

Mini Review

Phosphodiesterase as a Drug Target of Alzheimer's Disease

Fuyuki Kametani*

Department of Dementia and Higher Brain Function,
Tokyo Metropolitan Institute of Medical Science, Japan*Corresponding author: Fuyuki Kametani,
Department of Dementia and Higher Brain Function
Research, Tokyo Metropolitan Institute of Medical
Science, Tokyo 156-8506, Japan

Received: December 12, 2014; Accepted: July 10, 2015;

Published: July 26, 2015

Abstract

Although amyloid hypothesis is widely accepted, recent findings indicate that the hypothesis may be incorrect, suggesting that A β 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; A β ; 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 (A β) production from amyloid precursor protein (APP) and A β amyloid fibril formation are considered the primary causes of Alzheimer's disease (AD). However, A β peptides are normal metabolic components, and there is little evidence that A β 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 A β including oligomeric species of A β 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 A β amyloid-focused clinical trials have failed [8]. Together these finding indicate that the amyloid hypothesis may be incorrect. Is A β 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. Other 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 observed 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

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	APP ^{swe} /PS1 ^{dE9} mice	[40]
PDE3i	Cilostazol	up	C57BL/6J mice treated with A β 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 A β 25-35 or A β 40	[46]
PDE4i	GEBR-7b	up	APP ^{swe} /PS1 ^{dE9} 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].

A β toxicity and reduction of cAMP and/or cGMP

It has been reported that A β 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 A β 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 A β toxicity [22,31]. The mechanisms underlying cAMP and/or cGMP reduction via A β 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 A β 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 A β 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 A β 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.

References

- Robakis NK. Mechanisms of AD neurodegeneration may be independent of A β and its derivatives. *Neurobiol Aging*. 2011; 32: 372-379.
- Boncrisiano S, Calhoun ME, Howard V, Bondolfi L, Kaeser SA, Wiederhold KH, et al. Neocortical synaptic bouton number is maintained despite robust amyloid deposition in APP23 transgenic mice. *Neurobiol Aging*. 2005; 26: 607-613.
- Spires TL, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, Nguyen PT, et al. Dendritic Spine Abnormalities in Amyloid Precursor Protein Transgenic Mice Demonstrated by Gene Transfer and Intravital Multiphoton Microscopy. *J Neurosci*. 2005; 25: 7278-7287.

4. Golde TE, Schneider LS, Koo EH. Anti- $\alpha\beta$ therapeutics in Alzheimer's disease: the need for a paradigm shift. *Neuron*. 2011; 69: 203-213.
5. Huang Y, Potter R, Sigurdson W, Kasten T, Connors R, Morris JC. β -amyloid dynamics in human plasma. *Arch Neurol*. 2012; 69: 1591-1597.
6. Edison P, Archer HA, Hinz R, Hammers A, Pavese N, Tai YF, et al. Amyloid, hypometabolism, and cognition in Alzheimer disease: an [^{11}C]PIB and [^{18}F]FDG PET study. *Neurology*. 2007; 68: 501-508.
7. Li Y, Rinne JO, Mosconi L, Pirraglia E, Rusinek H, DeSanti S, et al. Regional analysis of FDG and PIB-PET images in normal aging, mild cognitive impairment, and Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2008; 35: 2169-2181.
8. Giacobini E, Gold G. Alzheimer disease therapy--moving from amyloid- β to tau. *Nat Rev Neurol*. 2013; 9: 677-686.
9. García-Barroso C, Ricobaraza A, Pascual-Lucas M, Unceta N, Rico AJ, Goicolea MA, et al. Tadalafil crosses the blood-brain barrier and reverses cognitive dysfunction in a mouse model of AD. *Neuropharmacology*. 2013; 64: 114-123.
10. Houslay MD, Milligan G. Tailoring cAMP-signalling responses through isoform multiplicity. *Trends Biochem Sci*. 1997; 22: 217-224.
11. Peng S, Sun H, Zhang X, Liu G, Wang G. Effects of selective phosphodiesterases-4 inhibitors on learning and memory: a review of recent research. *Cell Biochem Biophys*. 2014; 70: 83-85.
12. Borrelli E, Montmayeur JP, Foulkes NS, Sassone-Corsi P. Signal transduction and gene control: the cAMP pathway. *Crit Rev Oncog*. 1992; 3: 321-338.
13. Denninger JW, Marletta MA. Guanylate cyclase and the NO/cGMP signaling pathway. *Biochim Biophys Acta*. 1999; 1411: 334-350.
14. Ohm TG, Bohl J, Lemmer B. Reduced cAMP-signal transduction in postmortem hippocampus of demented old people. *Prog Clin Biol Res*. 1989; 317: 501-509.
15. Ikezu T, Okamoto T, Komatsuzaki K, Matsui T, Martyn JA, Nishimoto I. Negative transactivation of cAMP response element by familial Alzheimer's mutants of APP. *Embo J*. 1996; 15: 2468-2475.
16. Ugarte A, Gil-Bea F, García-Barroso C, Cedazo-Minguez Á, Ramírez MJ, Franco R, et al. Decreased levels of guanosine 3', 5'-monophosphate (cGMP) in cerebrospinal fluid (CSF) are associated with cognitive decline and amyloid pathology in Alzheimer's disease. *Neuropathol Appl Neurobiol*. 2015; 41: 471-482.
17. Huang H, Wang H, Figueiredo-Pereira ME. Regulating the ubiquitin/proteasome pathway via cAMP-signaling: neuroprotective potential. *Cell Biochem Biophys*. 2013; 67: 55-66.
18. Carlyle BC, Nairn AC, Wang M, Yang Y, Jin LE, Simen AA, et al. cAMP-PKA phosphorylation of tau confers risk for degeneration in aging association cortex. *Proc Natl Acad Sci U S A*. 2014; 111: 5036-5041.
19. Vitolo OV, Sant'Angelo A, Costanzo V, Battaglia F, Arancio O, Shelanski M. Amyloid β -peptide inhibition of the PKA/CREB pathway and long-term potentiation: reversibility by drugs that enhance cAMP signaling. *Proc Natl Acad Sci U S A*. 2002; 99: 13217-13221.
20. Smith DL, Pozueta J, Gong B, Arancio O, Shelanski M. Reversal of long-term dendritic spine alterations in Alzheimer disease models. *Proc Natl Acad Sci U S A*. 2009; 106: 16877-16882.
21. España J, Valero J, Miñano-Molina AJ, Masgrau R, Martín E, Guardia-Laguarta C, et al. β -Amyloid disrupts activity-dependent gene transcription required for memory through the CREB coactivator CRTC1. *J Neurosci*. 2010; 30: 9402-9410.
22. Tong L, Thornton PL, Balazs R, Cotman CW. β -amyloid-(1-42) impairs activity-dependent cAMP-response element-binding protein signaling in neurons at concentrations in which cell survival is not compromised. *J Biol Chem*. 2001; 276: 17301-17306.
23. Gong B, Vitolo OV, Trinchese F, Liu S, Shelanski M, Arancio O. Persistent improvement in synaptic and cognitive functions in an Alzheimer mouse model after rolipram treatment. *J Clin Invest*. 2004; 114: 1624-1634.
24. Caccamo A, Maldonado MA, Bokov AF, Majumder S, Oddo S. CBP gene transfer increases BDNF levels and ameliorates learning and memory deficits in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2010; 107: 22687-22692.
25. Yiu AP, Rashid AJ, Josselyn SA. Increasing CREB function in the CA1 region of dorsal hippocampus rescues the spatial memory deficits in a mouse model of Alzheimer's disease. *Neuropsychopharmacology*. 2011; 36: 2169-2186.
26. Bonkale WL, Winblad B, Ravid R, Cowburn RF. Reduced nitric oxide responsive soluble guanylyl cyclase activity in the superior temporal cortex of patients with Alzheimer's disease. *Neurosci Lett*. 1995; 187: 5-8.
27. Vallebuona F, Raiteri M. Age-related changes in the NMDA receptor/nitric oxide/cGMP pathway in the hippocampus and cerebellum of freely moving rats subjected to transcranial microdialysis. *Eur J Neurosci*. 1995; 7: 694-701.
28. Chalimoniuk M, Strosznajder JB. Aging modulates nitric oxide synthesis and cGMP levels in hippocampus and cerebellum. Effects of amyloid β peptide. *Mol Chem Neurobiol*. 1998; 35: 77-95.
29. Paris D, Town T, Parker TA, Tan J, Humphrey J, Crawford F, et al. Inhibition of Alzheimer's β -amyloid induced vasoactivity and proinflammatory response in microglia by a cGMP-dependent mechanism. *Exp Neurol*. 1999; 157: 211-221.
30. Baltrons MA, Pedraza CE, Heneka MT, García A. β -amyloid peptides decrease soluble guanylyl cyclase expression in astroglial cells. *Neurobiol Dis*. 2002; 10: 139-149.
31. Puzzo D, Vitolo O, Trinchese F, Jacob JP, Palmeri A, Arancio O. Amyloid- β Peptide Inhibits Activation of the Nitric Oxide/cGMP/cAMP-Responsive Element-Binding Protein Pathway during Hippocampal Synaptic Plasticity. *The Journal of Neuroscience*. 2005; 25: 6887-6897.
32. Kametani F, Haga S. Accumulation of carboxy-terminal fragments of APP increases phosphodiesterase 8B. *Neurobiol Aging*. 2015; 36: 634-637.
33. Pera M, Alcolea D, Sánchez-Valle R, Guardia-Laguarta C, Colom-Cadena M, Badiola N, et al. Distinct patterns of APP processing in the CNS in autosomal-dominant and sporadic Alzheimer disease. *Acta Neuropathol*. 2013; 125: 201-213.
34. Robakis NK, Georgakopoulos A. Allelic interference: a mechanism for trans-dominant transmission of loss of function in the neurodegeneration of familial Alzheimer's disease. *Neurodegener Dis*. 2014; 13: 126-130.
35. Kametani F. Epsilon-secretase: reduction of amyloid precursor protein epsilon-site cleavage in Alzheimer's disease. *Curr Alzheimer Res*. 2008; 5: 165-171.
36. Wiley JC, Hudson M, Kanning KC, Schecterson LC, Bothwell M. Familial Alzheimer's disease mutations inhibit gamma-secretase-mediated liberation of beta-amyloid precursor protein carboxy-terminal fragment. *J Neurochem*. 2005; 94: 1189-1201.
37. Pérez-Torres S, Cortés R, Tolnay M, Probst A, Palacios JM, Mengod G. Alterations on phosphodiesterase type 7 and 8 isozyme mRNA expression in Alzheimer's disease brains examined by in situ hybridization. *Exp Neurol*. 2003; 182: 322-334.
38. Gupta S, Sharma B. Protective effects of phosphodiesterase-1 (PDE1) and ATP sensitive potassium (KATP) channel modulators against 3-nitropropionic acid induced behavioral and biochemical toxicities in experimental Huntington's disease. *European Journal of Pharmacology*. 2014; 732: 111-122.
39. Beaumont V, Park L, Rassoulpour A, Dijkman U, Heikkinen T, Lehtimäki K, et al. The PDE1/5 Inhibitor SCH-51866 Does Not Modify Disease Progression in the R6/2 Mouse Model of Huntington's Disease. *PLoS Curr*. 2014; 6.
40. Sierksma AS, Rutten K, Sydlik S, Rostamian S, Steinbusch HW, van den Hove DL, et al. Chronic phosphodiesterase type 2 inhibition improves memory in the APP^{swe}/PS1^{dE9} mouse model of Alzheimer's disease. *Neuropharmacology*. 2013; 64: 124-136.
41. Park SH, Kim JH, Bae SS, Hong KW, Lee D-S, Leem JY, et al. Protective effect of the phosphodiesterase III inhibitor cilostazol on amyloid β -induced

- cognitive deficits associated with decreased amyloid β accumulation. *Biochemical and Biophysical Research Communications*. 2011; 408: 602-608.
42. Sakurai H, Hanyu H, Sato T, Kume K, Hirao K, Kanetaka H, et al. Effects of cilostazol on cognition and regional cerebral blood flow in patients with Alzheimer's disease and cerebrovascular disease: a pilot study. *Geriatr Gerontol Int*. 2013; 13: 90-97.
43. Maki T, Okamoto Y, Carare RO, Hase Y, Hattori Y, Hawkes CA, et al. Phosphodiesterase III inhibitor promotes drainage of cerebrovascular β -amyloid. *Ann Clin Transl Neurol*. 2014; 1: 519-533.
44. Yanai S, Semba Y, Ito H, Endo S. Cilostazol improves hippocampus-dependent long-term memory in mice. *Psychopharmacology (Berl)*. 2014; 231: 2681-2693.
45. Yang L, Calingasan NY, Lorenzo BJ, Beal MF. Attenuation of MPTP neurotoxicity by rolipram, a specific inhibitor of phosphodiesterase IV. *Exp Neurol*. 2008; 211: 311-314.
46. Cheng YF, Wang C, Lin HB, Li YF, Huang Y, Xu JP, et al. Inhibition of phosphodiesterase-4 reverses memory deficits produced by A β 25-35 or A β 1-40 peptide in rats. *Psychopharmacology (Berl)*. 2010; 212: 181-191.
47. Sierksma AS, van den Hove DL, Pfau F, Philippens M, Bruno O, Fedele E, et al. Improvement of spatial memory function in APP^{swe}/PS1^{dE9} mice after chronic inhibition of phosphodiesterase type 4D. *Neuropharmacology*. 2014; 77: 120-130.
48. Rutter AR, Poffe A, Cavallini P, Davis TG, Schneck J, Negri M, et al. GSK356278, a Potent, Selective, Brain-Penetrant Phosphodiesterase 4 Inhibitor That Demonstrates Anxiolytic and Cognition-Enhancing Effects without Inducing Side Effects in Preclinical Species. *J Pharmacol Exp Ther*. 2014; 350: 153-163.
49. Puzzo D, Staniszewski A, Deng SX, Privitera L, Leznik E, Liu S, et al. Phosphodiesterase 5 inhibition improves synaptic function, memory, and amyloid-beta load in an Alzheimer's disease mouse model. *J Neurosci*. 2009; 29: 8075-8086.
50. Cuadrado-Tejedor M, Hervias I, Ricobaraza A, Puerta E, Pérez-Roldán JM, García-Barroso C, et al. Sildenafil restores cognitive function without affecting β -amyloid burden in a mouse model of Alzheimer's disease. *British Journal of Pharmacology*. 2011; 164: 2029-2041.
51. Fiorito J, Saeed F, Zhang H, Staniszewski A, Feng Y, Francis YI, et al. Synthesis of quinoline derivatives: Discovery of a potent and selective phosphodiesterase 5 inhibitor for the treatment of Alzheimer's disease. *Eur J Med Chem*. 2013; 60: 285-294.
52. Zhang J, Guo J, Zhao X, Chen Z, Wang G, Liu A, et al. Phosphodiesterase-5 inhibitor sildenafil prevents neuroinflammation, lowers beta-amyloid levels and improves cognitive performance in APP/PS1 transgenic mice. *Behavioural Brain Research*. 2013; 250: 230-237.
53. Devan BD, Pistell PJ, Duffy KB, Kelley-Bell B, Spangler EL, Ingram DK. Phosphodiesterase inhibition facilitates cognitive restoration in rodent models of age-related memory decline. *NeuroRehabilitation*. 2014; 34: 101-111.
54. Perez-Gonzalez R, Pascual C, Antequera D, Bolos M, Redondo M, Perez DI, et al. Phosphodiesterase 7 inhibitor reduced cognitive impairment and pathological hallmarks in a mouse model of Alzheimer's disease. *Neurobiol Aging*. 2013; 34: 2133-2145.
55. Schwam EM, Nicholas T, Chew R, Billing CB, Davidson W, Ambrose D, et al. A multicenter, double-blind, placebo-controlled trial of the PDE9A inhibitor, PF-04447943, in Alzheimer's disease. *Curr Alzheimer Res*. 2014; 11: 413-421.