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PDE3 Inhibitors Repurposed as Treatments for Age-Related Cognitive Impairment

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Abstract

As the population of older individuals grows worldwide, researchers have increasingly focused their attention on identifying key molecular targets of age-related cognitive impairments, with the aim of developing possible therapeutic interventions. Two such molecules are the intracellular cyclic nucleotides, cAMP and cGMP. These second messengers mediate fundamental aspects of brain function relevant to memory, learning, and cognitive function. Consequently, phosphodiesterases (PDEs), which hydrolyze cAMP and cGMP, are promising targets for the development of cognition-enhancing drugs. Inhibitors that target PDEs work by elevating intracellular cAMP. In this review, we provide an overview of different PDE inhibitors, and then we focus on pharmacological and physiological effects of PDE3 inhibitors in the CNS and peripheral tissues. Finally, we discuss findings from experimental and preliminary clinical studies and the potential beneficial effects of the PDE3 inhibitor cilostazol on age-related cognitive impairments. In the innovation pipeline of pharmaceutical development, the antiplatelet agent cilostazol has come into the spotlight as a novel treatment for mild cognitive impairment. Overall, the repurposing of cilostazol may represent a potentially promising way to treat mild cognitive impairment, Alzheimer's disease, and vascular dementia. In this review, we present a brief summary of cAMP signaling and different PDE inhibitors, followed by a discussion of the pharmacological and physiological role of PDE3 inhibitors. In this context, we discuss the repurposing of a PDE3 inhibitor, cilostazol, as a potential treatment for age-related cognitive impairment based on recent research.

Keywords Phosphodiesterase (PDE) inhibitor · Cilostazol · Memory · Dementia · Aging

Introduction

Aging populations continue to expand in many developed countries [1]. As humans approach their maximum possible lifespan [2], average lifespan also increases. While this can be seen as a great technological, medical, and societal success, it is accompanied by an increase in the number of people suffering from age-related health issues, such as cognitive and memory decline. Memory decline due to aging negatively impacts healthy aging, because memory is the basis of a variety of other higher cognitive functions, including thought, language, and emotion (reviewed by [3, 4]). Given the existential aspect of memory, it is not surprising that great efforts have been made to reverse age-related memory decline.

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To date, cognitive impairment has been treated with various acetylcholinesterase (AChE)/butyrylcholinesterase (BChE) inhibitors (e.g., [5, 6]). Among these cholinergic strategy-based inhibitors (e.g., donepezil, galantamine, and rivastigmine), donepezil has undergone extensive study [7, 8]. Donepezil is now considered to be the first-line treatment in patients with mild-to-moderate Alzheimer's disease (AD) [7, 8]. Recent studies using a mouse model of AD has provided new insights on the effects of donepezil. For example, donepezil effectively ameliorates age-related attentional deficits [9] and reduces soluble amyloid β (Aβ) protein and the number of plaque deposits [10]. For typical AChE inhibitors, such as donepezil, however, such protective effects against cognitive impairment do not persist, becoming less effective with time [11]. Moreover, many patients experience adverse drug reactions, such as emetic and other problematic side effects [11]. While AChE-BChE inhibitors have brought relief to many dementia sufferers, they have made little impact on dampening the global tsunami of older individuals with AD.

Researchers have more recently been looking beyond existing cholinergic-based strategies (reviewed by [12, 13]),

instead focusing their attention on identifying other molecular targets for possible therapeutic interventions. Numerous behavioral studies have reported that certain psychotropic compounds, including amphetamine, methylphenidate, and fluoxetine, show some therapeutic efficacy as treatments for age-related cognitive disorders [14–16]. While such drug repurposing has its advantages, the downside with these compounds is that patients taking them require close monitoring, because they possess strong psychotropic effects and sustained use may produce physical or psychological dependency associated with withdrawal [17].

In recent years, an increasing number of studies have focused on the cellular cascade triggered by the activation of 3′, 5′-cyclic adenosine monophosphate (cAMP) as an alternative strategy to treat age-related cognitive deficits. cAMP and its signal transduction pathways mediate the long-term neuronal plasticity that underlies learning and memory (reviewed by [18–20]).

In this review, we present a brief summary of cAMP signaling and different PDE inhibitors in the context of drug repurposing. We then focus our discussion on the pharmacological and physiological role of phosphodiesterase 3 (PDE3) inhibitors. In this context, we also discuss, based on recent research, using the PDE3 inhibitor cilostazol as a potential therapeutic intervention for cognitive impairments.

cAMP and Memory

Regulation of cAMP Like other homeostatic mechanisms, regulation of intracellular concentration of cAMP is achieved through a balancing of its synthesis via adenylate cyclase and its hydrolysis via phosphodiesterases (PDEs). A major downstream target of cAMP is cAMP-dependent protein kinase (PKA) [21]. Activated PKA phosphorylates a variety of proteins to evoke tightly controlled physiological reactions. The phosphorylation of cAMP response element-binding protein (CREB) bound to cAMP response element (CRE) on genes triggers the recruitment of other transcriptional components and then initiates transcription of downstream genes [22–25]; reviewed in [18, 26, 27]. cAMP also directly binds to and regulates the function of ion channels, such as hyperpolarization-activated cyclic nucleotide-gated channels [28] and a few other cyclic nucleotide-binding proteins, including Epac1 and Epac2 [29]. PDEs are enzymes that hydrolyze cyclic nucleotides, including cAMP and/or cGMP, by breaking their phosphodiester bond [30, 31]. The inhibition of PDE leads to an elevated level of intracellular cAMP and cGMP concentrations (reviewed in [32]).

cAMP-Regulated Memory The cAMP-PKA-CREB signaling pathway plays a variety of physiological roles (reviewed by [33, 34]). In the CNS, the pathway mediates the long-term neuronal plasticity that underlies learning and memory (reviewed by [18–20]). Furthermore, the endogenous CREB antagonist, inducible cAMP early repressor (ICER), which suppresses the function of CREB during transcription, plays an important role in memory [35, 36]. The CREB system works as an accelerator, while the ICER system works as a suppressor of memory function [35]. As observed in other physiological systems, the ICER system acts to prevent the storage of excess memories [35, 36]. Despite the abundance of evidence that CREB would be a promising molecule to target for memory enhancement, not many direct CREB-regulating drugs have been isolated [37]. Although enhancing CREB functions may lead to enhanced neural plasticity and memory, it also non-specifically affects all body tissues, including those having non-nervous system functions [33]. This is because cAMP and its downstream components exist ubiquitously throughout the body (reviewed by [38, 39]).

Basic research on therapeutic interventions for cognitive decline have been conducted on a large library of small molecules, with the aim of identifying drugs that maintain and/or prolong the CREB activity induced by memory-related neuronal activity. For this purpose, PDEs have attracted attention for memory enhancement and maintenance, since they are important for regulating cAMP levels in specific brain regions. Different PDE families reside in different tissues, permitting tissue-specific therapeutic targeting. PDE inhibitors enhance synaptic plasticity by elevating the concentration of intracellular cAMP (reviewed by [40]). For these reasons, PDE inhibitors are promising candidates for therapeutic relief of cognitive impairment. This approach of treating cognitive decline is a manifestly different strategy from existing cholinergic-based strategies [20, 41–45].

PDE Inhibitors for Relieving Cognitive Impairment

PDE and Memory Since the first isolation and biochemical characterization of a PDE in the early 1970s [46, 47], 11 major PDE families have been identified. In mammalian tissues, they have been characterized according to their pharmacological function, substrate specificity, tissue localization, and gene characteristics (Table 1, [48]).

Among the 11 types of PDEs, PDE6 and PDE11 are not expressed in the CNS. Therefore, these two PDEs likely will not be relevant targets for memory enhancement [50]. Recent studies demonstrate that several inhibitors selective for certain PDEs ameliorate or enhance memory and cognitive functions in rodent models. Examples include inhibitors of PDE2 (bay 60-7550, reviewed by [51]); PDE4 (rolipram, reviewed by [52, 53]); PDE5 (sildenafil and zaprinast, reviewed by [54]); PDE7 (S14, [55, 56]); PDE9 (bay 73-6691, [57–59]); and PDE10 (MP-10, SEP-39, and TAK-063, reviewed by [60]).

Table 1 Classification of PDE subtypes in mammalian tissues and inhibitors[a]

Type	Number of isoforms	Localization		Substrate specificity	Representative inhibitor
		Peripheral tissue	CNS		
PDE1	3	+	+	cAMP/cGMP	IC224, vinpocetine
PDE2	1	+	+	cAMP/cGMP	BAY60-7550, EHNA
PDE3	2	+	+	cAMP/cGMP	Amrinone, cilostamide, cilostazol, milrinone
PDE4	4	+	+	cAMP	GEBR-7b, HT-0712, roflumilast, rolipram
PDE5	1	+	+	cGMP	Sildenafil, tadalafil, verdenafil, zaprinast
PDE6	3	+	−	cGMP	(Sildenafil)[b]
PDE7	2	+	+	cAMP	BRL50481, IC242
PDE8	2	+	+	cAMP	Dipyridamole
PDE9	1	+	+	cGMP	BAY73-6691
PDE10	1	+	+	cAMP/cGMP	MP-10, SEP-39, TAK-063
PDE11	1	+	−	cAMP/cGMP	(Tadalafil)[b]

[a] Revised from [48]

[b] Inhibition of PDE6 and PDE11 could be caused by non-specific inhibition of sildenafil and tadalafil [49]

Many studies have been conducted to determine the effects of the PDE4-selective inhibitor rolipram on cognitive function (reviewed by [52, 53]). These studies stem from the pioneering work of Wachtel [61], who discovered rolipram and found that it has antidepressant effects. Recent studies have extended the therapeutic potential of rolipram to a variety of CNS disorders, including AD, Parkinson's disease, and schizophrenia (reviewed by [52]). Due to its beneficial and promising effects in a number of pre-clinical studies, rolipram underwent a number of clinical trials on depression relief (reviewed by [52]). Clinical development of PDE4 inhibitors, however, has been mostly terminated because of their potent emetic side effects in humans [62]. In order to be clinically useful as an anti-dementia drug, it is important for it to have few or no side effects. Currently, several new PDE4-specific inhibitors have been developed that in effect have a wider therapeutic window, because the emetic side effects have been reduced (GEBR-7b, HT-0712, and roflumilast, reviewed by [42]).

Characterization of PDE3

Enzymatic and Kinetic Properties Recently, PDE3 inhibitors have attracted much attention for treating cognitive decline because of their multiple pharmacological actions [20, 63–65]. Among all the PDEs, PDE3 is distinguished by having the highest affinities for both cAMP and cGMP (Table 2) [68, 69]. Because PDE3 exhibits this high affinity in a mutually competitive manner (Table 2) [68, 69], it is known also as cGMP-inhibited PDE [69, 70]. The presence of a 44-amino-acid insertion in the catalytic domain is a unique characteristic of PDE3 (reviewed by [32]). There are no major differences in the Michaelis-Menten kinetics value of PDE3 for cAMP and cGMP; Km values for cAMP and cGMP are 0.47 and 0.29 μM, respectively [67]. This means that PDE3 binds cAMP and cGMP with similar affinity. However, cAMP is hydrolyzed at a 2- to 10-fold higher rate than cGMP; Vmax values for cAMP and cGMP are 8.5 and 2.0 μmol/min/mg, respectively [48]. cGMP's low Vmax value compared to cAMP makes cGMP a competitive inhibitor for cAMP hydrolysis [71]. This, in turn, results in an increase in cAMP in the presence of similar local concentrations of cAMP and cGMP [72].

Genes and Distribution The cDNAs for two distinct but related PDE3 isoforms have been cloned from human [73, 74] and rabbit [75], namely PDE3A and PDE3B. In humans, PDE3A and PDE3B genes are located on chromosomes 11 and 12, respectively [74, 76, 77]. Although these two PDE3 isoforms have similar structures and pharmacological and kinetic properties (Table 2) [48, 78, 79], they have different tissue distributions (Table 3). Because of its distribution in peripheral tissues, PDE3A is mainly implicated in cardiovascular function and fertility; it is abundant in platelets, heart, vascular smooth muscle, and oocytes. On the other hand, because of the prominent distribution of PDE3B in adipocytes, hepatocytes, and developing spermatocytes, it is mainly implicated in lipolysis [69, 81, 82]. In the CNS, both PDE3A and PDE3B are localized in hippocampus, cortex, and olfactory bulb. However, PDE3A, but not PDE3B, is distributed within striatum, amygdala, and hypothalamus [83].

To date, a relatively large number of selective PDE3 inhibitors have been developed. Representative selective PDE3

Table 2 Enzymatic and kinetic properties and localization of PDE3 isoforms

	Isoform	
	PDE3A	PDE3B
Km (μM)		
cAMP	0.18[a]–0.24[b]	0.47[b]
cGMP	0.02[a]–0.09[b]	0.29[b]
Vmax (μmol/min/mg)		
cAMP	3.0[a]	8.5[c]
cGMP	0.28-0.35[a]	2.0[c]
Localization		
Peripheral tissue	Heart, vascular smooth muscle, platelets, oocytes, kidney	Vascular smooth muscle, adipocytes, hepatocytes, spermatocytes
CNS	Hippocampus, striatum, cortex, olfactory bulb, amygdala, hypothalamus	Hippocampus, cortex, olfactory bulb

[a] Values are from [66]

[b] Values are from [67]

[c] Values are from [48]

inhibitors and their IC_{50} values are summarized in Table 3, and their chemical structures are shown in Fig. 1. Since PDE3A and PDE3B have similar inhibitory potencies, their inhibitors do not distinguish between PDE3A and 3B [72]. These characteristics of PDE3 and its inhibitors suggest that it might be repurposed for treating cognitive decline. Physiological studies of PDE3 inhibitors show that they have been useful in treating other conditions of cognitive decline [20, 63–65].

Physiological Roles of PDE3

Peripheral Tissues Because PDE3 was found to be involved in the regulation of cardiac and vascular smooth muscle contractility, the clinical history of PDE3 inhibitors followed this theme, initially being used in the treatment of cardiovascular disease. Milrinone [84] and amrinone [85] have been used to treatment congestive heart failure resulting from dilated cardiomyopathy; these PDE3 inhibitors behave as positive inotropes by inhibiting the hydrolysis of cAMP, resulting in increased myocardial contractility [86, 87].

The clinical significance of PDE inhibitors can be found in results derived from the treatment of other medical conditions, not just in the treatment of congestive heart failure. Because of its effectiveness in decreasing platelet aggregation, cilostazol has been used in several countries to treat chronic peripheral arterial occlusion [88, 89]. In the USA, cilostazol was approved by the US Food and Drug Administration (FDA) in 1999 for the treatment of intermittent claudication [90, 91]. In addition to its use for treating peripheral arterial occlusive disease, cilostazol's use has been expanded as therapeutics for other diseases. A recent study showed that cilostazol prevents secondary stroke in patients who had experienced a cerebral infarction [92].

CNS In addition to its peripheral mechanism of action, cilostazol is attractive because of its pharmacological actions in the CNS (Table 4), as it may directly affect memory circuits. Imaging studies of the human brain have revealed that structural and functional declines in the hippocampus are prominent during the course of aging [102, 103]. Thus, chronological age is a significant risk factor for dementia [104, 105]. These changes may explain why age-related decline in memory is observed mainly in hippocampal-dependent declarative memory (reviewed by [106, 107]). For these reasons, behavioral tests that tap into hippocampal-dependent memory are frequently used in rodents to evaluate pharmacological interventions aimed at treating human dementia [108, 109].

In studies using a mouse model of AD, in which Aβ25–35 is injected intracerebroventricularly, oral administration of

Table 3 IC_{50} values for PDE3 inhibitors[a]

Inhibitor	IC50 (μM)		Diseases applied
	PDE3A	PDE3B	
Amrinone	16.7	31.2	Congestive heart failure
Cilostamide[b]	0.027	0.050	
Cilostazol	0.2	0.38	Peripheral arterial occlusion, intermittent claudication
Milrinone	0.45	1.0	Congestive heart failure

[a] Adapted from [67]

[b] Although cilostamide has strong inhibitory effects, its clinical development has been terminated because of its strong cardiotropic side effects, such as increasing heart rate [80]

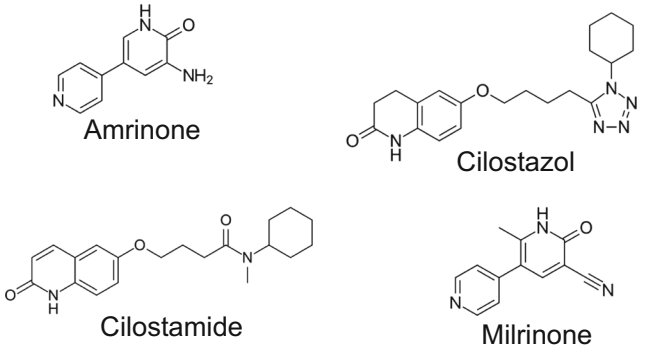

Fig. 1 Chemical structures of representative PDE3-specific inhibitors

cilostazol significantly ameliorated deficits in several tasks [64, 93]. Cilostazol administration also rescued the Aβ25–35-induced impairment in spontaneous alternation task performance. This test is an ethologically based task that requires short-term working memory to correctly alternate maze arm traversals on successive trials [93]. Similarly, cilostazol ameliorated spatial memory impairment in the Morris water maze task [64] and in the radial arm maze task [98]. These latter two tasks both assess long-term spatial memory. However, different types of motivation are required to perform these tasks: escaping an aversive situation (water) in the Morris water maze task [110, 111] and eliminating a hungry state in the radial arm maze task [112]. Notably, the Morris water maze task is one of the most widely used tasks to assess spatial memory in rodents (reviewed by [113]).

The beneficial effect of cilostazol on memory performance was also observed in associative learning, specifically, contextual fear conditioning [100]. This task requires the association of an aversive stimulus and a particular neutral context (reviewed by [114]). We reported that cilostazol administration ameliorated the impaired contextual fear memory in senescence-accelerated mouse prone 8 (SAMP8). SAMP8 possesses a distinct feature, the early-onset of age-related cognitive impairment, compared to that of the normal aging control senescence-accelerated mouse resistant 1 (SAMR1) [100]. Considering the dissociable contributions of the hippocampus and amygdala in fear memory [115, 116], cilostazol administration appears to preferentially ameliorate hippocampus-dependent memory, not amygdala-dependent fear. In addition to showing that hippocampus-dependent memory is enhanced [64, 93, 98, 100], we recently reported that long-term, mixed-in-feed administration of cilostazol for 10 months enabled aged C57BL/6J mice to maintain spatial memory performance in the Morris water maze task to the same level as that of middle-aged mice [101]. Surprisingly, in young mice, cilostazol can enhance performance in the Morris water maze and in a contextual fear-conditioning task [45]. Importantly, cilostazol had no detectable side effects on emotional states or physical ability, such as locomotion, swimming, and pain sensitivity [45, 100, 101]. These physiological studies on cilostazol show that PDE inhibitors could possibly be repurposed for treating other conditions of cognitive decline that are related to disrupted hippocampal function.

Multiple Pharmacological Actions In concert with the hypothesis that the cAMP-PKA-CREB signaling pathway mediates long-term neuronal plasticity underlying learning and

Table 4 CNS-related effects of cilostazol administration[a]

Disease/model	Task/evaluation	Effect of cilostazol	Reference
Mouse, Aβ25–32 injection (i.c.v.)	Spontaneous alternation	Ameliorate	[93]
Mouse, Aβ25–32 injection (i.c.v.)	Morris water maze	Ameliorate	[64]
Human, Alzheimer and cerebrovascular disease	ADAS, Wechsler Memory Scale, Trail Making Test	Maintain	[94]
Human, MCI[a]	MMSE	Suppress the decline	[63]
Mouse, young	Morris water maze, fear conditioning	Ameliorate	[45]
Rat, chronic cerebral hypoperfusion	Radial arm maze	Ameliorate	[95]
Rat, ischemia/reperfusion	Morris water maze	Ameliorate	[96]
Rat, L-methionine injection (p.o.)	Morris water maze	Ameliorate	[97]
Mouse, chronic cerebral hypoperfusion	Radial arm maze	Ameliorate	[98]
Human, MCI[a]	MMSE, CDR-SB	Suppress the decline	[99]
Mouse, accelerated senescence	Fear conditioning	Ameliorate	[100]
Mouse, normal aging	Object recognition, Morris water maze	Maintain	[101]

[a] Concurrent administration of cilostazol with donepezil [63] or with AChE inhibitor (details unknown) [99]

i.c.v., intracerebroventricular; p.o., per os; ADAS, Alzheimer's Disease Assessment Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating Sum of Boxes

memory [18, 25, 117], cilostazol increases the number of phosphorylated CREB-positive cells in the dentate gyrus of the hippocampal region [45, 100]. This finding is significant when the flow of sensory information from higher cortical areas is processed in the hippocampus. Sensory and other information is first funneled into the dentate gyrus for further information processing in the hippocampus [118]. Long-term cilostazol administration may maintain this type of information processing at the early stages of hippocampal processing to somewhat normal levels, a function that normally declines during the course of aging. This could be accomplished via modulation of the cAMP pathway in this first stage of hippocampal memory processing, which occurs in the dentate gyrus.

Brain-derived neurotrophic factor (BDNF) gene, which is among the genes regulated in a CREB-dependent manner, is highly expressed in the hippocampus [119]. BDNF is known to be a potent regulator of memory [120, 121], and an inducer of neurogenesis in the dentate gyrus [122, 123]. Manipulating BDNF levels in the dentate gyrus could be a possible mechanism for retarding cognitive decline. Disruption in BDNF expression leads to age-related cognitive impairment [124] and decreased neurogenesis, which can be reversed by exogenous BDNF administration [125]. Cilostazol administration might ameliorate memory dysfunction through a cilostazol-induced increase in the number of hippocampal neurons, especially in the dentate gyrus [45, 100, 126–128].

Cilostazol may also contribute to maintenance of blood-brain barrier (BBB) integrity or to dampening of its age-related decline [100]. Disruption of the BBB leads to CNS inflammation (reviewed by [129, 130]), which then can start a cascade of age-related impairment in cognitive functions (reviewed by [131–133]). Cilostzol's beneficial effects can potentially improve the brain environment, boosting memory function [100]. Furthermore, cilostazol may contribute to the maintenance of a healthy brain environment by enhancing the clearance of accumulations of Aβ. This has been demonstrated in a mouse model of cerebral amyloid angiopathy [65]. Consistent with this finding is that cilostazol suppresses Aβ-induced neurotoxicity in human-derived SH-SY5Y cells grown in culture [134]. Cilostazol also reduces Aβ production in human induced-pluripotent stem cell (iPSC)-derived neurons [135]. Overall, cilostazol has a number of pharmacological actions that could be leveraged in new and beneficial ways to stave off cognitive decline.

Drug Repurposing to Treat Age-Related Cognitive Impairment

Therapeutic Intervention for MCI In addition to pre-clinical studies, some preliminary clinical studies on the effects of cilostazol on MCI and in AD patients have been conducted. In retrospective [63] and case control [99] studies of MCI patients, patients who took donepezil combined with cilostazol showed significantly slowed cognitive decline compared to those who took donepezil alone [63, 99]. Similarly, cilostazol-treated patients with AD and cerebrovascular disease showed increased regional cerebral blood flow in the right cingulate cortex [94]. Also, cognitive function assessed with widely used AD cognitive assessment tests showed that this improvement was maintained over 6 months [94]. Based on these positive findings, a clinical trial is now underway (Spring 2018) in Japan to treat MCI patients with cilostazol (ClinicalTrials.gov NCT02491268, UMIN Clinical Trials Registry UMIN000017764; [136]).

In the stream of innovative pharmaceutical development, drug repurposing has slowly come into the spotlight [137, 138]. The time required for drug development is shorter for repurposed drugs because pre-clinical and most clinical drug-safety trials can be largely skipped for an already-approved drug [137, 138]. Examples include using thalidomide, originally developed for insomnia or gastritis, to treat multiple myeloma [139]; sildenafil, originally developed for *angina pectoris*, to treat erectile dysfunction [140]; and raloxifene, originally developed for breast cancer, to treat osteoporosis [141]. Similarly, cilostazol, originally developed to treat symptoms of intermittent claudication in individuals with peripheral vascular disease [90, 91], may be repurposed as a new medication to treat cognitive impairment.

Potential Combination Therapy With pharmacological approaches in treating diseases, using a combination of two or more drugs is often more effective than using a single drug [142]. Such a strategy, however, has not been applied to the clinical treatment of cognitive impairment. The main purpose of combination therapy is (1) to achieve a synergistic therapeutic effect, (2) to reduce drug doses and side effects normally present with higher doses, and (3) to minimize or delay the induction of drug resistance [143]. Reducing dose and side effects is an important issue, especially for the elderly, because drug metabolism is often slower in older patients, and thus leads to stronger effects and stronger side effects [144, 145]. Together with its established safety profile [89, 90], cilostazol also has the advantage of being available in a generic. This can translate to lower cost of medical care for elderly patients [146]. The combined use of a PDE inhibitor and an AChE inhibitor has already been shown to enhance, to some extent, cognitive function both in animal models of chronic cerebral hypoperfusion [147], and in patients with moderate AD [148] and MCI [63, 99]. Concurrent administration of a PDE inhibitor with another anti-dementia drug, such as donepezil, may lead to pharmacological combination therapy for cognitive disorders, including vascular dementia and progressive neurodegenerative disorders.

Conclusions and Final Comments

Thanks to modern medical achievements, the population of older people continues to grow worldwide. Unfortunately, this growth is accompanied by a rapid increase in the number of people with dementia. In 2015, it was estimated that 46.8 million people worldwide were living with dementia and cognitive impairment, or cognitive decline [1]. That number is projected to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 [1]. As aging is a significant risk factor for dementia [104, 105], it is urgent to find a way to prevent or slow down the incidence of dementia.

To achieve healthy aging, society must address issues salient to the aging population, such as the prevention of age-related diseases (reviewed by [149]). It is well-known that exercise [150, 151], or a combination of cognitive training and exercise (the portmanteau, *cognicise*; reviewed in [152]), is beneficial for maintaining memory functions. However, there are older people with locomotive syndromes, who have difficulties exercising regularly, or who are hospitalized. As these people cannot benefit from exercise, their inactivity can increase their risk for dementia (reviewed in [153]). Monotherapy or concurrent administration of cilostazol with existing cholinergic-based drugs may represent a ray of hope for people with locomotor difficulties or those who are hospitalized. Cilostazol has been routinely prescribed around the world for more than two decades, and its safety is well established [89, 90]. Minor adverse effects occur with cilostazol, including headache, diarrhea, and palpitations [154]. However, these symptoms rarely require discontinuation of the drug, as they are mild to moderate in severity and often transient [155]. In addition, several studies report that patients treated with cilostazol are not at increased for bleeding [156, 157]. Moreover, cilostazol has been shown to increase cerebral blood flow [94, 158], decrease the size of cerebral infarcts [159], and ameliorate the degradation of BBB integrity [100, 160]. It is reasonable, therefore, to conclude that cilostazol might also be effective for treating vascular dementia. In fact, cilostazol administration has been shown to ameliorate cognitive impairment in a rodent model of vascular dementia [96, 97, 100]. Further basic study of cilostazol in the context of learning and memory will enhance our knowledge and understanding of its molecular mechanism of actions in the CNS. Randomized controlled trials with proven basic evidence will elevate cilostazol as a new therapeutic candidate for treating different types of cognitive impairment in humans.

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Abbreviations AChE, acetylcholinesterase; Aβ, amyloid β; AD, Alzheimer's disease; ATP, adenosine triphosphate; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; BChE, butyrylcholinesterase; cAMP, 3′,5′-cyclic adenosine monophosphate; cGMP, 3′,5′-cyclic guanosine monophosphate; CNS, central nervous system; CRE, cAMP response element; CREB, cAMP response element-binding protein; DG, dentate gyrus; MCI, mild cognitive impairment; PDE, phosphodiesterase; PKA, cAMP-dependent-protein kinase A; SAMP, senescence-accelerated mouse prone

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