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Review

Phosphodiesterase inhibitors say NO to Alzheimer's disease

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ABSTRACT

Phosphodiesterases (PDEs) consisted of 11 subtypes (PDE1 to PDE11) and over 40 isoforms that regulate levels of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP), the second messengers in cell functions. PDE inhibitors (PDEIs) have been attractive therapeutic targets due to their involvement in diverse medical conditions, *e.g.* cardiovascular diseases, autoimmune diseases, Alzheimer's disease (AD), etc. Among them; AD with a complex pathology is a progressive neurodegenerative disorder which affect mostly senile people in the world and only symptomatic treatment particularly using cholinesterase inhibitors in clinic is available at the moment for AD. Consequently, novel treatment strategies towards AD are still searched extensively. Since PDEs are broadly expressed in the brain, PDEIs are considered to modulate neurodegenerative conditions through regulating cAMP and cGMP in the brain. In this sense, several synthetic or natural molecules inhibiting various PDE subtypes such as rolipram and roflumilast (PDE4 inhibitors), vinpocetine (PDE1 inhibitor), cilostazol and milrinone (PDE3 inhibitors), sildenafil and tadalafil (PDE5 inhibitors), etc have been reported showing encouraging results for the treatment of AD. In this review, PDE superfamily will be scrutinized from the view point of structural features, isoforms, functions and pharmacology particularly attributed to PDEs as target for AD therapy.

1. Introduction

Phosphodiesterases (PDEs) are a large family of enzymes whose main role is to produce 5′-cyclic nucleotides through hydrolysing the 3′-phosphodiester bond in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) involved in signal-transduction pathways. Therefore, they possess a critical contribution in the important pathways in various pharmacological processes including

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cell function via adjusting levels of the cAMP and cGMP (Boswell-Smith et al., 2006). Consequently, PDE family has been an attractive multi-potential target related to many disease pathologies for researchers. Being an outsized enzyme group, PDEs consist of 11 isoenzyme families (PDE1 to PDE11) whose differences are based on substrate specificities and affinities, kinetic properties, tissue and subcellular distributions, regulatory mechanisms, drug and mediator sensitivities (Beavo et al., 1994; Abusnina and Lugnier, 2017). These isoenzyme families have been reported to reach over 40 PDE isoforms in total (encoded by 21 genes), which are specific either to cAMP (*i.e.* PDE4, PDE7, and PDE8) or cGMP (*i.e.* PDE5, PDE6, and PDE9), whereas some of those PDEs can act on both cAMP and cGMP (*i.e.* PDE1, PDE2, PDE3, and PDE11) (Wallace et al., 2005; DeNinno, 2012; Miller and Leslie, 1994). Existence of various isoforms in PDE families were revealed in 1970s in experimental animals (Beavo et al., 1970). Therefore, it points out to the fact that isoform/subtype-specific inhibitors should be developed due to richness of isoforms and subtypes in this enzyme family, a quite challenging task in pharmaceutical research. On the other hand, a great effort is being done recently to discover new PDEIs as subtype-selective agents targeting a number of diseases via experimental and computational methods.

Interestingly, history of PDEs started with careful observation of Henry Hyde Salter in 1886, who noticed the relieving effect of caffeine in himself as an asthmatic patient, while he was hungry (Boswell-Smith et al., 2006). This was followed by discovery of cAMP and cGMP as well as involvement of PDE in mechanism of bronchodilatory activity of caffeine (Sutherland and Rall, 1958; Ashman et al., 1963). Then, calcium-calmodulin (CaM), cAMP, and cGMP-related PDEs were explored and several different isoforms were characterized between 1980s and 1995 (Hidaka, 1984; Nicholson et al., 1991). In mammals, the molecular structure of PDEs have been recognized, indicating that these enzymes consisted of approximately 45% similar catalytic domain with 300 amino acids near the carboxyl terminus, where conserved histidine residues that bind with zinc, play their essential catalytic activities. On the other hand, amino terminal domains and the phosphorylation sites affect the membrane localization of some PDEs have been shown to be rather variable in PDE families with distinct features (Conti et al., 1995; Beavo, 1995).

The best-known PDEIs are methylxanthines (*e.g.* caffeine) acting as non-selective inhibitors on single isoforms of PDEs, whereas many other selective inhibitors against certain PDE subtypes also developed clinical expediency. For instance; an extensive research has been focused on the molecules (*e.g.* cilostazol, milrinone) with inhibitory effects against PDE3 for possible clinical use for cardiovascular diseases. Besides, selective PDE3, PDE4, and PDE5 inhibitors have been shown to possess the most significant anti-cough effects (Mokry et al., 2018). Moreover, one of the well-established examples of PDE-inhibiting drugs is sildenafil citrate, a reputed inhibitor of PDE5, which was discovered for cardiovascular disorders, particularly hypertension and angina pectoris and currently used as the first line therapy of erectile dysfunction (Andersson, 2018). In fact, the discovery of sildenafil led to development of more of its derivatives such as tadalafil and vardenafil. Despite their several side effects, PDE4 inhibitors have been confirmed to have promising antidepressant effect (Bolger, 2017; Zhang et al., 2017). It should be also mentioned that PDE families are rather complex due to their subtypes encoded by various genes (*e.g. PDE1A, PDE1B, PDE1C*, etc) and linked to the pathology of many diseases. For instance, PDE3A is located at cardiac tissues and platelets, while PDE3B is vastly expressed in adipocytes and the liver (Scapin et al., 2004).

PDEIs also display a promising effect in treatment of Alzheimer's disease (AD), a neurological disease with progressive nature that gradually destroys memory as well as cognitive skills along with behavioral abilities. As being the most common form of dementia, the pathogenesis of AD is quite complicated as characterized by various abnormalities in the brain such as irregular amyloid-β (Aβ) metabolism, tau hyperphosphorylation, oxidative stress, microglial variations, and some other pathological procedures (Wang et al., 2017a). In this manner, current therapeutic approaches have focused on major neuropathological aspects of AD: acetylcholine deficiency, glutamate excitotoxicity, Aβ and tau formation, as well as neuroinflammation. So far, several drugs have been developed and many are under trials. Major prescribed medications include cholinesterase inhibitors to reduce symptoms of mild, moderate to severe AD such as galantamine, rivastigmine, donepezil, memantine and etc. Studies in clinical trials mainly targeted acetylcholinesterase inhibitors, agonists and antagonists of neurotransmitter receptors (i.e. intepirdine), β- or γ-secretase inhibitors (i.e. E2609, AZD3293, verubecestat), vaccines or antibodies able to eliminate/reduce Aβ (i.e. crenezumab, gantenerumab, aducanumab) or tau plaques/aggregation (i.e. TRx0237), and anti-inflammatory agents. Although, nonamyloid-based mechanisms of action and biomarker-based AD drugs are of increasing interest in drug development (Hung and Fu, 2017; Cummings et al., 2018). Since only symptomatic treatment of AD is available by cholinesterase inhibitors, as the most prescribed class of drugs at the moment in clinic, the discovery of new drugs and treatment options are still in great demand to combat the disease. Since, the correlation between PDEs and the pathology of AD have been shown clearly (Bender and Beavo, 2006a; Maurice et al., 2014; Tokuchi et al., 2014; Wu et al., 2018), AD is one of the most prevalent age-related neurodegeneration associated with neuroinflammation and loss of mental ability (memory and cognitive function). The incidence of AD is expected to increase in the upcoming years due to increase of life expectancy (Huang and Mucke, 2012; Kontis et al., 2017). At molecular level loss of mental abilities associated with neuronal death involved in impairment of adult neurogenesis and clearance machinery, which lead to extracellular deposits of fibrillar Aβ and hyperphosphorylation and accumulation of cytoskeletal tau filaments (Hollands et al., 2016; Tarasoff-Conway et al., 2015). The cAMP response element binding protein (CREB), which is abundantly expressed in hippocampus, is regulated by cAMP/cGMP and promotes the neuronal survival through mechanisms associated with the stimulation of synaptic strengthening and memory formation (Teich et al., 2015). The memory consolidation and performance is regulated positively by CREB through upregulating the brain derived neurotrophic factor (BDNF) (Ran et al., 2012; Suzuki et al., 2011). It has been found that in the hippocampus of mice, acute neuroinflammation affects learning and memory-related CREB signaling through tumor necrosis factor (TNF)-α-dependent mechanisms (Ettcheto et al., 2018; Jensen et al., 2017). Moreover, Aβ decreases the BDNF levels through a mechanism involving transcription factor CREB downregulation (Rosa and Fahnestock, 2015) is well known that the majority of agents that interfere neurodegeneration improvement such as cognition enhancers, target a specific neurotransmitter. PDEs inhibition involved in process of neurodegeneration through increasing the intracellular availability of cGMP and/or cAMP. In the human brain PDEs are highly expressed, though, the levels of cAMP and cGMP can regulate the processes of neurodegeneration (Wu et al., 2018; Reneerkens et al., 2009; Wang et al., 2015). In a general point of view, PDE-inhibitors could improve cognition by regulating neuronal communication through manipulating presynaptic neurotransmitter release and postsynaptic intracellular pathways after extracellular neurotransmitter binding (Heckman et al., 2017).

Moreover, PDEIs positively effect on cognition improvement by means of information processing, attention, memory, and executive functioning (Reneerkens et al., 2009).

There are limited data on clinical effect of PDE-inhibitors on cognitive performance in AD and most of current data come from preclinical animal models of AD, i.e. transgenic mice or central injection of Aβ. Clinical trials demonstrated that considering AD management, the hippocampal mRNA expression of PDE4D and 8B were changed in age-associated memory impaired subjects as well as in patients with mild to moderate AD. The outcomes of behavioral preclinical and clinical investigations exhibited that DE7 improved the memory performance in

Table 1
Location, function and family type of PDEs.

Family	Location	Function or biological activity in the organism	Reference
PDE1	Smooth muscle, lung, heart, sperm, brain,	–	Bender and Beavo (2006b).
PDE2	Adrenal gland, liver, heart, brain, and endothelial cells	Adrenal aldosterone secretion, endothelial cell proliferation and permeability, angiogenesis, cardiac function, and platelet aggregation	(Yanaka et al., 2003; Van Staveren et al., 2004).
PDE3	Cardiac myocytes, platelets, and oocytes, lipocytes, liver and pancreas	Regulation of energy metabolism	Shakur et al. (2000).
PDE4	Brain, cardiovascular system, smooth muscle and innate immune cells	Memory performance, pathophysiology of depression and neuroinflammation	(Houslay et al., 2005). (Gurney et al., 2015; Zhang et al., 2002a)
PDE5	Platelets, lung, brain, especially in Purkinje neurons	Regulation of platelet aggregation, participate in recognition, memory functions and in cardiac remodeling	(Shimizu-Albergine et al., 2003; Giordano et al., 2001). (Apostoli et al., 2014; Takimoto et al., 2005; Prickaerts et al., 2004).
PDE6	Retina and cone cells, pineal gland	Suppression of melatonin synthesis by light.	(Ridge et al., 2003; Morin et al., 2001).
PDE7	Brain, lung, spleen, thymus, striatum	key contributor in dopaminergic cascade with a role in memory function	(Lugnier, 2006) (Sasaki et al., 2004).
PDE8	Brain, testis, liver, kidney, spleen, heart, thyroid gland, and skeletal muscle	–	(Keravis and Lugnier, 2012; Wang et al., 2001).
PDE9	Immune tissues and brain	PDE9 inhibition exert promising hypoglycemic effects in cell-based assays	(Wang et al., 2003; Van Staveren et al., 2002). (Shao et al., 2014; DeNinno et al., 2009).
PDE10	Brain, especially in the striatial area	Management of psychiatric diseases, cognitive impairment, Huntington's disease	(Fujishige et al., 1999; Soderling et al., 1999). (Beaumont et al., 2016; Schmidt et al., 2008; Rodefer et al., 2005).
PDE11	Skeletal muscle, prostate and in lesser amounts in liver, heart, brain, and pituitary gland	–	(Yuasa et al., 2001; Fawcett et al., 2000).

- Not reported.

AD and altered the PDE7A mRNA expression in the AD brain (Perez-Gonzalez et al., 2013a; Pérez-Torres et al., 2003). Heckman et al. suggested that inhibition of PDE4D isoform subtypes is a proper target for AD therapeutics (Heckman et al., 2015).

PDEIs may perform as a new target for AD therapy (Rutten et al., 2009; Hiramatsu et al., 2010; Taguchi et al., 2013; Dyck et al., 2017). As mentioned so far, PDEs are an important class of enzymes involved in many disease pathologies. Thus, a large literature survey underlines that inhibitors of PDEs emerge as promising useful pharmaceutical agents for the illnesses threating human health, which quite inspired us to realize the present review. In this article, our intention was to scrutinize PDEs covering their molecular structural differences, their isoforms in terms of function and pharmacology, along with the importance of PDEIs with synthetic and natural origins, as some drugs are already in clinical use with special attribution to AD.

2. Functional significance of PDE isoforms

A total of 21 isoforms of PDE classified into 11 families (PDE1-PDE11) characterized by specific tissue distribution and function (Lugnier, 2006) (Table 1). Most families comprise 1 to 4 distinct genes, which are expressed in different tissues and are subjected to alternative splicing processes, resulting in more than 100 different PDE proteins (Bender and Beavo, 2006a; Keravis and Lugnier, 2012). The PDE families 1, 2, 3, 10 and 11 can hydrolize cAMP and cGMP at different rates. On the other hand, PDE4, 7 and 8 act specifically on cAMP, while PDE5, 6, and 9 only hydrolize cGMP. The high diversity and complexity of the PDE family makes it difficult to know the physiological relevance of different isoforms. It seems that although there may be some redundancy between different isoforms, in general each of the PDE variants performs its own physiological functions.

PDE from family 1 are calcium- and calmodulin-dependent enzymes. This family is composed of three different isoforms, PDE1A, PDE1B, and PDE1C, derived from three different genes and presented in different variants due to alternative splicing and/or different transcriptional start sites. PDE1 isoforms are expressed in different tissue and regulate several processes in a calcium-dependent manner. However, the absence of specific and permeable inhibitors for PDE1 family makes it difficult to confirm the experimentally crosslink between cAMP/cGMP signaling and the intracellular calcium levels. The PDE2 family is capable of hydrolysing cAMP and cGMP and is highly stimulated by allosteric binding of cGMP (Martins et al., 1982). Members of the PDE2 family have been reported in many organs such as adrenal gland, liver, heart, brain, and endothelial cells (Yanaka et al., 2003; Van Staveren et al., 2004). The existence of PDE2 selective inhibitors allowed elucidating its functions. PDE2 participates in a diversity of physiological activities including adrenal aldosterone secretion, endothelial cell proliferation and permeability, angiogenesis, cardiac function, and platelet aggregation (Keravis and Lugnier, 2012; Beavo et al., 2006; Fischmeister et al., 2005; Nikolaev et al., 2005).

The PDE3 family includes three different isoforms from the gene *Pde3a* and only the one from the *Pde3b* gene (Bender and Beavo, 2006a). The isoforms of PDE3A are largely found in cardiac myocytes, platelets, and oocytes, while PDE3B is found in lipocytes, liver and pancreas (Shakur et al., 2000). PDE3 inhibitors have a significant effect on PDE3A functions, resulting in antiplatelet, positive inotropic and vasorelaxant effects (Movsesian et al., 2018; Conti et al., 2002). PDE3B exerts important actions in the regulation of energy metabolism, since its inhibition leads to the alterations in glucose disposal and favors insulin resistance and weight gain (Degerman et al., 2011). PDE4 family acts on cAMP and is constituted by four different genes, with different variants within each gene, being the largest member of the PDE family (more than 20 different variants). The members of this family are mainly presented in the brain but also in cardiovascular system, smooth muscle and innate immune cells (Houslay et al., 2005). PDE4 may involve in modulating recognition and memory performance and pathophysiology of depression, also, the inhibition of PDE4 can significantly reduce neuroinflammation (Gurney et al., 2015; Zhang et al., 2002a). PDE4 participates in the modulation of β2-adrenergic signaling in the myocardial cells and pulmonary smooth muscle, modulates vascular permeability, and stimulates the inflammatory responses (Fertig and Baillie, 2018; Schafer et al., 2014).

The PDE5 members are encoded by only one gene and specifically hydrolyze cGMP without being affected by Ca/calmodulin. PDE5 isoforms are mostly found in platelets, lung, and also in the brain, especially in Purkinje neurons (Shimizu-Albergine et al., 2003; Giordano et al., 2001). The presence of PDE5 members in the corpus cavernosum and in lung tissue led to the discovery of new inhibitors for the

improvement of erectile dysfunction and pulmonary hypertension (Andersson, 2018; Steiner et al., 2005). Furthermore, PDE5 has a significant contribution in the regulation of platelet aggregation, in recognition and memory functions and in cardiac remodeling (Apostoli et al., 2014; Takimoto et al., 2005; Prickaerts et al., 2004). PDE6 are comprised by three different genes and are only found in the retina and cone cells (Ridge et al., 2003), being essential for allowing cGMP-dependent visual cascade (Cote, 2004).

PDE6 was also found in pineal gland, suggesting that the enzyme can participate in suppressing the melatonin synthesis by light (Morin et al., 2001). Members of the PDE7 family are specific to cAMP and consisted of two different genes, *Pde7a* and *Pde7b*. Although, the PDE7 level is elevated in immune cells such as T-lymphocytes and other pro-inflammatory cells, the function of this enzyme remained vague (Smith et al., 2004). Besides, the PDE7 mRNA has been reported in several tissues like brain, lung, spleen as well as thymus (Lugnier, 2006). PDE7B has been found to be expressed in striatum and seems to be a key contributor in dopaminergic cascade with a role in memory function (Sasaki et al., 2004).

The PDE8 members are highly specific for cAMP and are encoded by *Pde8a* and *Pde8b*. Members of this family are widely distributed in many tissues specially in testis, liver, kidney, spleen, heart, thyroid gland, and skeletal muscle (Keravis and Lugnier, 2012; Wang et al., 2001). The isoform PDE8B3 is the predominant form in the brain (Hayashi et al., 1998). Similar to the isoforms of PDE7 family, the specific role of PDE8 has not been elucidated yet. The family PDE9 showed high affinity toward cGMP, although multiple variants can be found in many tissues including immune tissues and brain (Wang et al., 2003; Van Staveren et al., 2002). This family is one of the most recently studied group, while its functional implications remained to be elucidated. Inhibition of PDE9 seems to exert promising hypoglycemic effects in cell-based assays (Shao et al., 2014; DeNinno et al., 2009). The family PDE10 is composed of only one gene with at least 18 splice variants hydrolysing both cAMP and cGMP (Keravis and Lugnier, 2012; Fujishige et al., 1999). PDE10 isoforms are mainly found in the brain, especially in the striatial area (Fujishige et al., 1999; Soderling et al., 1999). Several studies suggested a possible role in the management of psychiatric diseases such as cognitive impairment suffered from schizophrenics or Huntington's disease (Beaumont et al., 2016; Schmidt et al., 2008; Rodefer et al., 2005).

The last member of the family, PDE11, is encoded by one gene with four splice variants, hydrolysing cAMP and cGMP. The expression of PDE11 was found to be elevated in skeletal muscle and prostate, and in lesser amounts in the liver, heart, brain, and pituitary gland (Yuasa et al., 2001; Fawcett et al., 2000). The function of PDE11 is still unknown, derived from the absence of specific inhibitors for this family. The PDE11A4 isoform is expressed in the central neuron system (CNS) and mostly in the hippocampal area using knockout mice, suggesting that PDE11 regulates the stabilization of mood and social memories formation (Kelly et al., 2010).

3. Phosphodiesterases structural biology

PDEs degrade cAMP and cGMP (Beavo et al., 1994; Beavo, 1995; Soderling and Beavo, 2000; Corbin and Francis, 1999; Bolger, 1994) which are important second messengers involved in many pharmacological processes like production and function of proinflammatory cytokines, muscle contraction, ion channel function, differentiation, learning, glycogenolysis, lipogenesis, gluconeogenesis, and apoptosis (Mehats et al., 2002). The human genome contains 21 known PDEs coding genes and difference in splicing and alternate initiation sites result in 53 identified isoforms (Bischoff, 2004; Lin et al., 2003). At the same time, huge variations exist in the regulatory domains reside (Maurice et al., 2003). Their catalytic domain is characterized by the presence of three helical sub domains such as cyclin-fold at N-terminal and a deep hydrophobic pocket. This domain consisted of four subsites like a metal linking or M site; core or Q pocket; hydrophobic or H pocket; and lid or L region. The M site possesses various metal atoms. Though the identity of the metal atoms is not known, some evidence suggested that zinc and magnesium may be the most frequently residing metal ions, helping to stabilize and activate catalysis. Zinc forms coordination sphere with three histidines (Jeon et al., 2005).

Three subtypes PDE1 family share the same structural features. They contain a conserved C-terminal catalytic domain as well as two N-terminal CaM binding domains. In the presence of Ca^{+2}/CaM, PDE1s have tetrameric structure with a pair of catalytic monomers and CaM molecules. Due to the unavailability of crystal structure of PDE1 holoenzyme, the orientation of CaM molecules is unknown.

Conversely, the crystal structure of PDE1B catalytic domain revealed its structural similarity to the other PDE catalytic domains (Zhang et al., 2004; Card et al., 2004). Different PDE1 enzymes show significant differences in affinity for Ca^{+2}/CaM, due to the existence of different N-terminal sequences in different variants (Ahmad et al., 2015). PDE2 shown to have significant cooperativity for both cAMP and cGMP (Martins et al., 1982), due to the linkage of the nucleotides to the allosteric GAF-B domain, leading to a conformational alteration in the protein and enhancing its activity in some subcellular compartments. Research on revealing the PDE2A holoenzyme structural information is in progress, in order to model its molecular mechanism.

The catalytic regions of PDE3A and PDE3B isoforms have identical amino acids, with very similar kinetic characteristics. Currently, the catalytic domain of PDE3B was explored and found to be compactly folded with 16 α-helices and amino-terminal domain with seven helices (Scapin et al., 2004). Moreover, it has been revealed to have similar structural features with PDE4B, PDE4D, and PDE5A (Scapin et al., 2004). Similarly, PDE4 has 18 different isoforms that are expressed in mammalian cells (Conti et al., 1995; Houslay, 2001). N and C terminal domains of the PDE4 protein perform a pivotal role in the conformation and function of the catalytic core.

PDE5 are cGMP-specific with high-affinity for the GAF-A area (Zoraghi et al., 2005), which becomes stable through the phosphorylation of serine residue (Francis et al., 2002) and the main kinase involved in this phosphorylation is PKG or PKA (Corbin et al., 2000). On the other hand, PDE6 possess a catalytically active heterodimer consisting of α (PDE6A) and β subunit (PDE6B) each with GAF-A and GAF-B N-terminus. PDE6 have the highest catalytic efficiency amongst known PDEs (Gillespie and Beavo, 1988). Due to lack of crystal structure of PDE6 complex, the exact structure has not been identified though, Cryoelectron microscopy revealed that GAF-A and GAF-B domains contact with α and β subunits forms a complete heterodimer (Tcheudji et al., 2001; Kajimura et al., 2002). Data suggested that the heterodimer is not essential for its activity, although it is a main isoform of this enzyme in mammalian tissues (Morin et al., 2001; Huang et al., 2004).

Information about the PDE7A and PDE7B structures and their functions are unavailable, it is thought that these enzymes may regulate the basal levels of cAMP. The primary structure of PDE8 enzyme includes N-terminal receiver domains (REC) and peripheral anionic site (PAS) domains, even if some variants do not possess these domains (Soderling et al., 1998a; Hayashi et al., 2002). In bacterial heme-regulated PDE oxidation, the state of a heme group affects its catalytic activity (Gilles-Gonzalez and Gonzalez, 2004; Galperin et al., 2001).

PDE9s differ from the other PDEs, in terms of not having any GAF domains or N-terminal regulatory domain. PDE9A is an exclusive cGMP hydrolysing enzyme with *K*m more than 1000 fold comparing with cAMP. Also, this isoform is somehow insensitive to common PDEIs and its catalytic domain has a very less homology to the other mammalian PDE catalytic domains (Fisher et al., 1998; Soderling et al., 1998b). In the same way, PDE10A, one of the isozyme of phosphodiesterase 10, generally hydrolyzed both cAMP and cGMP *in vitro*, but there is a lack of report on its *in vivo* substrates. Kinetic studies suggested higher affinity of the enzyme for cAMP than for cGMP (Fujishige et al., 1999;

Soderling et al., 1999; Loughney et al., 1999). The regulation of the enzyme *in vitro* and *in vivo* is not fully understood. Recent study showed the GAF domains of PDE10 bound to cAMP (Gross-Langenhoff et al., 2006). Likewise, PDE11A of phosphodiesterase 11 enzyme family hydrolyzes both cAMP and cGMP. Though most of the molecular mechanisms are still unexplored, it has been found that the PDE11 GAF domains can stimulate the cGMP binding on adenylyl cyclase (Gross-Langenhoff et al., 2006).

4. Preclinical pharmacology of PDEs

TIn the mid-1960s, it was found that caffeine has the ability to inhibit a cAMP-specific PDE (Butcher and Sutherland, 1962; Prickaerts et al., 2017). There are hundred particular human PDEs (Bender and Beavo, 2006a), each of them possess a particular localization at the human tissues (Wang et al., 2003; Esposito et al., 2009; Rentero et al., 2003).

A few specific PDEIs have been appeared to enhance learning in rat models of cognition. cAMP and cGMP both are critical secondary messenger in the developed brain that are specifically associated with processes of memory recovery (Rutten et al., 2007). The cAMP-PKA signaling activation modulated the transcription of various agents for example CREB, persuading the factors that are mandatory for recognition and memory recovery (Abel et al., 1997; Bernabeu et al., 1997). Moreover, ongoing researches have additionally connected the cGMP pathway to the cognitive function (García-Osta et al., 2012).

Inhibition of PDEs that particularly intercede the cGMP hydrolysis in the brain results in increasing the cyclic nucleotide levels, which thus can alleviate the commencement of age-associated dementia (Domek-Łopacińska and Strosznajder, 2010). A particular PDE1 inhibitor vinpocetine is assessed for managing memory dysfunction, which was found to encourage long term potentiation (Molnár and Gaál, 1992) and improved memory recovery in passive avoidance in rats (DeNoble, 1987) and also upgraded the cognitive performance in humans (Hindmarch et al., 1991). Recent investigations exhibited that vinpocetine likewise enhanced the synaptic versatility in fetal alcohol spectrum disorder models, where there was an impaired cortical and cognitive function (Krahe et al., 2009; Medina et al., 2006).

A PDEI is a pharmacological compound that blocks at least one of the PDE subtypes (Bender and Beavo, 2006a; Heckman et al., 2018). Several PDEIs were evaluated in different preclinical studies. Grauer et al. investigated papaverine and MP-10, two PDE10A inhibitors, to comprehend the preclinical profile of PDE10A inhibition, providing the proof that recommends a PDE10A inhibitor could give procognitive as well as antipsychotic effects (Grauer et al., 2009). It has been estimated that the hindrance of the cyclic nucleotide PDE 10A will lead to another restorative way to deal with the management of schizophrenia (Menniti et al., 2000). PDE10A hindrance might be less typically problematic than approaches focusing on just a single pathway (Schmidt et al., 2008). Preclinical evaluation for PDE10A suppression to manage schizophrenia has used PDE10A knock-out animals (Schmidt et al., 2008; Siuciak et al., 2006). Moreover, compound TP-10 delivered abstemiously less levels of catalepsy in the rodents, that is an indicator of extrapyramidal adverse impacts (Schmidt et al., 2008; Wadenberg and Hicks, 1999; Coskran et al., 2006; Polli and Kincaid, 1994).

ARolipram is a PDE4 specific inhibitor which viably modulated procognition as well as memory shortfalls in animal model (Cheng et al., 2010); similar comparative outcomes were additionally delivered from sildenafil (PDE5I) (Puzzo et al., 2009; Lakics et al., 2010). The activity of PDE3 was inhibited by cilostazol, also PDE3administration shielded transgenic mice from Aβ oligomer interceded harm, diminished Aβ accumulation and phosphorylation of tau (Park et al., 2011; Schwenkgrub et al., 2017). A number of PDEIs developed *in vivo* condition such as BCA-909, AVE-8112, and THPP-1 (Froestl et al., 2013). It has been tentatively demonstrated that inhibition of phospholipase A2 (PLA2) is involved in managing cognitive impairment (Schaeffer et al., 2005). Rilapladib, which is a PLA2 inhibitor, is under clinical evaluation (NCT01428453) for cognitive disorder (Kumar and Singh, 2015; Oliveira et al., 2010).

Another potential drug target for AD which is extensively studied is PDE9 (García-Osta et al., 2012; Domek-Łopacińska and Strosznajder, 2010; Claffey et al., 2012; Hutson et al., 2011; Kroker et al., 2012, 2014; Meng et al., 2012; Reyes-Irisarri et al., 2007). Su et al. (2016) designed and synthesized some novel series of PDE9 inhibitors and found that the majority of these compounds possessed strong PDE9 inhibitory effect. Another study evaluated a sequence of novel pyrazolopyrimidinone derivatives coupled with antioxidant pharmacophore by dynamics simulations and docking studies and developed high selective PDE9 inhibitors (Zhang et al., 2018).

5. Inhibitors of PDEs

Despite known beneficial effects of PDEIs, they may share several common adverse effects including headache, facial flushing, dyspepsia, nasal congestion, nasopharyngitis, Back pain and myalgia, visual abnormalities, high sensitivity to light, dizziness, Sudden hearing loss, and dyspepsia (Huang and Lie, 2013).

6. Synthetic inhibitors

POut of 11 PDEs isoforms, only three of them (PDE3, PDE4 and PDE5) are approved in clinical practices. An increasing number of data indicated that many compounds are just being investigated in preclinical and clinical study to search for their significance in many physiological functions, including cognitive process, remembering and learning. The ligands that have shown effects on memory processes in preclinical and clinical studies are described below. The involvement of PDEIs in memory processes, their action mechanisms, their pharmacological activities, used doses, rout of administration and subjects (animals or human) were summarized in Table 2.

6.1. PDE1 ligands inhibitors

PDE1 is known to regulate both cAMP and cGMP concentrations. Apart from natural xanthines, such as teophylline or caffeine, synthetic pentoxifylline is also able to inhibit PDE1. Although pentoxifylline improves the rheological properties of blood and is a popular drug used to treat intermittent claudication, yet, its potential therapeutic role in vascular dementia has not been fully confirmed (Michael and Callahan, 2003). The next example of well-known PDE1 inhibitor is nimodipine (Schächtele et al., 1987), which also belongs to the calcium channel blockers. Nimodipine extends the cerebral arteries and reduces the severity of neurological deficits in patients who have had hemorrhage (Tomassoni et al., 2008). In a clinical study, it was evidenced that nimodipine can be a valuable tool in therapy of patients with dementia due to AD or vascular damages (Birks and López-Arrieta, 2002). Another synthetic and potent PDE1 inhibitor, ITI-214, demonstrated to improve memory performance in animal model of novel object recognition (Snyder et al., 2016). This effect was observed in a broad range of doses of ITI-214 (0.1–10.0 mg/kg).

6.2. PDE2 inhibitors

More and more experimental data confirmed that treatment with PDE2 inhibitors also supports cognitive functions. PDE2 inhibitors elevate both cAMP and cGMP levels in cells. One of the most prominent PDE2 inhibitor is BAY 60–7550. In experimental studies this compound (3 mg/kg) significantly ameliorated formation and consolidation of memory in animal experiment (Lueptow et al., 2016). In another study, BAY 60–7550 (1.0 mg/kg) improved the memory dysfunction caused by scopolamine in rodents (Reneerkens et al., 2013). Moreover, BAY 60–7550 (1.0 and 3.0 mg/kg) alleviated cognitive impairments induced

Table 2
Involvement of PDEIs in memory processes.

Mechanism of action	Drug	Doses	Rout of administration	Experimental procedure	Subject	References
Synthetic PDEIs						
	Pentoxifylline	1.200 mg/day, 3–9 months	po	Vascular dementia	Human	Sha and Callahan (2003)
	Nimodypine	30–180 mg/day; 3–6 month	po	Vascular dementia	Human	(Lopez-Arrieta and Birks, 2002; Davidson and Stern, 1991; Parnetti et al., 1993)
	ITI-214 [6a*R*,9a*S*)-2-(4-(6-fluoropyridin-2-yl)benzyl)-5-methyl-3-(phenylamino)-5,6a,7,8,9,9a-hexahydrocyclopenta- (Wallace et al., 2005; DeNinno, 2012)imidazo[1,2-*a*]pyrazolo[4,3-*e*] pyrimidin-4-(2*H*)-one phosphate salt]	0.1–10.0 mg/kg; acute	po	Object recognition test	Rats	Snyder et al. (2016)
PDE2 inhibitor	BAY 60–7550 [2-[(3,4-dimethoxyphenyl)methyl]-7-[(1R)-1-hydroxyethyl]-4-phenylbutyl]-5-methyl-imidazo (DeNinno, 2012) (Boswell-Smith et al., 2006; Beavo et al., 1994; Wallace et al., 2005)triazin-4(1H)-one]	3.0 mg/kg; acute	ip	Object recognition test;	Mice	Lueptow et al. (2016)
		1.0 and 3.0 mg/kg; 2 weeks	ip	Object recognition test; Morris water maze; location task		Xu et al. (2015)
		0.3–3 mg/kg	po	Scopolamine-induced and MK-801-induced memory dysfunction in object recognition	Rats	Reneerkens et al. (2013)
		3.0 mg/kg; 14 days	ip	β-amyloid-induced memory impairments in water maze test	Mice	Wang et al. (2017b)
	Lu AF64280*	10 mg/kg 1 and 10 mg/kg; acute,	sc	phencyclidine-induced deficits in object recognition test intradimensional/ extradimensional shift task	Rats	Redrobe et al. (2014)
PDE2 and PDE10 inhibitor	Lu AF33241*	3 and 10 mg/kg; acute,	sc	Object recognition test	Rats	Redrobe et al. (2015)
	TAK-915 (N-((1S)-1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethyl)-7-methoxy-2-oxo-2,3-dihydropyrido (Beavo et al., 1994)pyrazine-4(1H)-carboxamide)	0.1 and 1 mg/kg, acute	po	Object recognition test	Rats	Mikami et al. (2017)
PDE3 inhibitor	Cilostazol [6-[− 4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2-(1*H*)-quinolinone]	0.1% cilostazol at 50 mg/kg per day	po	Morris water maze	Rats	Watanabe et al. (2006)
		30 and 100 mg/kg; 8 days	po	Y-maze, passive avoidance test	Mice	Hiramatsu et al. (2010)
		10 and 20 mg/kg; 6 weeks	po	β-amyloid-induced memory impairments in Morris water maze task	Mice	Park et al. (2011)
		30, 60 mg/kg; 2 weeks	po	Morris water maze task	Mice	Yanai et al. (2014)
		0.3%, or 1.5 [w/w]%; 1, 2, or 4 months	po	Object recognition, Morris water maze task	Mice	Yanai et al. (2018)

(*continued on next page*)

Table 2 (*continued*)

Mechanism of action	Drug	Doses	Rout of administration	Experimental procedure	Subject	References
PDE4 inhibitor	Rolipram	7.5 μg/side; intra-hippocampal infusions		the single-trial step-down inhibitory avoidance task	Rats	Roesler et al. (2014)
		0.1 mg/kg; acute	ip	Object recognition	CBP $^{\pm}$ mice	Bourtchouladze et al. (2003)
		0.05 and 0.1 mg/kg; 2 weeks	ip	Streptozocin-induced memory deficits Morris water maze test;	Mice	Kumar and Singh (2017)
		0.3 mg/kg; 3 weeks	ip	object location test	Mice	Soares et al. (2016)
		0.05 and 0.1 mg/kg; 6 days	ip	Object recognition; Morris water maze test	Mice Mice	Akar et al. (2014) Akar et al. (2015)
		0.1, 0.3, 1.0 mg/kg; 10 days	ip	object recognition test	Rats	Jabaris et al. (2015)
	Roflumilast	0.03 mg/kg; acute	ip	Object location; Y-maze object recognition test	Mice Rats	Vanmierlo et al. (2016)
		0.1, 0.3, 1.0 mg/kg; 10 days	ip	object recognition test	Rats	Jabaris et al. (2015)
	Ibudilast	4 and 12 mg/kg; 2 weeks	ip	β-amyloid-induced memory impairments in Morris water maze; Y-maze test	Mice	Wang et al. (2014)
	MK-0952 [(1R,2R)-2-(3'-(3-(cyclopropylcarbamoyl)-4-oxo-1,8-naphthyridin-1(4H)-yl)-3-fluoro-[1,1′-biphenyl]-4-yl)cyclopropane-1-carboxylic acid]	0.1 mg/kg; 1–5days	po	Object recognition test, Water maze test	Rats	Gallant et al. (2010)
	HT-0712 [(3S,5S)-5-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[(3-methylphenyl)methyl] piperidin-2-one]	0.1 mg/kg; 3 weeks	ip	Morris water maze test	Mice	Peters et al. (2014)
	GEBR-32a fluorinated derivative of the 4-(difluoromethoxy)-3-hydroxybenzaldehyde	0.003 mg/kg; acute 0.03 mg/kg; 23 days;	sc	Object location task; Y-maze	Mice	Ricciarelli et al. (2017)
	FFPM [1-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)-3-methylbutan-1-one]	0.5 mg/kg; 3 weeks;	po	Morris water maze test; Step-down passive avoidance test	Mice	Guo et al. (2017)
PDE5 inhibitors	Zaprinast	3 and 10 mg/kg	ip	Object recognition test	Mice	Akar et al. (2014)
	Sildenafil	2 mg/kg for 28 days	ip	Morris water maze test, Object recognition test	Multiple infarction based vascular dementia rats	Venkat et al. (2019)
		25 mg/kg/day, Acute administration and chronic administration for 14 days	po	Object recognition test	Rats	Ozbeyli et al. (2015)
		1 and 3 mg/kg	ip	Inhibitory avoidance test	CF-1 mice	Boccia et al. (2011)
		10.0 mg/kg, fot 10 days	ip	Object recognition test	APP/PS1 transgenic (Tg APP/PS1) mice	Zhang et al. (2013)
		7.5 mg/kg for 4 weeks	ip	Morris water maze test	Mouse-prone 8 (SAMP8) strain of mice	Orejana et al. (2013)
	Sildenafil/tadalafil	15 mg/kg/day	po	Morris water maze test	J20 transgenic mouse model of AD	Garcia-Barroso et al. (2013)
	Yonkefanil	2, 6, or 18 mg/kg	ip	Morris water maze test	APP/PS1 transgenic mice AD model	Zhang et al. (2013)
PDE7 inhibitors	S14*	15 mg/kg/day, For 5 weeks	po	Object recognition test	APP/PS1 transgenic mice AD model	Bartolome et al. (2018)
		10 mg/kg for 4 weeks	ip and po	Object recognition test T maze tast	APP/PS1 transgenic mice AD model	Perez-Gonzalez et al. (2013b)

(*continued on next page*)

Table 2 (*continued*)

Mechanism of action	Drug	Doses	Rout of administration	Experimental procedure	Subject	References
PDE8 inhibitors	–	–	–	Morris water maze test	Adult PDE8B knock out mice	Tsai and Beavo (2012)
PDE9 inhibitors	BAY 73–6691 1-(2-Chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methylpropyl]-1,5-dihydro-4H-pyrazolo (Abusnina and Lugnier, 2017)pyrimidine-4-one	0.2, 1, or 5 mg/kg 0.3, 1, 3 mg/kg for 4 days	po ip	Object recognition test Morris water maze test	Tg2576 mice Mice subjected to intracerebroventricular injection of Aβ25 (AD model)	Kroker et al. (2012) Li et al. (2016)
Natural PDEIs						
Non-selective PDEIs	Caffeine	1.84 mg caffeine of CC per day 0.3 g/L for 10 months	po po	Morris water maze test Morris water maze test	J20 mouse line, an AD mouse model THY-Tau22 transgenic mouse model of progressive AD-like tau pathology	Chu et al. (2012) Laurent et al. (2014)
	Icarrin	30 and 60 mg/kg	po	Y-maze tasks	APP/PS1 transgenic AD mice	Jin et al. (2014)
	Resveratrol	10, 20 and 40 mg/kg for 21 days	po	Morris water maze test	Mice subjected to hippocampal injection of Aβ25 (AD model)	Wang et al. (2016)

Table 1 presents the view on the literature data regarded to the role of PDEIs in memory processes.
*no data about chemical structure.

by stress in animals and improved stress-induced hippocampal remodeling, which resulted in increasing dendritic branches and length (Xu et al., 2015). Other authors revealed that BAY 60–7550 (0.3 mg/kg) improved AD-related cognitive dysfunctions in transgenic mice (APPSwe/PSEN1dE9), although it did not influence on β-amyloid aggregation or CREB concentration. Authors suggested an involvement of other signaling pathways in that effect of BAY 60–7550 (Sierksma et al., 2013). In another study, BAY 60–7550 (3.0 mg/kg) reversed β-amyloid-induced cognitive dysfunctions in animal models and restored changes in neuroinflammatory factors (Interleukin (IL)-17, IL-22, Bax, Bcl-2, BDNF), suggesting neuroprotective properties of BAY 60–7550 (Wang et al., 2017b). Immunohistochemical analysis of developing fibers of mesolimbic areas (in ventral tegmental area and substantia nigra) showed an obvious enhancement of fiber density in cell cultures treated with BAY 60–7550 and the other PDE2 inhibitor, ND 7001, proposing that this agent may promote an axonal outgrowth in neuroregeneration (Heine et al., 2013). All these data support the notion that BAY 60–7550, as PDE2 inhibitor, might be a suitable candidate for cognitive impairments in AD. There are also novel brain-penetrant PDE2 inhibitors, such as Lu AF64280, a selective PDE2 inhibitor, and Lu AF33241, a dual PDE2 and PDE10 inhibitor, showing the beneficial effect on cognitive processes. Up to date, their effectiveness has been only confirmed as attenuation of phencyclidine-induced deficits in animal models, suggesting their potential relevance in impairment of cognition in Schizophrenia (Redrobe et al., 2014, 2015). Similarly, the latest data presents novel PDE2 inhibitors, such as PF-05270430 (Chen et al., 2016) and TAK-915 (Mikami et al., 2017), as a possible targets for the management of procognitive impairments. Further studies are needed to confirm their significance in AD-induced memory disturbances.

6.3. PDE3 inhibitors

Cilostazol, an important example of selective PDE3 inhibitor is used for intermittent claudication as well as artery obstruction. PDE3 hydrolyzes both cAMP and cGMP, of which, the elevation of cAMP concentration is a key pharmacological function of this drug (Ikeda, 1999). The first data on the involvement of cilostazol in cognitive processes was described in 2006. Authors demonstrated that cilostazol enhanced spatial learning memory in animal (Watanabe et al., 2006). Immunohistochemical analysis showed that cilostazol exerted neuroprotective effect *via* CREB phosphorylation pathway. In another experiment using β-amyloid-induced model of neurotoxicity in human neuroblastoma cells, cilostazol counteracted the neurotoxicity *via* reduction of oxidative stress, caspase-3 and -9 activations, proapoptotic protein - Bax and p38 mitogen-activated protein kinase (MAPK) phosphorylation, and upregulation of CREB and antiapoptotic protein Bcl-2 (Oguchi et al., 2017). Abovementioned data shows that various cerebral pathways are involved in the effect of cilostazol. The attenuation of cognitive dysfunctions by cilostazol in cerebral hypoperfusion with type II diabetes in animals was also mentioned in several studies (Kwon et al., 2015). Later, a retrospective study reported that treatment with cilostazol in patients with mild cognitive dysfunction significantly improved the cognitive performance (Taguchi et al., 2013). Mounting evidence revealed an important role of cilostazol in AD-induced cognitive impairments and further studies are focused on that process. It was evidenced that cilostazol reduced β-amyloid production (Lee et al., 2012, 2014; Maki et al., 2014) and tau phosphorylation *in vitro* (Lee et al., 2012, 2014). Chronic treatment of cilostazol (30 mg/kg) is able to alleviate β-amyloid-induced memory dysfunctions in animal model. That effect was associated with reduction of oxidative damage factors in the brain tissue of studied mice (Hiramatsu et al., 2010). Two weeks administration of cilostazol (10 and 20 mg/kg) in mice, before the intracerebroventricular application of β-amyloid, prevented the aggregation of β-amyloid, reduced tau immunoreactivity and improved memory impairments. These effects, however, were not observed when

cilostazol was administered for four weeks after the β-amyloid application (Park et al., 2011). The involvement of cilostazol in cognitive dysfunctions was also confirmed by other studies (Yanai et al., 2014, 2018).

ICilastamide, a novel PDE3 inhibitor has been discovered recently (Hosseini et al., 2017). Up to date, there is no data on their involvement in AD-induced cognitive disturbances. Further studies provide more information on its involvement in cognitive properties.

6.4. PDE4 inhibitors

FAmong PDE4 inhibitors, rolipram is the well-recognized drug in memory disturbances. Rolipram injection into the dorsal hippocampus enhanced fear-related memory in rats (Roesler et al., 2014). Pretreatment of mice with rolipram (0.1 mg/kg) before training, corrected retention performance task 24 h later (Bourtchouladze et al., 2003). In another study, 14 days *i.p.* administration of rolipram significantly reduced the memory dysfunctions in animals, and it was related to its anticholinoesterase, anti-amyloid, antioxidative and anti-inflammatory activities, indicating that rolipram might be a valuable pharmacological target in dementia (Kumar and Singh, 2017). Rolipram (0.3 mg/kg) also improved memory and emotional state in C56B6/7 mice subjected to transient global ischemia. In these mice, rolipram also reduced neurodegeneration in CA3 hippocampal area (Soares et al., 2016). Rolipram (0.05 and 0.1 mg/kg) also enhanced visual memory in rats (Akar et al., 2014) and spatial learning in the Morris water maze test (Akar et al., 2015). The beneficial effect of combination of subthreshold doses of rolipram (PDE4 inhibitor) with vardenafil (PDE5 inhibitor) on long-term synaptic plasticity was also experimentally confirmed (Bollen et al., 2015). In addition, rolipram (0.05 mg/kg, 0.1 mg/kg) improved cognitive deficits in generally accepted behavioral model of AD, meaning that, Streptozotocin-induced recognition dysfunction in miceand the involvement of anticholinesterase mechanism in the effect of rolipram (Kumar and Singh, 2017).

Moreover, there are some experiments demonstrating the involvement of others PDE4 inhibitors in memory process. For example, combination of subthreshold dose of donepezil, a typical anticholinergic drug, with ineffective dose of roflumilast (PDE4 inhibitor) improved synaptic plasticity as well as memory formation in rats (Vanmierlo et al., 2016). Both roflumilast (0.1, 0.3, 1.0 mg/kg, *p.o.*) and rolipram (0.03, 0.1, 0.3 mg/kg, *i.p.*) were effective in hypertension-induced memory deficits in rats (Jabaris et al., 2015). Another PDE4 inhibitor, ibudilast, was shown to possess neuroprotective effect on neural cell death (Mizuno et al., 2004) and neuroinflammation in animal model of ischemic brain damage (Lee et al., 2012). Pre-treatment with ibudilast improved β-amyloid-induced memory impairments and reduced neurotoxicity in mice (Wang et al., 2014). In therapeutic approaches for cognitive deficits, novel PDE4 inhibitors are also promising agents. MK-0952 is considered for therapy of memory impairment and mild cognitive damage (Gallant et al., 2010). Acute use of HT-0712 meaningfully ameliorated long-term memory in aged mice (Peters et al., 2014). GEBR-32a and FFPM enhanced memory in AD transgenic mice (Ricciarelli et al., 2017; Guo et al., 2017).

Although PDE4 inhibitors are promising drugs in memory and cognitive dysfunctions, they are able to induce vomiting, the major adverse effect of PDE4 inhibitors. Rolipram, as an old generation drug, belongs to the 1st generation of PDE4 inhibitors and possesses stronger emesis properties. Novel inhibitors, such as roflumilast or cilomilast, induce weaker emesis response and belong to the 2nd generation of PDE4 inhibitors (Robichaud et al., 1999). It is confirmed that emesis response is closely associated with stimulation of neurons in area postrema. There is lack of a specific blood-brain barrier in that area, so it is more sensitive for various substances, generally defined as emetic toxins (Miller and Leslie, 1994). The analysis of distribution of PDE4 isoforms in area postrema demonstrated a particular higher expression of subtypes PDE4D and PDE4B isoforms in that area in comparison with other brain areas (Mori et al., 2010). Thus, PDE4 inhibitors elevate the PDE4 level inducing emesis reflex.

The participation of serotonin 5-HT3 receptors and neurokinin NK1 receptors were confirmed in that phenomenon, although it is not exactly defined, it seems that emesis response is mainly associated with central, but not peripheral mechanisms (Robichaud et al., 1999).

6.5. PDE5 inhibitors

The first synthesized selective PDE5 inhibitor was zaprinast. It was effective bronchodilator in exercise-associated asthma (Rudd et al., 1983) and was able to produce smooth muscles relaxation and a NO/cGMP - dependent relaxation of corpus cavernosum (Elhwuegi, 2016). However, the prototype of all PDE5 inhibitors is sildenafil - originally developed as anti-hypertensive drug- but, finally, approved by FDA in 1998 for male erectile dysfunction (Boolell et al., 1996; Goldstein et al., 1998). The next PDE5Is approved by FDA for erectile dysfunction treatment were – vardenafil, tadalafil (both introduced in 2003), and avanafil (in 2012). Another drugs – lodenafil, udenafil, and mirodenafil are also commercially available, but none of them have been approved by FDA yet (Elhwuegi, 2016; Hong et al., 2017). They are commonly used at the following oral doses: sildenafil - 25, 50, 100 mg/kg, tadalafil - 2.5, 5, 10, 20 mg/kg, vardenafil - 5, 10, 20 mg/kg, avanafil – 50, 100, 200 mg/kg, lodenafil – 80 mg/kg, udenafil – 100, 200 mg/kg and mirodenafil – 50, 100 mg/kg (Amano et al., 2018; Carson et al., 2014; Cho and Paick, 2014; Corona et al., 2016; Lombardi et al., 2012; Park et al., 2014; Scaglione et al., 2017; Zurawin et al., 2016).

PDE5 inhibitors are equally effective and safe (Yafi et al., 2018). All of them are distributed in different tissues, plasma, as well as semen. Most of PDE5Is are metabolized by CYP34A enzymes, through hepatic metabolism and to a lesser extent by CYP2C (Hong et al., 2017; Scaglione et al., 2017). However, they vary in potency, duration of action, and their degree of isoenzyme selectivity; the most important factor that determines their side effects (Gupta et al., 2005). PDE5 inhibitors affect the PDE5 in the smooth muscle of the corpus cavernosum, but the similarities between this type of inhibitors and other PDE isoforms can result in non-specific inhibition of PDE isoforms in other tissues. For example, it has been documented that PDE5 inhibitors react with PDE6 in the photoreceptors of the human retina, causing mild visual disturbances (Corona et al., 2016; Gupta et al., 2005; Sperling, 2017). Furthermore, inhibition of PDE11 isoform in skeletal muscle by PDE5 inhibitors results in myalgia and lower back pain (Scaglione et al., 2017). Other side effects of PDE5 inhibitors, such as headache, dyspepsia, flushing, and nasal congestion are usually mild in nature (Yafi et al., 2018; Sperling, 2017; Yuan et al., 2013). Tadalafil has a higher selectivity for PDE5 than sildenafil and possesses the highest long-lasting action (Daugan et al., 2003) and it was reported to be the most effective drug and the most preferred by patients (Lombardi et al., 2012). Sildenafil, vardenafil, and avanafil are also potent PDE6 inhibitors, however they induce strong visual impairments (Corona et al., 2016; Sperling, 2017). Regarding PDE5Is interaction with other drugs, it is known that PDEIs potentiate the vasodilatory and hypotensive effects of organic nitrate and NO donors, causing severe hypotension that results from combined action of these drugs on NO/cGMP pathway (Yafi et al., 2018; Yuan et al., 2013).

PDE5 inhibitors are available as the first-choice drugs for men with erectile dysfunctions resulted from a wide range of underlying diseases (Hong et al., 2017; Lombardi et al., 2012; Scaglione et al., 2017; Yafi et al., 2018). Due to the expression of PDE5 in urinary tract and relaxation of related smooth muscle (Keravis and Lugnier, 2012), inhibition of this enzyme is considered to be a clinical benefit for managing many other urological diseases. It was shown that PDE5 inhibitors, especially combined with β-blockers, are very effective for lower urinary tract complications and benign prostatic hyperplasia (BPH) (Yan et al., 2014). Though, only tadalafil is approved by FDA in 2011 for the management of BPH (Carson et al., 2014). The serial

clinical trials of Burnett et al. (2006) revealed that long-term, low-dose sildenafil or tadalafil treatment reduced the frequency and duration of disordered erection in men with recurrent priapism. Studies on benefits of sildenafil in the management of premature ejaculation also suggest a promising potential, especially in combination with selective serotonin reuptake inhibitors (SSRIs) (Chen et al., 2003). Furthermore, many experiments indicated the potential benefits of PDE5Is in overactive bladder and female sexual disturbances (Zhang and Zhang, 2016).

Several preclinical and clinical studies have focused on PDE5Is for the management of non-urological conditions, especially cardiovascular disorders and diabetes (Anderson et al., 2016; Barone et al., 2017; Das et al., 2011, 2015; Zhuang et al., 2014). Current evidence show that these drugs can reduce different signs and complications of myocardial ischemia/reperfusion (I/R) injury (Koka et al., 2013; Guazzi et al., 2009), ischemic and diabetic cardiomyopathy (Koka et al., 2010; Mátyás et al., 2017), and cardiac hypertrophy (Takimoto et al., 2005). Furthermore, there are reports that sildenafil or tadalafil have significant therapeutic effects on the endothelial dysfunction of patients with type 2 diabetes (Desouza et al., 2002; Rosano et al., 2005). Sildenafil and tadalafil, are approved by FDA for the management of pulmonary arterial hypertension (Ribaudo et al., 2016).

Furthermore, there are experiments indicating neuroprotective effect of PDE5Is. In animal models of ischemic stroke, the administration of PDE5Is at the doses relevant to human use, can diminish brain inflammation, oxidative stress, CNS apoptosis and stroke lesion volume (Ölmestig et al., 2017). The study of Zhang et al. (2002b), exhibited that sildenafil reduced the neurologic impairment, improved recognition and memory, and promoted recovery subsequent to stroke in young and aged rats (Zhang et al., 2006). It also attenuated infarct size and oxidative damage caused by cerebral ischemia-reperfusion (Gulati and Singh, 2014). This neuroprotective effect implicates that PDE5Is have clinical benefits in neurodegenerative (Huntington's disease) and demyelinating diseases (*e.g.* multiple sclerosis) (Peixoto et al., 2015). Administration of sildenafil and vardenafil significantly diminished neuronal dysfunction and death in a Huntington's disease model (Puerta et al., 2010). Sildenafil was also found to promote remyelination and microglia/macrophages activation in a murine model of multiple sclerosis. It also suppressed the cuprizone-induced demyelination as well as expression of proinflammatory cytokines (Nunes et al., 2012). There are also data indicating the favaroble effects of PDE5Is in reducing amyloid β levels in mouse models (Orejana et al., 2014; Li et al., 2015). Sildenafil and tadalafil also possess significant role in reversing memory impairments in several mouse models of AD (Puzzo et al., 2009). In a pilot study on men with erectile dysfunctions, two months administration of udenafil enhanced cognitive performance (Shim et al., 2014), suggesting that PDE5Is could enhance the learning and memory processes (Peixoto et al., 2015). Apart from commonly used PDE5Is, the novel selective PDE5Is, such as icariin, a phenolic compound, and yonkefanil found to increase the memory performance in a different animal model of AD (Jin et al., 2014; Zhu et al., 2015).

TOverall, PDE5Is induce a broad spectrum of pharmacological activity and, in the future, this group may be a valuable tool, not only in erectile dysfunctions but also in neurological disturbances including AD and other cognitive impairments.

6.6. PDE6 inhibitors

PDE6 isoform specifically influence on cGMP, and is mainly expressed in photoreceptor of pineal gland. Currently, the significance of PDE6Is in cognitive, memory, and learning processes is not clarified yet.

6.7. PDE7 inhibitors

PDE7 is known to be responsible for controlling intracellular concentration of cAMP in the immune system and the brain (Keravis and Lugnier, 2012). Morales-Garcia et al. (Morales-Garcia et al., 2017), have shown that PDE7Is are neuroprotective agents and can prevent endogenous neurodegenerative processes. It was indicate that specific inhibition of PDE7 by S14 caused a significant impact on the proliferation and differentiation of neuronal stem cells as well as enhancing the spatial learning (Morales-Garcia et al., 2017). Other PDE7Is, such as VP1.15 and TC3.6 are able to enhance oligodendrocyte precursor survival and differentiation (Medina-Rodríguez et al., 2013). These neurodegenerative properties of PDE7Is seem to be extremely important in therapy of neurodegenerative disorders including AD.

6.8. PDE8 inhibitors

PDE8 isoform mainly hydrolyzes cAMP and is expressed in the brain areas including, hippocampus, ventral striatum, and cerebellum, which are important for cognitive properties. In PDE8 transgenic mice the improvement of contextual fear, spatial memory and memory function in motor-coordination were observed (Tsai and Beavo, 2012).

6.9. PDE9 inhibitors

PDE9 isoform has considerable affinity towards cGMP. Inhibition of PDE9A isoform, may be an important target in therapy of memory dysfunction which is associated with endogenous neurodegenerative disorders including AD. Kroker et al. (2014) demonstrated that the administration of BAY 73–6691, a PDE9I, leads to the enhancement of long-term memory recovery and procognitive activity in animals. Furthermore, it was found that BAY 73–6691 restored long-term memory impairment induced by amyloid β-42 and increased memory activity in tg2576 mouse (Kroker et al., 2012). Procognitive effect of this selective PDE9Iwas also observed in different model of learning and memory tasks in rodents. BAY 73–6691 increased acquisition, consolidation, and recovery of long-term memory. It also improved the retention dysfunction induced by scopolamine in rats (Van Der Staay et al., 2008). Further investigations are necessary to confirm the involvement of PDE9Isin cognitive properties, however it seems that PDE9Ismight be considered as precognitive compounds.

6.10. PDE10 inhibitors

The involvement of the next PDE isoform - PDE10 in cognition, memory and learning is not well recognized. PDE10 is able to hydrolyze cAMP and cGMP. One of the oldest drugs acting on PDE10 is papaverine. For many, it was used as spasmolytic agent in clinical practices. Novel studies demonstrated that papaverine is also involved in brain functions (Rodefer et al., 2012). For instance, papaverine was able to attenuate phencyclidine-induced cognitive deficits in rats indicating that it may be valuable target to treat cognition deficits in Schizophrenia. In another study, papaverine improved cognition deficits in model of Huntington disease in mice (Rodefer et al., 2012; Giralt et al., 2013). Another inhibitor of PDE10, PQ-10 (0.3 mg/kg), lessened the scopolamine-induced memory deficits in rodents (Reneerkens et al., 2013). MP-10, another PDE10I, protected long-term memory deficits associated with sleep deprivation in rats (Guo et al., 2016). Considering these studies, it is difficult to discuss its usefulness in therapy of cognitive disturbances, including AD.

6.11. PDE11 inhibitors

PDE11 isoform hydrolyzes both cAMP and cGMP. Current data on the involvement of PDE11 isoform in cognitive dysfunctions is poor. It was demonstrated that the expression of PDE11 is particularly high in ventral hippocampus (Kelly et al., 2010). The behavioral experiments on PDE11 transgenic mice showed impairments in social memory consolidation during adolescence (Hegde et al., 2016), therefore, it seems, PDE11 isoform is involved in social memory formation. Further experiments are necessary to recognize the properties of PDE11 isoform

in brain function.

7. Natural inhibitors of PDE

Caffeine was shown to induce PDE inhibition in several experimental models (Arendash and Cao, 2010; Francis et al., 2011a; J Titus et al., 2015). In this context, caffeine was found to attenuate the neuronal deficits *in vivo* models of AD. Zeitlin et al. (2011) reported that caffeine (3 mg/kg) upregulated signaling pathways involved in neuronal protection in the striatum of the mice with familial AD Swedish mutation (APPK670N, M671L). Similarly, Chu et al. (2012) have reported that crude caffeine, which is a by-product of the process of decaffeination of coffee, attenuated memory impairment and reduced the hippocampal levels of amyloid-$\beta_{1\text{-}42}$ peptide in the J20 mouse (which presents the Swedish and the Indian familial mutations in the APP gene). Laurent et al. (2014) also found that caffeine caused beneficial effects in an experimental model of AD such as tau pathology (THY-Tau22 transgenic mouse model). The authors have shown several effects indicating that caffeine would be able to modulate different signaling pathways in the mice hippocampus, causing neuroprotection. Importantly, caffeine upregulated the expression of transcription nuclear factor erythroid 2-related factor 2 (Nrf2), an event that is related to the enhancement of the expression of Mn-SOD (the mitochondria-located enzyme which has a key role in the conversion of superoxide anion radical into hydrogen peroxide) and EAAT3 (a transporter involved in the uptake of cysteine into neurons). Nonetheless, the authors did not analyze whether crude caffeine affected the PDE activity in that experimental model.

In contrast, Jin et al. (2014) have revealed that icariin (ICA; 30–60 mg/kg), a PDE5I, ameliorated learning and memory in the APPswe/PS1dE9 (APP/PS1) mice by a mechanism associated with the NO/cGMP signaling pathway (Fig. 1). These animals overexpressed both APP and presenilin 1 and have been utilized as an animal model of AD. ICA administration decreased the expression and protein levels of APP, amyloid-$\beta_{1\text{-}40 \text{ and } 1\text{-}42}$, and PDE-5. The expression and protein levels of three isoforms of the NOS enzyme were otherwise upregulated by ICA, as well as the production of NO and cGMP, in the cortex of APP/PS1 transgenic mice. Altogether, data indicated a mechanism by which ICA would be a potential therapeutic agent in the case of AD treatment. However, analysis of the bioavailability and toxicological effect of ICA should be performed in order to avoid negative consequences.

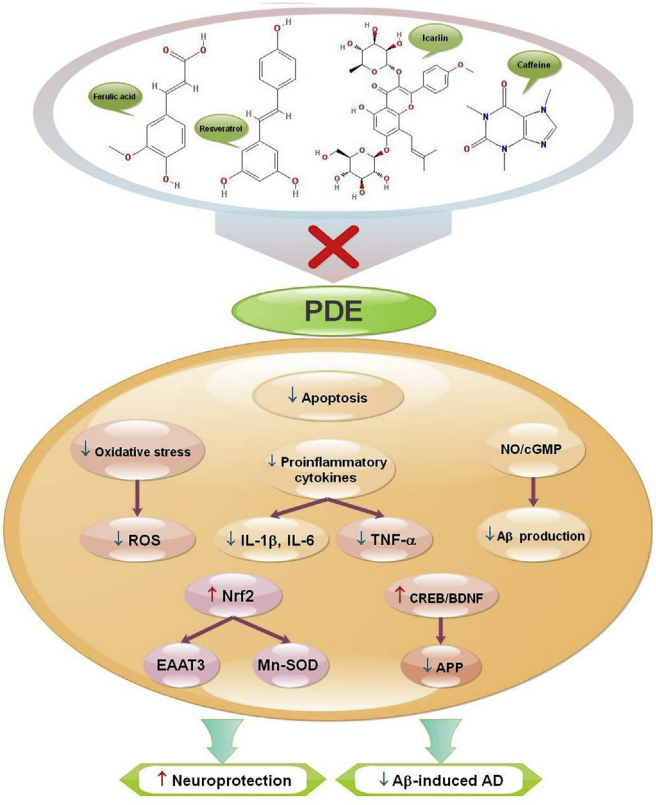

Fig. 1. Underlying mechanisms of actions of natural products as PDEs inhibitors for the treatment of AD.

Wang et al. (2016) recently found that resveratrol (40 mg/kg), an inhibitor of PDE-4, upregulated signaling pathways associated with neuronal survival (Bcl-2, CREB, BDNF) and downregulated the levels of markers of inflammation (IL-1β, IL-6) in the hippocampus of the ICR mice subjected to microinjections of amyloid-$\beta_{1\text{-}42}$ into the hippocampus. Resveratrol also reduced the immunocontents of PDE4A5, PDE4AB1, and PDE4D3 in the hippocampus of amyloid-injected mice. Even though, a direct link between PDE4 downregulation and behavioral and biochemical amelioration was not addressed by the authors in that work, it is very likely that the modulation in the PDE4 proteins levels is associated with the benefits caused by resveratrol in AD-like mice. Future research would be needed in order to investigate whether the doses of resveratrol utilized by the authors would be effective in humans. In the inflammation-related context, ferulic acid (FA) has been used *in vitro* experimental model in which PC12 cells were treated with lipopolysaccharides (LPS) and the production of pro-inflammatory agents and PDE4B were measured (Huang et al., 2016). The authors reported that FA (10–40 μM) downregulated the production of IL-1β and TNF-α in PC12 cells in a concentration-dependent manner. Additionally, FA inhibited the PDE activity and reduced the expression and protein levels of the PDE4B isoform in LPS-treated PC12 cells. FA also upregulated CREB in that experimental model, showing a mechanism by which this natural inhibitor of PDE probably induces neuronal protection.

Considering AD, natural compounds exert several brain protective effects whose mechanisms are not completely understood. Moreover, natural agents like the ones mentioned herein may serve as a structural model in order to develop more effective inhibitors of PDE and/or modulators of other pro-survival signaling pathways downregulated in AD (Fig. 2).

8. Emesis response of phosphodiesterase inhibitors

Emesis is a dose-dependent adverse event of PDE4Is, limiting the clinical development of this class of compounds. The mechanism of emetic response induced by PDE4Is is not well understood, but, this reflex is suggested to be activated by central and/or peripheral sites of action (Hirose et al., 2007; Barnette et al., 1995). The peripheral emetic action of PDE4Is results from the elevation of cAMP content in parietal cells and secretion of acid gastric. The excitation of neurons in the CNS emetic centers is identified as the leading cause of emetogenic response induced by PDE4Is (Carpenter et al., 1988). The area postrema is considered as the chemoreceptor trigger zone (CTZ) for vomiting. This area is a region with poorly developed blood-brain barrier, which detects cerebrospinal fluid and blood stream substances that activate CTZ (Miller and Leslie, 1994). The area postrema, nucleus tractus solitarius and dorsal vagal motor nucleus make up the dorsal vagal complex, the termination site of vagal afferent nerve fibers (Miller and Leslie, 1994). The nucleus tractus solitarius are the other regions of CNS with poor blood-brain barrier, which are implicated in emetic reflux (Andrews et al., 2001). The mRNAs coding for PDE4B and PDE4D have been found in neuronal cells of human brainstem. The mRNAs of PDE4B and PDE4D have been detected in the human area postrema, nucleus tractus solitarius and dorsal vagal motor nucleus. The expression levels of these PDE4 subfamilies is higher in area postrema in comparison with other human brainstem nuclei. The elevated level of cAMP in the area postrema is associated with the emetic reflux of PDE4Is in human brainstem (Mori et al., 2010). cAMP leads to the activation of CREB *via* protein

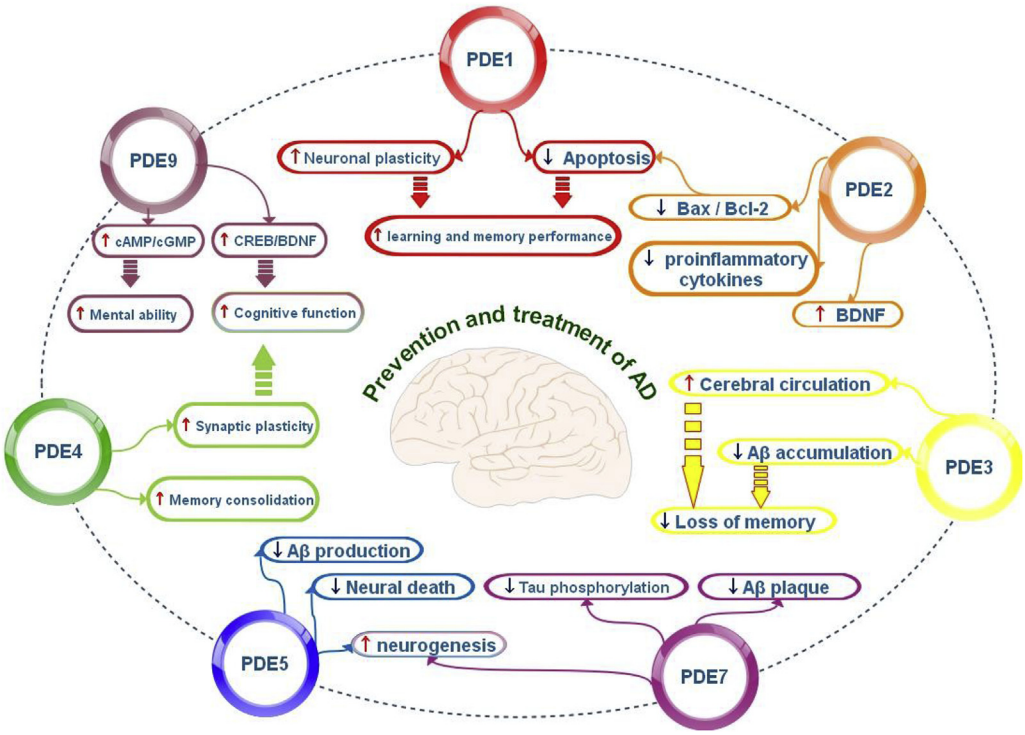

Fig. 2. Cellular signaling pathways involved in therapeutic effect of PDE inhibitors in AD.

kinase A. The transcriptional regulating factor CREB subsequently activates the immediate early gene c-fos, encoding a nuclear protein Fos. Detection of Fos protein in neurons of medulla oblongata is used to identify pathways mediating nausea and vomiting. PDE4Is have been reported to elevate Fos-like immunoreactivity (FLI) in the area postrema, which this reflects the vagal nerves activity or direct action of PDE4Is on CTZ (Bureau et al., 2006). PDE4Is are suggested to mimic the pharmacological action of alpha2-adrenoceptor antagonists through elevating cAMP in sympathetic neurons, which involves in activation of mediators that play key roles in initiation of emesis (*e.g.* noradrenaline, 5-HT, and substance P) (Robichaud et al., 2001).

The PDE4D and PDE4B isoforms are localized at the nodose ganglion and several parts of the medulla including area postrema and nucleus tractus solitaries, proposing the involvement of these isoforms in the emetic adverse effects of PDE4Is (Mori et al., 2010; Cherry and Davis, 1999; Lamontagne et al., 2001). The PDE4D-deficient mice, but not those deficient in PDE4B have reduced α2-adrenoceptor–mediated anesthesia, which is considered as a marker of emesis in non-vomiting animals (Robichaud et al., 2002). Furthermore, medulla PDE4D-expressing neurons are innervated by substance P-enriched terminals; the role of substance P in PDE4Is-induced emetic response supports the involvement of PDE4D in emesis (Robichaud et al., 1999; Lamontagne et al., 2001). Although PDE4D has a critical contribution in the emetic response of PDE4Is, this subtype of PDE4 is predominantly expressed in hippocampal CA1 region and is suggested to influence memory processes. The selective inhibition of PDE4D increases the cognitive process of memory (Pérez-Torres et al., 2000; Li et al., 2011). However, cilomilast, which has low emetic potential compared to rolipram, is more selective for PDE4D than PDE4A and PDE4B (Francis et al., 2011b).

The emetic response and the increasement of acid gastric secretion were associated with the affinity of PDE4Isfor the rolipram high-affinity binding sites (HARBS) on PDE4 (Hirose et al., 2007; Barnette et al., 1995). Cilomilast and roflumilast, with similar affinity for both HARBS and low-affinity towards the rolipram binding sites (LARBS, catalytic activity), have lesser degrees of emesis compared to rolipram (Bamette et al., 1996; Souness et al., 1996). The emetic potential of roflumilast is 10 times lower than that of rolipram, while its ability to improve spatial memory is equal with rolipram (Vanmierlo et al., 2016). The low emetic effect of cilomilast may result from its decreased potency for HARBS or its negative charge at physiological Ph, retarding its ability to enter area postrema (Souness et al., 1996; Torphy et al., 1999; Barnette et al., SB, 207499, 1998). However, some of the cellular functions regulated by PDE4Is are modulated by HARBS, which this may limit the beneficial aspects of low-emetic PDE4Is (Bamette et al., 1996; Barnette et al., SB, 207499, 1998). Although cilomilast and roflumilast induce emesis less than rolipram, these compounds are not void of emesis complication. In this regard, there is a challenge to develop new PDE4Is able to enhance cognition without emetic adverse effect.

It has been reported that new developed PDE4Isincluding GEBR-7b, GEBR-32a, GSK356278, D159687, L-454560, chlorbipram and BPN14770 can improve memory in experimental and human investigations in association with reduced emetic effects. GEBR-7b, GEBR-32a and GSK356278; selective inhibitors of PDE4D; ameliorated the cognitive alterations in animals at doses that did not cause emetic-like effects (Ricciarelli et al., 2017; Bruno et al., 2011; Rutter et al., 2014). D159687, a partial inhibitor of PDE4D, showed cognitive enhancing properties in rodents with an increased tolerability due to the low emetic potency (Zhang et al., 2017). L-454560 is a potent inhibitor of PDE4 A, 4B and 4C, which developed to treat asthma. This compound also enhances memory function without emesis-like behavior (Huang et al., 2007). Chlorbipram is a partial inhibitor of PDE4D, which has anti-depressive and cognitive enhancement effects with reduced emetic activity compared to rolipram (Zhang et al., 2017). BPN14770 is another PDE4D partial inhibitor which its beneficial effects on cognition has been reported in elderly subjects. Clinical studies have reported that BPN14770 is safe and could be tolerated by healthy young and elderly subjects (Prickaerts et al., 2017).

9. PDEs in AD

Neurotransmitters are molecules synthetized by neurons and are essential for regulating signal transduction mechanisms in the nervous system. The neurotransmitters through a mechanism involving the

adenylate cyclase and guanylate cyclase are able to induce the production of cAMP and cGMP, respectively, which have a key role in neuroplasticity and neuroprotection. The enzymes responsible for the hydrolysis and degradation of cAMP and cGMP are called PDEs, so far, up-to 11 isoforms are identified. The role of cAMP and cGMP dysregulation in different pathological conditions has been reported, for example in kidney diseases (Shen et al., 2016); type 2 diabetes mellitus (Suslova et al., 2015); platelet hyperactivity (Smolenski, 2012); cancer (Desman et al., 2014); cardiovascular (Zaccolo and Movsesian, 2007) or neurodegenerative diseases (Domek-Łopacińska and Strosznajder, 2010; Bergantin and Caricati-Neto, 2016). The details about the associations of PDEs and AD has been already described (see introduction). It is well-known that cognitive dysfunctions and loss of memory are linked to AD. In this context, functional studies in different experimental animal models proposed that overexpression of specific PDEs isoforms are involved in AD progression. For example, PDE1, which is highly expressed in hippocampus and cortical neurons, has been suggested to contribute with AD, in fact, different authors have reported that selective PDE1Is significantly improve neuronal plasticity and long-term memory in different animal models (Rosa and Fahnestock, 2015; Li et al., 2016; Medina, 2011) (Fig. 2). PDE2 is highly expressed in the limbic nervous system, and its inhibition enhances learning and memory performance, decreases the pro-inflammatory cytokines expression (IL-22 and IL-170), apoptosis (ratio of Bax/Bcl-2), and increases BDNF, cAMP/cGMP levels and PKA/PKG dependent pathway in Aβ-induced memory disorders mice models (Sierksma et al., 2013; Wang et al., 2017b; Gomez and Breitenbucher, 2013; Zhang et al., 2015). PDE3 is upregulated in cerebral blood vessels of AD and cerebral amyloid angiopathy subjects (Maki et al., 2014). PDE3Is improve cerebral circulation, decrease the Aβ accumulation (Park et al., 2011) and are able to reduce the loss of memory in rat and mice with cognitive dysfunction caused by cerebral hypoperfusion (Kitamura et al., 2017) or by aging (using senescence-accelerated mouse prone 8) (Yanai et al., 2017). Among PDE4 isoforms, PDE4D1 level increased up-to 2.6-fold in hippocampus of advanced AD patients (McLachlan et al., 2007), and selective PDE4Is enhanced the memory consolidation, attenuated the cognitive impairment and hippocampal synaptic plasticity in animal models of AD (Ricciarelli et al., 2017; Zhuo et al., 2016; Wang et al., 2012) (Fig. 2). Despite the very low expression of PDE5 in hippocampus and the cortical areas, PDE5Is have improved cognitive impairment, attenuated neuronal death and promoted neurogenesis, inhibited the activation of microglia, decreased amyloid plaque and the Aβ production in experimental models of AD (Zhu et al., 2015; Fiorito et al., 2013; Sheng et al., 2017; Yan et al., 2017). Upregulation of PDE7 has also been associated with AD. In fact, PDE7 inhibition can stimulate neurogenesis, enhance cognitive impairments, reduced the Aβ plaque accumulation, decreased tau phosphorylation and cell death in normal (Morales-Garcia et al., 2017) and AD animal models (Perez-Gonzalez et al., 2013a). Since other isoform associated with AD is PDE9, the use of PDE9Is improved cognitive impairments in AD and cognition animal experimental models (Hutson et al., 2011; Kroker et al., 2014). Disruption of cAMP/CREB/BDNF pathway can negatively affect the circuits neuronal thereby, in AD, modulation of cAMP/cGMP, PDE, and CREB/BDNF pathway can restore the mental abilities impairments (Fig. 2).

10. Clinical prospects

PDEIs could have effective potential for AD treatment. Novel biochemical and immunohistochemical approaches are utilized to recognize PDE subtypes at RNA and protein levels, and to reveal their specific functions in neural system. Also, Positron Emission Tomography (PET) based ligands is utilized to evaluate the PDEs functions, which can be useful for revealing dynamic alterations or task-based changes of the enzymes or their inhibitors in AD. Such clinical studies can result in understanding mechanisms underlying the AD onset towards the time scales that engage the PDEs cascades (Knott et al., 2017).

Regarding the significant role of PDEs in AD development, various pilot trials in different countries have focused on these types of enzymes including the evaluation of safety and efficacy of FDA-approved PDEIs in AD patients (https://clinicaltrials.gov). In a clinical trial, the intake of HT-0712 resulted in significant increase in long-term memory in patients with age-associated memory dysfunction. The PDE4I was well-tolerated and no severe adverse effect was observed in 28 days administration (http://www.dartneuroscience.com/ClinicalTrials.php).

11. Conclusion and future prospects

Mounting experimental and human investigations revealed that pharmacological targets which are involved in blocking PDEs can be considered as new medicinal approaches in cognitive disorders and dementia. PDEs are a large group of enzymes whose key activities are hydrolysing the cyclic nucleotides into monophosphate isoforms. It has been found that cyclic nucleotides are among second messengers, possessing pivotal roles in transducing the signal of hormones and neurotransmitters. Disturbance in the physiological function of PDEs may cause deregulation of various cellular pathways including the immune system, transduction and transcription signaling pathways and inflammatory response, which possess key contributions in neurodegenerative disorders. Present review article demonstrated that various PDEs encompass a principal role in induction and development of AD. Results obtained from our review showed that several neuropsychopharmacological mechanisms are involved in therapeutic effect of PDEsIs in AD, including modulating neuronal plasticity, reducing tau phosphorylation, pro-inflammatory cytokines and apoptosis, improving cognitive impairment and cerebral circulation, decreasing Aβ plaque accumulation and increasing the level of BDNF as well as cAMP/cGMP. Numerous cellular signaling pathways are involved in neuropharmacological mechanisms of PDEs in AD such as PKA/PKG dependent cascade and cAMP/CREB/BDNF pathway. There is a real necessity for novel medicinal approaches in order to prevent and treat AD. It is worth mentioning that many of the PDE specific drugs have a number of other pharmacological actions that may account for their activities. Additionally, some of these drugs are not explored enough for their other probable pharmacological activities. Besides, about issues like protective effects of such drugs, which are directly attributed to the PDS inhibition, other pharmacological effects of the drugs may also be impressive, such as neurotransmitter receptor activity or some downstream effects (i.e. vasodilation). PDEs are emerging as practical targets for exploring novel pharmacotherapeutic agents to manage AD. Further well-designed clinical investigations are mandatory to evaluate the effectiveness and safety of PDEs inhibitors in AD patients.

11.1. Expert commentary

AD is one of the most prevalent age-related neurodegeneration pathological condition, typically associated with neuroinflammation and loss of mental ability. The enzymes responsible for the hydrolysis and degradation of cAMP and cGMP, which are called PDEs. The role of cAMP and cGMP dysregulation in different pathological conditions has been reported. Cognitive dysfunctions and loss of memory are linked to AD. In this context, the upregulation of specific PDE isoforms are reported to be involved in AD. Disruption of cAMP/CREB/BDNF pathway can negatively affect the neural performance, thus, in AD condition the modulation of cAMP/cGMP, PDE, and CREB/BDNF pathway can restore the mental abilities impairments. Current review revealed that various PDEs are key contributors in induction and development of AD. Also, several neuropsychopharmacological mechanisms are involved in therapeutic effect of PDEIs in AD, including modulating neuronal plasticity, reducing tau phosphorylation, pro-inflammatory cytokines and apoptosis, improving cognitive impairment and cerebral

circulation, decreasing Aβ plaque accumulation and increasing the level of BDNF as well as cAMP/cGMP. In addition, various pilot trials have focused on safety and efficacy of PDEIs in AD patients. Mounting evidence revealed that novel therapeutic approaches are mandatory in order to prevent and treat AD. PDEs are emerging as practical targets for exploring novel pharmacotherapeutic agents for managing AD.

11.2. Five years view

In increasingly aging communities AD is becoming a growing concern. AD is a neurological disease with progressive nature that gradually destroys memory as well as cognitive skills along with behavioral abilities. It has been suggested that PDEIs possess a promising effect in treatment of AD. AD pathogenesis is quite complicated as characterized by various abnormalities in the brain such as irregular Aβ metabolism, tau hyperphosphorylation, oxidative stress, microglial variations, and some other pathological procedures. Since cholinesterase inhibitors are the only available symptomatic treatment for AD, the most prescribed drugs in clinic at the moment, the discovery of new drugs and treatment options are still in great demand to combat the disease. Regarding the association between PDEs and pathology of AD, PDEIs may be considered as new targets for AD therapy.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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