree of dementia, loss of neurons, the distribution of dystrophic neurites, or cytoskeletal abnormality have been obtained [2-4]. The levels of soluble Aβ including oligomeric species of Aβ are significantly greater in younger adults than older adults with or without AD [5]. Recent neuroimaging studies have revealed that amyloid deposits are present in cognitively normal individuals, whereas some AD patients showed no amyloid deposits in a positron emission tomography analysis [6,7]. In addition, all Aβ amyloid-focused clinical trials have failed [8]. Together these finding indicate that the amyloid hypothesis may be incorrect. Is Aβ thus a suitable target for AD drug development?

Phosphodiesterase inhibitor as a drug for cognitive enhancement

To date, the use of many inhibitors of phosphodiesterase (PDE) has been reported to produce cognitive enhancement. Accumulating evidence indicates that the inhibition of PDE activity may be an appropriate target for AD. The effectiveness of the administration of PDE inhibitors has been demonstrated in several animal models of AD and in clinical trials as shown in Table 1.

Function of PDE

PDE isoenzymes are classified into 11 families (PDE1–PDE11). PDEs play a central role in signal transduction and in processes of neuroplasticity, such as long-term potentiation, by regulating intracellular levels of cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP) [9-11]. One of the major intracellular signaling pathways that has been implicated in synaptic and structural plasticity is the cAMP signaling pathway. cAMP activates the cAMP-dependent protein kinase (PKA) or cAMP response element-binding protein (CREB), which induce protein phosphorylation or gene expression [12]. The cyclic nucleotide is generated by Adenylate cyclases (ACs) and hydrolyzed by PDEs. These signaling elements cascade in numerous brain functions such as learning and memory. cGMP, like cAMP, is also a second messenger. In this signaling pathway, nitric oxide (NO)-sensitive soluble guanylyl cyclases (sGCs) and cGMP-dependent protein kinases (cGKs) are generators and effectors, respectively. In addition, neuronal cGMP signalling can be transmitted through cyclic nucleotide-gated (CNG) or hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels. In the brain, the NO/sGC/cGMP/cGK pathway modulates long-term changes of synaptic activity and contributes to distinct forms of learning and memory [13]. These signaling cascades are negatively controlled by PDEs that breakdown cAMP and/or cGMP and turn off the cAMP and/or cGMP signaling pathways. Inhibitors of PDEs are expected to increase cAMP and/or cGMP levels and to improve the signaling. PDE4, 7 and 8 selectively hydrolyze cAMP. PDE5, 6, and 9 selectively hydrolyze cGMP. Oher PDEs can hydrolyze both cAMP and cGMP.

PDE in the brain

In the brain, PDE1, PDE2, PDE3, PDE4, PDE5A, PDE7A, PDE7B, PDE8B, PDE9A, PDE10A, and PDE11A have been obsearved to be expressed in the brain. As these enzymes control the levels of cAMP and/or cGMP in cells that are crucial for neural function, PDE inhibitors represent promising candidate drugs for the treatment of altered cognition states [9].

cAMP and/or cGMP reduction in AD brain

In hippocampal tissues of demented individuals, a significant

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Table 1: The effectiveness of PDE inhibitors.

PDEi	name	cognition	animal models or patients	published article
PDE1i	Vinpocetine	up	3-NP induced HD symptoms in rats	[38]
PDE1i/5i	SCH-51866	not	R6/2 mice model of HD	[39]
PDE2i	?	up	APPswe/PS1dE9 mice	[40]
PDE3i	Cilostazol	up	C57BL/6J mice treated with Aβ 25-35	[41]
PDE3i	Cilostazol	? (rCBF up)	20 patients with AD and CVD	[42]
PDE3i	Cilostazol	prevent decline or up	AD/CAA patients and Tg-SwDI mice	[43]
PDE3i	Cilostazol	up	C57BL/6 J mice (various behavioral tasks)	[44]
PDE4i	Rolipram	up	Tg mice with APP (K670M:N671L) and PS1 (M146L)	[23]
PDE4i	Rolipram	up	C57BL/6 mice treated with MPTP	[45]
PDE4i	Rolipram	up	Rats treated with Aβ 25-35 or Aβ 40	[46]
PDE4i	GEBR-7b	up	APPswe/PS1dE9 mice	[47]
PDE4i	GSK356278	up	Model of anxiety in common marmosets	[48]
PDE5i	Sildenafil	up	Tg mice with APP (K670M:N671L) and PS1 (M146L)	[49]
PDE5i	Sildenafil	up	Tg2576 mice	[50]
PDE5i	Tadalafil	up	J20 mice	[9]
PDE5i	Compound 7a	up	AD mice model	[51]
PDE5i	Sildenafil	up	Tg APP/PS1 mice	[52]
PDE5i	Sildenafil, Vardenafil	up	Aged rodent models	[53]
PDE7i	S14	up	AD tg mice	[54]
PDE9i	PF-04447943	not	mild to moderate probable Alzheimer's disease	[55]

reduction in basal as well as stimulated Adenylate Cyclase activity was found. This reduction in cAMP signal transduction is not caused by simple cell loss [14]. It has also been reported that the negative regulation of the CRE transactivation signal was evoked by the FAD mutant APPs, but not by wild-type APP695, in a whole-cell system [15]. cGMP levels, were significantly lower in the CSF of AD patients [16]. Disruption of CREB signaling may contribute to memory deficits in AD, but the mechanisms underlying the medication of early synaptic dysfunction and memory loss in AD are unknown. In addition, the level of cAMP and/or cGMP links to ubiquitin/proteasome pathway [17] and to Tau phosphorylation [18].

Aβ toxicity and reduction of cAMP and/or cGMP

It has been reported that Aβ negatively affect hippocampal synaptic plasticity, memory and synapse loss by deregulating cAMP/Ca2+-mediated CREB signaling [19-22]. Consistently, CREB-signaling activation ameliorates learning and/or memory deficits in transgenic AD mouse models [23-25]. Moreover, a decrease in cGMP levels has been detected either in vessels and neurons after Aβ treatment or in aged brains [26-30]. Therefore, impairment of the cAMP/PKA/CREB pathway and/or the NO/cGMP/cGK pathway in AD has been attributed mainly to Aβ toxicity [22,31]. The mechanisms underlying cAMP and/or cGMP reduction via Aβ accumulation in AD brain are poorly understood.

Increased PDEs in AD brain

However, we recently found that PDE8B was significantly increased in CHO cells accumulating APP C-terminal fragments (CTFs) without Aβ involvement [32]. This suggests that APP-CTF accumulation triggers the hydrolysis of cAMP and subsequent cAMP/PKA/CREB pathway impairment in the AD brain without Aβ involvement. Accumulations of APP CTFs due to impairment of APP metabolism are common phenomena in AD [33-36]. Moreover, it was reported that PDE7B and PDE8B were increased in cortical areas and parts of the hippocampal formation of AD patients [37]. Significant increase in PDE5 expression was detected in temporal cortex of AD patients compared to that of age-matched healthy control subjects [16]. These findings suggest that the expressing levels of PDEs are increased in the AD brain and that cAMP and/or cGMP are broken by PDEs. As for the precise molecular mechanism by which the impairment of APP metabolism induces an increase in the level of PDEs, further studies are required.

Conclusion

In the AD brain, increases in the levels of PDEs occurs independent of Aβ involvement, following cAMP/PKA/CREB and/or NO/cGMP/cGK pathway impairment. Therefore, PDEis may be used in fundamental therapy for AD, not as a palliative therapy for cognitive impairment.

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