Journal Pre-proof

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PII:	S1043-6618(20)31386-4
DOI:	https://doi.org/10.1016/j.phrs.2020.105078
Reference:	YPHRS 105078
To appear in:	*Pharmacological Research*
Received Date:	18 March 2020
Revised Date:	9 July 2020
Accepted Date:	10 July 2020

Please cite this article as: Bhat A, Ray B, Mahalakshmi AM, Tuladhar S, Nandakumar D, Srinivasan M, Essa MM, Chidambaram SB, Guillemin GJ, Sakharkar MK, Phosphodiesterase-4 enzyme as a therapeutic target in neurological disorders, *Pharmacological Research* (2020), doi: https://doi.org/10.1016/j.phrs.2020.105078

Phosphodiesterase-4 enzyme as a therapeutic target in neurological disorders

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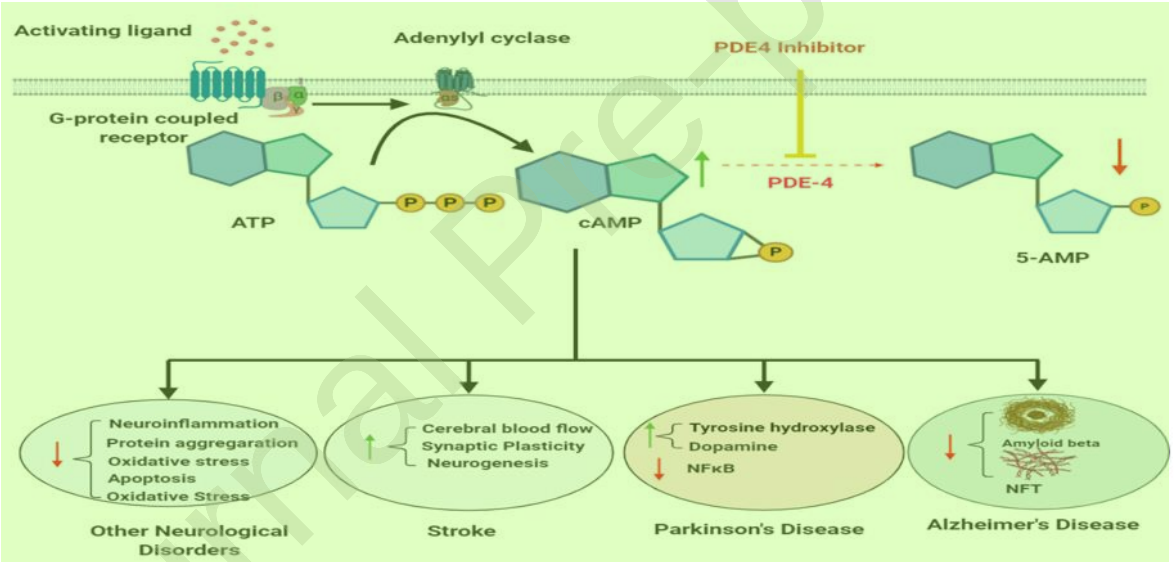
Graphical abstract



Abstract

Phosphodiesterases (PDE) are a diverse family of enzymes (11 isoforms so far identified) responsible for the degradation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) which are involved in several cellular and biochemical functions. Phosphodiesterase 4 (PDE4) is the major isoform within this group and is highly expressed in the mammalian brain. An inverse association between PDE4 and cAMP levels is the key mechanism in various pathophysiological conditions like airway inflammatory diseases − chronic obstruction pulmonary disease (COPD), asthma, psoriasis, rheumatoid arthritis, and neurological disorders etc. In 2011, roflumilast, a PDE4 inhibitor (PDE4I) was approved for the treatment of COPD. Subsequently, other PDE4 inhibitors (PDE4Is) like apremilast and crisaborole were approved by the Food and Drug Administration (FDA) for psoriasis, atopic dermatitis etc. Due to the adverse effects like unbearable nausea and vomiting, dose intolerance and diarrhoea, PDE4 inhibitors have very less clinical compliance. Efforts are being made to develop allosteric modulation with high specificity to PDE4 isoforms having better efficacy and lesser adverse effects. Interestingly, repositioning PDE4Is towards neurological disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS) and sleep disorders, is gaining attention. This review is an attempt to summarize the data on the effects of PDE4 overexpression in neurological disorders and the use of PDE4Is and newer allosteric modulators as therapeutic options. We have also compiled a list of on-going clinical trials on PDE4 inhibitors in neurological disorders.

Abbreviations

AD: Alzheimer's disease; **AIDS:** Acquired immunodeficiency syndrome; **AMP:** Adenosine monophosphate; **AMPK:** 5' AMP-activated protein kinase; **AMPAR:** α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **APP:** Amyloid precursor protein **; ATP:** Adenosine triphosphate; **AB:** Amyloid-β; **BDNF:** Brain-derived neurotrophic factor; **CA1:** cornu ammonis-1; **cAMP:** Cyclic adenosine monophosphate; **CAR:** Conditioned avoidance response; **CBP:** CREB-binding protein; **cGMP:** cyclic guanosine monophosphate; **CNS:** Central nervous system; **COPD:** Chronic obstruction pulmonary disease; **CREB:** cAMP-response element binding protein; **DA:** Dopamine; **DISC1:** Disrupted in schizophrenia 1; **DNA:** Deoxyribonucleic acid; **EAE:** Experimental autoimmune encephalomyelitis; **EGF:** Epidermal growth factor; **ERK:** Extracellular signal-regulated kinase; **fALS:** Familial Amyotrophic Lateral Sclerosis; **FDA:** Food and Drug Administration; **fMRI:** Functional magnetic resonance imaging; **GABA:** Gamma aminobutyric acid; **GBM:** Glioblastoma; **GluR1:** Glutamate receptor1; **H_2O_2:** Hydrogen peroxide; **HD:** Huntington's disease; **Htt:** Huntingtin; **IBs:** Inclusion bodies; **IFN-γ:** Interferon gamma; **IL-1 β:** Interleukin-1beta; **IL-12:** Interleukin-12; **IL-23:** Interleukin-23; **IL-6:** Interleukin-6; **JNK:** c-Jun N-terminal kinase; **LPS:** Lipopolysaccharides; **LTP:** Long term plasticity; **MAPK:** Mitogen-activated protein kinase; **MDM2:** Mouse double minute 2 homolog; **MPP^+:**1-methyl-4-

phenylpyridinium; **MPTP:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **MS:** Multiple sclerosis; **NA:** Noradrenaline; **NFT:** Neurofibrillary tangles; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **NGF:** Nerve growth factor; **NMDAR:** *N*-methyl-D-aspartate-type glutamate receptors; **NO:** Nitric oxide; **NOS:** Nitric oxide synthase; **NT-3:** Neurotrophin-3; **NT-4:** Neurotrophin-4; **PC12:** Pheochromocytoma cells; **PD:** Parkinson's disease; **PDE:** Phosphodiesterase; **PDE4:** Phosphodiesterase 4; **PDE4I:** Phosphodiesterase 4 inhibitor; **PKA:** Protein kinase A; **PKG:** Protein kinase G; **PSD-95:** Postsynaptic density protein 95; **RSK2:** Ribosomal S6 kinase 2; **SAH:** Subarachnoid hemorrhage; **sALS:** Sporadic amyotrophic lateral sclerosis; **sGC:** Soluble guanylyl cyclase; **SH-SY5Y:** Human neuroblastoma; **SNpc:** substantia nigra pars compacta; **SSRI:** Selective serotonin reuptake inhibitor; **TBI:** Traumatic brain injury; **TH:** Tyrosine hydroxylase; **TNFα:** Tumor necrosis factor alpha; **UCR:** Upstream conserved region; **VD:** Vascular dementia

Keywords: Phosphodiesterase, cAMP, cGMP, neurological disorders, PDE4 inhibitors, central nervous system

1. Introduction

Phosphodiesterases (PDEs) are a super-family of enzymes reported to be involved in inflammatory diseases like chronic obstructive pulmonary disease (COPD) and asthma (1). A total of 11 PDE enzymes have been identified and are present in almost all the cells in mammals. PDE enzymes hydrolyse cyclic nucleotides – cAMP and cGMP and thus plays important roles in cellular functions (1,2). PDE4 enzyme is predominant amongst the 11 PDE super-family enzymes and has four isoforms - PDE4A, PDE4B, PDE4C and PDE4D. PDEs interact with myomegalin (a structural protein), which is highly expressed in skeletal and cardiac muscles and play crucial role in cardiac contractility (3). Colocalization of myomegalin and PDE4D in Golgi-centrosomal structure is involved in cytoskeletal assembly and disassembly and organellar movements indicating that PDE4 plays crucial role in cellular functions (4). The deleterious effects of increased expression of PDE4 in different pathological conditions was confirmed in experimental models (5–7). Clinically, overexpression of PDE4 is recorded in cancer (8), retinal degeneration (9), acrodysostosis (10), Alzheimer's disease (AD) (11), stroke (12) and in several neurological disorders (13,14). PDE4 enzymes hydrolyse cAMP and PDE4Is increase cAMP levels by preventing its breakdown. The ability of PDE4Is to increase cAMP in different pathological conditions has attracted clinical attention (15,16). US-FDA has approved PDE4Is for the treatment of various diseases, for example, PDE4B inhibitor (Roflumilast and Apremilast) , for COPD (17) and psoriasis treatment, respectively. These inhibitors supress TNFα, IL-17, IL-23 expression and up-regulate the anti-inflammatory gene IL-10 (18). Interestingly, PDE4 enzyme is highly expressed in the brain and is deemed to be a potential target in the treatment of neurological disorders. Several PDE4Is are in Phase I and II clinical trials for neurological disorders like Parkinson's disease (PD), Huntington's disease (HD), AD, depression, and multiple sclerosis (MS). However, these inhibitors have dose limiting side effects such as nausea, vomiting and gastric acidity that has resulted in low clinical compliance (19).

Other PDE subfamily inhibitors like PDE5 and PDE7 inhibitors have shown neuroprotective ability in preclinical investigations but have serious side effects like non-arteritic anterior ischemic optic neuropathy (20) and hearing loss and hence are not a preferred option clinically (21). Furthermore, these PDE5 and PDE7 inhibitors exert undesirable effects on the cardiovascular functions including tachycardia and reduced peripheral blood pressure (22). No clear information on the safety and efficacy of PDE8, 10 and 11 inhibitors are available as of today and this need to be investigated. Recently, PDE4 allosteric modulators -GSK256066, GEBR-7b, D159687, D159797 and TAK-648 were developed and have shown improved blood brain barrier penetrability, high potency and low side effects (23,24). These allosteric modulators are found to have improved efficacy in inflammatory diseases (25), diabetes (26), autoimmune disorders (27) and neurological disorders (28). The current review summarises data on the structure and localization and the role of PDE4 and PDE4Is in key molecular signalling pathways in brain. The therapeutic potential of PDE4 inhibitors in various neurological disorders and the data on the on-going clinical trials on PDE4Is for treating neurological disorders is also presented.

1. Structure of PDE4

PDE enzymes possess conserved catalytic domain (25-49%) with almost 300 amino acids that suggests comparable three dimensional configurations of these enzyme domains (PDB code 1TB7) (29). PDE4 is highly specific for cAMP and has a low Km of 1–3 μM(30). PDE4 has four isoforms 4A, 4B, 4C, and 4D that have upstream conserved region (UCR) which regulates intracellular signalling (29). Based on the UCRs they possess, PDE4s are divided into subgroups such as long, short, and super short isoforms **(Fig. 1)**. Long isoforms have both UCR1 and UCR2, short isoforms have UCR2, while super-short isoforms have a truncated UCR2 (30,31) leading to variance in the regulation as UCR1 phosphorylates protein kinase A (PKA) dependent enzyme activation. Phosphorylation of short isoforms in catalytic domain by phosphoinositide-3-kinase and extracellular signal-regulated kinase (ERK) results in inhibition of PDE4 (32,33). The catalytic domain of PDE4B folds into a novel compact structure composed of 17-α helices and three sub-domains (34). Subdomain 1 is also known as N-terminal domain and comprises of seven α-helices (H1–H7). Subdomain 2 contains four α-helices (H8–H11) while subdomain 3 is made up of five α-helices (H12–H16) with an extended loop that forms aβ hairpin between H12 and H13 (35). The three sub-domains join to form a compact pouch which has 12 (out of 17) residues fully conserved in all PDE families. This is the catalytic pocket and has a volume of about 450Å^3 and can accommodate a molecule of about 250Å^3 in size (such as cAMP). In the crystal structure of PDE4B, residues of the catalytic pocket and Helix 17 (residue 496–508) interact through crystallographic symmetry. Also, the random loop of residues 422–434 in PDE4D2 corresponds to helix H17 in PDE4B **(Fig.2)**. The conformational modification of the C-terminal residues in the PDE4 family along with the sequence multiplicity in the 11 PDE families suggests that the C-terminus is involved in the regulation of PDE hydrolytic activity. There are two conserved Zn^{2+} binding consensus motifs in the amino terminal segment of the catalytic site of the PDEs, and both sides are reportedly involved in the catalysis. Of these, site A has five conserved amino acids with a sequence HNXzHG/AX2, while site E and site B have a sequence $HDZXHX_{24\text{-}26}E$, sharing more homology with the known Zn^{2+} binding site of thermolysin (36). Divalent metals like Mg^{2+}, Co^{2+}, Mn^{2+}, Ni^{2+} and Zn^{2+} are needed for the enzymatic activity of PDE4. The number of zinc atoms required for binding is under debate. Reports suggest that one Zn^{2+} ion per PDE4A monomer, two Zn^{2+} ions for PDE7 (*Vibrio fischeri)* and PDE4A, and three Zn^{2+} ions for PDE5 are required for activation. The enzymatic site of PDE4 comprises two metal ions separated by 3.9 Å, suggesting its simultaneous interaction with the two metal binding sites. The first metal atom is located at the bottom of the catalytic pocket in association with the two histidine (H164, H200 in PDE4D2) and two aspartic acid residues (Asp201 and Asp318) (37). As the metal binding residues belong to the three PDE4 sub-domains, the metal ions stabilize the protein structure. It has been reported that in the PDE4–adenosine monophosphate (AMP) structure, the metal ion forms two coordinates: one with His164, His200, Asp201, Asp318, and two phosphate oxygen atoms of AMP; and the second with Asp318, two phosphate oxygen atoms of AMP, and three bound water molecules. Therefore, it has a catalytic role (38). The strong irregular dispersion at the wavelength of the zinc absorption range is reflective of the fact that the first metal ion that activates the enzyme is zinc (36). In PDE4D2, the second metal ion interacts with D318, binds to water and the phosphate group of the substrate. However, due to the weak binding at this site, the second divalent metal ion is not known; although, magnesium (Mg) or manganese (Mn) are suggested by biochemical studies (39).

2. Expression and localization of PDE4

Expression of PDE4 is ubiquitous (40), although it varies both at regional and cellular levels (37). PDE4 overexpression promotes the progression of neurological disorders like AD, PD, MS, ALS, glioma, stroke, depression etc. PDE4 are mainly expressed in the brain, smooth muscles, cardiovascular tissues and are nearly absent in platelets **(Table. 1).** Intriguingly, expression of PDE4A, B, D was found to be high in rat brain, particularly in the anterior brain, cortex and olfactory bulb, whereas PDE4C was found to be high in the olfactory bulb (41).

3. PDE4 and PDE4Is in key molecular signalling pathways in brain

3.1. *cAMP–PKA, CREB and BDNF signal*

PDE4 hydrolyses cAMP which play a significant role in long term potentiation (LTP) and synaptic plasticity (42). cAMP activates protein kinase A which controls the transcription of brain derived neurotropic factors (BDNF) and thus it has a pivotal role in cognitive functions (43). Mounting evidence confirms that PDE inhibitors enhance cAMP/cGMP signalling and in turn cAMP Response Element-Binding Protein (CREB) phosphorylation and the downstream effectors (44–46). Mutations in CREB causes cognitive dysfunction, mood disorders and alterations in neural regeneration (47). Rodents with a mutated form of CREB binding protein (CBP), a coactivator for major transcription factors, exhibit developmental aberrations like patients with mental retardation. These mouse models also suffer from memory dysfunction (48).

Rolipram is reported to improve long-term memory and CREB signalling instigated by CBP mutations (49). It also promotes neurogenesis in the hippocampal region and enhances the neuronal survival via cAMP/CREB signalling (50,51). Rolipram administered with imipramine significantly increased the level of CREB and BDNF in the cortex and hippocampal regions of rats (52). Activation of cAMP/CREB/BDNF signalling by rolipram is shown to exert antidepressant-like effects (53). On the other hand, receptor for activated C kinase 1 (RACK1), called as guanine nucleotide-binding protein subunit beta-2-like 1 (GNB2L1) is tightly linked to cAMP/PKA pathway (54). RACK1 interacts (inhibits) with PDE4D5 and stimulates cAMP/PKA pathway (55). Activation of cAMP/PKA pathway in the hippocampal neurons dissociates RACK1 from NMDA-receptors allowing channels activity (56) which corroborates with its involvement in memory functions.

3.2. NO/cGMP/PKG pathway

Nitric oxide (NO) signalling is extensively involved in synaptic plasticity and cognitive functions (57). NO is a soluble gas formed by the transformation of L-arginine to L-citrulline in the presence of Ca^{2+}regulated enzyme nitric oxide synthase (NOS). NO plays pivotal role at pre- and post-synapses. NO plays major effects in the hippocampus, cerebellum and lateral nucleus of the amygdala which are critical for memory formation (58,59). One immediate downstream effector of NO is soluble guanylyl cyclase (sGC) (60), which is responsible for cGMP synthesis and activation of cGMP dependent protein kinase (PKG). PKG, in turn, mobilises presynaptic vesicles and facilitate the release of neurotransmitters. It also activates postsynaptic PKG signalling leading to the activation of transcription factors that are important for LTP and memory formation (59,61). Pharmacological activation of NO/cGMP/PKG signalling is shown to enhance memory. Phosphodiesterase enzymes impede the signal transduction by affecting the second messengers like cAMP and cGMP (42). Stimulation of *N*-methyl-D-aspartate-type glutamate (NMDA) receptors activates NO synthase and increases cGMP levels (65). Inhibiting the breakdown of cGMP with a specific PDE2 inhibitor (Bay 60-7550) is shown to improve memory consolidation in MK801-induced memory deficits in mice (66). Preclinical studies have shown that PDE5 inhibitors increase NO/cGMP/PKG signalling in turn synaptic plasticity and cognitive performance in rodents (67,68). Zaprinast, a PDE5 inhibitor blocks cGMP specific phosphodiesterase and activates cGMP and cGMP-dependent ion channels, thereby potentiates calcium entry into presynaptic terminals and neurotransmitter release (69). Similarly, PDE5 inhibition with KJH-1002 was shown to improve cognitive function via activation of CREB signal in scopolamine intoxicated rats (70). Inhibition of PDE4 with rolipram elicited anxiolytic effects through activation of cAMP/CREB/BDNF signalling (53). These data indicate the PDE enzymes influence NO/cGMP/PKG pathway and elicits beneficial effects in brain disorders.

3.3. MAPK-ERK signal

The role of the mitogen-activated protein kinase (MAPK) pathway in synaptic plasticity and memory is well-established (71,72). Activation of ERK signalling enhances LTP (73,74). Furthermore, both cyclic AMP/protein kinase A (PKA) and MAPK/ ERK are found to interact with each other (75). PDE4 is a common link between cAMP/CREB/BDNF and ERK signalling pathways in mediating memory. Inhibition of PDE4 enzymes by epidermal growth factor (EGF) via ERK activation increases cAMP levels (76). Crosstalk between cAMP and ERK signalling in hippocampal cornu ammonis-1(CA1) region is shown to be involved in synaptic plasticity (77,78). MAPK pathway activates CREB via p90 ribosomal S6 kinase 2 (RSK2) (79). Administration of MAPK and PKA inhibitors is shown to inhibit CREB phosphorylation. This suggests that MAPK-PKA pathways are involved in CREB function (80). Inhibition of MAPK/ ERK signalling is found to produce cognitive deficits and reduce hippocampal synaptic plasticity (72). ERK signalling affects PDE4 activity in neuronal cells (81). PDE4 inhibition by rolipram reverses ERK inhibition induced memory deficits in rats (74). Activation of NMDA receptors is a pre-requisite for LTP induction which is primarily mediated through MAPK (82). AP5, a NMDA receptors antagonist blocks the effects of rolipram on LTP (83). This shows that rolipram potentially trigger NMDA receptors mediated MAPK/ERK pathway and causes phosphorylation of CREB (84). Rolipram is reported to block MAPK signalling cascade by PKA initiated inhibition of Raf-1 activity (85). Furthermore, cAMP activates ERK via stimulation of B-Raf (86). Thus, inhibitors of PDEs have potential benefits in modulating the MAPK-ERK-CREB cascade primarily by cAMP and by altering changing NMDA receptor functions.

4. PDE4 inhibitors and neuroplasticity

Neuroplasticity is the capacity of neuronal cells to rewire or reorganize the structure and functions in normal or diseased state (87). Newer connections are established by normal cells which takes functional role of damaged neurons (88). Clinical and animal studies confirm that plasticity of brain is the main mechanism by which functional connectivity is restored after an injury (89). Multiple targets are shown to improve neuroplasticity, cAMP is one of them (90). Dysregulation of cAMP-PKA-CREB and cAMP-ERK1/2-CREB signalling cascades is linked to disruption of neuroplasticity (91). cAMP/ PKA/CREB signalling regulates the transcription of BDNF which plays a vital role in the maintenance of hippocampal LTP (92,93). Upregulation of BDNF also accelerates neurogenesis and synaptic plasticity (94).

PDE4 hydrolyses cAMP and all the three isoforms (PDEA, B, D) are shown to inhibit neuroplasticity. PDE4 isoforms are highly expressed in cortex, hippocampus and amygdala (95). PDE4A5 is shown to reduce LTP and dendritic spine number and morphology in CA1 region of hippocampus due to the degradation of cAMP (96). Neuronal cell proliferation in dentate gyrus region of hippocampus is observed in PDE4A knockout mice (97). Inhibition of PDE4 is considered to be an ideal strategy in repairing the deficits in synaptic plasticity (98,99). PDE4 inhibition is shown to improve hippocampal LTP and dendritic spines density by activation of cAMP/PKA/CREB/BDNF signal (100,101). Rolipram is shown enhance the neural progenitor cell production in dentate gyrus region (102). Inhibition of proinflammatory cytokines release by PDE4I is linked to enhanced neuroplasticity. Mutation in PDE4 reduce the levels of interleukin-1-beta (IL-1β), TNF-α, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and increase the expression of pCREB and BDNF in the hippocampal region of amyloidβ-42 injected mice (103). Interestingly, FFPM, a PDE4 inhibitor, exerts dual action viz activation of PKA, BDNF and CREB phosphorylation and simultaneously reduced NF-κB, p65, inducible nitric oxide synthase (iNOS), TNF-α and IL-1β levels in hippocampus of APP/PS1 transgenic mice as well as in lipopolysaccharides (LPS) injected mice (99,104). Roflumilast prevents primary blast-induced deficits in synaptic plasticity and increases the expression of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA)-glutamate receptor1(GluR1) (total and pGluR1-Ser831), and pStargazin-Ser239/240, and postsynaptic density protein 95 (PSD-95) that play a key role in LTP (101). PDE4 inhibition with Rolipram facilitates synaptic plasticity by activating cAMP/PKA/MAPK/CREB pathway and LTP in hippocampus of MK801, a non-competitive NMDA receptor antagonist of NMDA, intoxicated animals (105).

5. PDE4 as a therapeutic target in neurological disorders

Phosphodiesterase have a pivotal role in neuronal functions and survival (42,106). PDEs hydrolyze cAMP and cGMP and decrease the levels of these secondary messengers are corroborated for cognitive decline, and progression of AD, PD, psychosis, and depression. Thus inhibition of PDE4 appear as potential target in the treatment of neurological disorders (44,107).

6.1 Alzheimer's disease

Alzheimer's disease is a fatal neurodegenerative disease with progressive cognitive decline (108). AD is distinguished by an increase in the accumulation of amyloid-β peptide (Aβ) neurofibrillary tangles (NFT), senile plaques which are made of Aβ peptide derived from amyloid precursor protein (APP) (108). γ-secretase enzymes cleave APP and produces insoluble β-amyloid protein which accumulates and forms plaques in the brain (109). NFT are aggregates of hyperphosphorylated tau proteins. Accumulation of Aβ, NFT and senile plaques inhibits LTP, disrupts the neuronal transport and ultimately leads to neuronal death (110). In addition, intracellular accumulation of Aβ decreases dendritic spine density and morphological alterations (111,112). Interestingly, cAMP and cGMP are shown to impact Aβ production by governing the conversion of the immature N-glycosylated APP, confined in the endoplasmic reticulum and Golgi apparatus, into the matured N- O-glycosylated protein (113). An increase in PDE4A and PDE4B expression are observed in the early stages of AD (114). Age related increase in cAMP dependent PKA plays a significant role in phosphorylation of tau in monkeys (115). Decreased levels of cAMP/ PKA/CREB have been found in the AD post-mortem brains (116–118). Inhibition of PDE4 enzymes improves long term potentiation, synaptic plasticity and corrects the memory deficits in double-transgenic mice having a high load of Aβ42 levels (119). FCPR03 is a novel PDE4 inhibits pro-inflammatory cytokines like TNF-α, IL-1β and IL-6 and improves the levels of cAMP in BV-2 microglial cells exposed to lipopolysaccharide exposed and in mice. This anti-inflammatory activity is mediated by the cAMP/PKA/CREB signalling pathway and NF-κB inhibition (99). PDE4 inhibition with rolipram enhances hippocampal LTP, and improve memory in contextual fear conditioning test in transgenic mice by stabilizing the synaptic circuitry and via cAMP/PKA/CREB signalling (119). Dendritic spine loss and dystrophic neurites in hippocampal regions of APP/PS1 transgenic mice which classically mimics postmortem changes in AD brains. Rolipram treatment increased dendritic spines in the hippocampal region of APP/PS1 mouse model of AD (120). It also produced a dose dependent increase in hippocampal CREB levels and cognitive function in Aβ injected animals (121). Notably, it promotes proteasome activity and tau clearance improves cognition via cAMP-PKA activation in double-transgenic rTg4510 mice (122). GEBR-7b, a novel PDE4D selective inhibitor improves the consolidation process and increase the levels of cAMP in the hippocampal region of AD rats (123). Selective blocking of

PDE4D by D159687 and D159797, two allosteric PDE4D inhibitors, has been shown to improve the retrieval process in female Cynomolgus Monkeys (124). These data indicate the PDE4 is linked directly or indirectly in the regulation of key AD proteins like Aβ, tau and NFT, cAMP/PKA/CREB signal and LTP that are involved in memory. In addition, PDE4 is also noted to play crucial role on dendritic spine morphology and numbers. Thus, PDE4 inhibitors might be beneficial in AD treatment.

6.2. Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disease characterized by decreased levels of dopamine and accumulation of α-synuclein aggregates in the substantia nigra and striatal region of brain (125–129). Sufficient evidence confirm the disruption of cyclic nucleotide signalling contributes to striatal dysfunction (130–132). Downregulation of CREB and neurotrophic factors like BDNF, nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) in substantia nigra (130) is well documented. An increase in the levels of cAMP has been reported to reduce the neuroinflammation by downregulating the expression of NF-κB and iNOS production (133). Pre-clinical and clinical studies have confirmed that PDE4 inhibitors appear to be promising drugs in the treatment of PD (130,134–136). FCPR16, a PDE4 inhibitor, prevents the dopaminergic loss by inhibiting reactive oxygen species production and preventing any change in the mitochondrial membrane potential in human neuroblastoma cells. This effect is reported to be mediated by cAMP/PKA/CREB and Epac/Akt signalling pathways (137). FCPR16 has also been found to trigger autophagy in 1-methyl-4-phenylpyridinium (MPP^+) intoxicated human neuroblastoma cells (SH-SY5Y cells) via 5' AMP-activated protein kinase (AMPK) pathway (138). XT-44 (1-n-butyl-3-n-propylxanthine), a PDE4 inhibitor increase the reuptake of DA and improve the intracellular dopamine levels in rat mesencephalic neurons. This protective effect was found to be mediated via cAMP/PKA/CREB pathway (139). Rolipram increases tyrosine hydroxylase (TH) phosphorylation and dopamine levels by increasing dopamine synthesis in the striatum without altering the dopamine release. Again, this action is found to be mediated via cAMP/PKA signalling (140). In addition, rolipram increased the striatal dopamine levels by preventing its metabolism and loss of tyrosine hydroxylase in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxicated C57BL/6 mice. Importantly, rolipram treatment improves the level of dopamine and alleviates the severity of Parkinsonism in a double-blind trial (141). On a different note, ibudilast, PDE4 inhibitor, is reported to protect the astrocytes by inhibiting the release of cytochrome c, caspase-3 activation, and nuclear condensation in hydrogen peroxide (H_2O_2) reperfusion rat model. The increase in cGMP levels through PDE inhibition is linked to the observed protection (142). These data indicate the crucial involvement PDE in pathology including α-syn accumulation, TH and dopamine turn over. Hence, PDE4 inhibition can be a potential option the management of PD **(Fig.3).**

6.3. Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease characterized by chronic neuroinflammation and demyelination which destroys oligodendrocytes, axons, and neurons. Inflammatory lesions found in white and grey matter are caused by over-activation of autoreactive T-cells and activated macrophages and microglia which form focal demyelinating plaques (143). Pro-inflammatory cytokines such as Interferon gamma (IFN-γ), TNF-α, Interleukin-6 (IL-6), Interleukin-12 (IL-12), and Interleukin-23 (IL-23) have been detected in post-mortem brains of MS patients (144) and in experimental autoimmune encephalomyelitis (EAE) model of MS (144,145). Pro-inflammatory mediators damage myelin and oligodendrocyte and disrupt the blood brain barrier (146). cAMP is recognized as a significant player in controlling the production of pro-inflammatory cytokines (147). Decreased levels of cAMP in the cerebrospinal fluid are linked to demyelination in MS patients (148). cAMP analogues are also reported to reduce inflammation and apoptosis. Previous studies have confirmed that cAMP analogue, Dibutyryl cyclic AMP, performs myelin repair in MS through recruitment of endogenous neural stem cells and their differentiation (149). Increasing cAMP levels through PDE4 inhibition suppresses the immune response and increases remyelination (150,151). PDE4 inhibition supresses monocytes, macrophages , and cytokine secretion and proliferation of type 1 T helper cells specific to the myelin basic protein (152).

Rolipram decreases TNF-α levels in J774 mouse macrophage cell line by increasing the expression of MAPK phosphatase-1(153) and by inhibiting NF-κB complexes in LPS intoxicated human chorionic cells PDE4 inhibition with rolipram reduced inflammation, demyelination and delayed onset of clinical signs in EAE rodent model of MS (154,155).Notably, rolipram prevents the development of clinical signs, demyelination and inflammation in marmosets (small monkeys) injected with human white matter, a gold standard model of EAE (156). Ibudilast is found to delay the onset of disease and inflammatory infiltration in EAE induced Dark August rats by increasing cAMP levels (157). BBB022, a PDE4 inhibitor, in combination with rolipram decreases the severity of EAE and stabilizes the blood brain barrier in EAE induced MS (158). Clinical trials are underway investigating the efficacy of PDE4 inhibitors in MS (23). Preclinical and clinical evidence clearly indicate that PDE participates in autoimmune function, cytokine release and demyelination. Further, few molecules under clinical trials indicate potential of PDE4 inhibition in MS treatment.

6.4. Schizophrenia

Schizophrenia is a serious psychiatric illness characterized by delusions, hallucinations, disorganized speech or behaviour, and impaired cognitive ability. The precise cause of schizophrenia is still not clear. However, the imbalance in neurochemicals such as dopamine , serotonin, and glutamate in brain are observed in schizophrenia patients (159). Recent studies have provided evidence on the possible role of PDE4 in schizophrenia (159–161). It has been reported that disrupted in PDE4B gene cause schizophrenia in two patients (162). Overexpression of PDE4B gene is shown to increase the risk of schizophrenia in the Scottish population (163). PDE4B associates with disrupted in schizophrenia 1 (DISC1), a genetic factor responsible for schizophrenia and related mental disorders (162). PDE4 with DISC1 and NDE1 or NDEL1 complexing suggests additional role of PDE4 in modulating cAMP levels via PKA and synaptic transmission. This reveals that PDE4 is a prime target in mental illness in schizophrenia research (164). Clapcote et al., (2007) found that production of two strains of DISC1-mutant mice with impaired affinity to PDE4B exhibit either schizophrenia or depression (165). Animal studies have given ample evidences on the possible role of PDE4 in schizophrenia (165). Rolipram is shown to antagonize the effects of phencyclidine and amphetamine-induced hyperactivity and to reduce methamphetamine-induced hyper-locomotion (166). It also reverses amphetamine-disrupted auditory sensory processing and prepulse inhibition (167) and NMDAR antagonist-induced deficits in latent inhibition (168). Roflumilast improves verbal learning and modulates the frontal brain area in schizophrenic patients. The improvement in memory, measured with functional magnetic resonance imaging (fMRI), is linked to the increase in cAMP levels and LTP (44,161). Thus, PDE4 inhibitors like rolipram and roflumilast possess antipsychotic-like properties and are interesting molecules for further research in schizophrenia.

6.5. Depression

Depression, the most common mental illness that severely limits psychosocial functioning and diminishes life quality (169). Enormous evidence suggests that there is a dysfunction of cAMP signalling in depressive patients (170–172). β1 and β2- adrenergic receptors produce anti-depressant like effects (173,174) and are shown to increase the formation of cAMP through adenylyl cyclase stimulation in brain (175). β1 and β2 receptors form complexes with PDEs, but their binding varies in terms of PDE4D splice variant recruited at the receptor. β1- adrenergic receptor preferentially associates with PDE4D8 whilst β2/β-arrestin complex has higher affinity to PDE4D5 (176). Zhang et al., (2005) demonstrated that PDE4 inhibition produced an "additive" anti-depressant effect when administered along with dobutamine, β1 agonist in rats. Similarly, a synergistic was observed when administered clenbuterol, β2- agonist, in rats. Though many studies reveal that β2 mediated cAMP signalling and antidepressant effects are more sensitive to PDE4 inhibition, still β-1 mediated noradrenergic anti-depressant effect has equal importance due to the greater sensitivity for the endogenous norepinephrine (177). Although, the interaction between β-adrenergic stimulation and PDE4 inhibition show prominent opportunity in depression research, involvement of cardiovascular risks hinders clinical investigation. On the other hand, administration of selective serotonin reuptake inhibitor along with rolipram, produced showed significant behavioural improvement in major depressive disorder patients (178), which indicate the PDE association with serotonergic system in brain.

Upregulation of PDE4 was observed the depressive rat cortex region (179–181). Surprisingly, decreased cAMP-PKA-CREB and cAMP-ERK1/2-CREB signalling and loss of dendritic spines are also observed in experimental depressive rodents (180). On a separate report, Fujita et al (2017) provide evidence on the decrease in cAMP levels in living depressive patients (178). Inhibition of PDE4 increases the level of cAMP, pCREB and has been reported to promote hippocampal neurogenesis which is corroborated to antidepressant-like effect (53,182). Clinical trials are underway to unravel the efficacy of PDE4 inhibitors in depression.

6.6. Huntington's disease

Huntington's disease is a neurological disorder caused by an increase in polyglutamine (polyQ) repeated inside the Huntingtin (Htt) protein. This mutant Huntingtin (Htt) protein with extended polyQ upon expression generates inclusion bodies (IBs), causes increased cellular toxicity and results in development of motor disabilities (183,184). Subcellular actions like production of oxidative stress, mitochondrial dysfunction, activation of inflammatory responses and transcriptional dysregulation play a part in the development of HD (185). Dysfunction of cAMP/CREB signalling in HD is a result of overexpression of PDE4 (186). Interestingly, rolipram is shown to increase the phosphorylation of CREB and BDNF and the survival rate, and also improves the clinical signs in rodent model of HD (187). It has also been established that PDE4 inhibitors reduce cortical and striatal neuronal degeneration in transgenic mouse model of HD (188). Since, PDE4 inhibitors improve the cAMP and BDNF, and can regulate the neuronal functions, they have been considered as potential drugs to treat HD. GlaxoSmithKline is performing a clinical trial to determine the efficacy of rolipram in HD which is in Phase 1 (clinicaltrial.gov).

6.7. Stroke

Stroke is a neurodegenerative disease caused by sudden disruption of blood flow to a specific region of the brain or the entire brain. Stroke causes weakness, lack of sensation, paralysis, slurred speech, aphasia, blurred vision (189). Disruption in the blood supply results in a series of metabolic and molecular alterations which leads to neuronal damage (189,190). Approximately 80% of strokes are ischemic while 20% are haemorrhagic in nature (189). An ischemic stroke occurs when blood to brain is blocked, while a haemorrhagic stroke occurs when an artery ruptures in brain (191). Gretarsdottir et al. (2003) reported a decrease in stroke risk with PDE4 inhibition (12). Several studies have elucidated the role of the PDE4 pathway in the pathogenesis of stroke (12,29). Increased expression of PDE4 in stroke plays a devastating role in mediating the neuronal cell death (192). Decrease in cAMP leads to activation of immune responses, oedema and hyperexcitability (12,29). Inhibition of cAMP-PDE4 reduces the infarct size in hippocampal region of rats and gerbil (193,194). Rolipram restores endothelial function in stroke by regulating vascular repair, inflammation and reduces the expression of tissue plasminogen which is connected to increased cAMP concentration via Epac pathway (195). Rolipram increases hippocampal neurogenesis and decreases ischemic injury in neuronal cultures (196). PDE4 inhibition prevents blood brain barrier disruption, thrombosis, and reduces the secretion of proinflammatory cytokines IL-1β, IL-6, and TNF-α, and inhibits neuronal apoptosis in rat model of cerebral stroke (197). Successive reports also conclude that the increased survival index, angiogenesis, and cognitive performance are connected to improvement in cAMP/CREB levels with PDE4 inhibition (196). More research works are being focused towards the reposition of PDE 4 inhibitors for its use in cerebral stroke (Fig. 4).

6.8. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a neurodegenerative disease that causes loss of motor neurons in the brain and spinal cord leading to atrophy of voluntary muscles (198). ALS affects the motor neurons of the cerebral cortex, brain stem and spinal cord. About 90% of ALS cases are considered sporadic amyotrophic lateral sclerosis (sALS) while 10% are familial amyotrophic lateral sclerosis (fALS) (18). Yet the pathophysiology of ALS is not elucidated clearly. Nonetheless, aggregation of intracellular toxins, oxidative stress, neuroinflammation, excitotoxicity and mitochondrial dysfunction are reported to be involved (198,199). TAR DNA binding protein (TDP-43) have been identified to be involved in the progression of ALS. Mutations in TDP-43 have been found in patients with ALS (200). Dysregulation of the kynurenine pathway and production of neuroactive metabolites is involved in the development of ALS (201). Neuroinflammation, oxidative stress and NMDA excitotoxicity caused by the quinolinic acid produced during tryptophan metabolism aggravates the progression of ALS (202). Ibudilast used for COPD is repurposed for ALS (203). Ibudilast markedly enhances the clearance of TDP-43 by promoting autolysosomes via mTORC1 inhibition in motor neurons (204) and also inhibits neuroinflammation and microglial activation by increasing the cAMP levels in neuron and microglia co-cultures (133). Ibudilast is also found to reduce oxidative stress and increase the level of neurotrophic factors such as glia-derived neurotrophic factor, NGF, NT-43 which supports the development and growth of neurons (133). Preclinical studies have shown that Ibudilast protects hippocampal neurons, oligodendrocytes and astrocytes from excitotoxicity and apoptosis. These effects were mediated by upregulation of cGMP/PKG signaling (142,205,206). Clinical trials (NCT02238626) are going on Ibudilast to confirm its efficacy in ALS. In 2016, the European Medicines Agency recommended the use of ibudilast for ALS **(Fig. 5).**

6.9. Glioma

PDEs are implicated in the development of various tumours. The role of cAMP on brain tumours was established in 1977 when cAMP was discovered (207). Particularly, the role of cAMP on the development of glioma is well studied in both *in vitro* and in vivo models (208–211). Warrington et al (2015) found that overexpression of PDE4 increases glioma formation in *Nf1* mice. Overexpression of PDE4 is observed in medulloblastoma, glioblastoma (GBM), oligodendroglioma, ependymoma, and meningioma (212) and the decreased adenylyl cyclase and cAMP levels shown to inhibit apoptosis and enhance tumour growth (213). cAMP regulates various physiological processes via cAMP/PKA or Epac1/Rap1-mediated pathways (214,215). Rolipram is shown to exert cytotoxicity in A172 and U87MG human glioblastoma cell lines via cAMP-dependent PKA and Epac1/Rap1-pathway (216,217). It induces apoptosis in U87MG cells through cAMP-dependent inhibition of AKT phosphorylation (218). Rolipram prevents the development of tumour resistance and produces tumour regression in U87 glioblastoma and Daoy medulloblastoma cells and xenograft model mice (219). It increases the life span in mice bearing glioblastoma when administered along with temozolomide (212). Rolipram increases the antitumor efficacy of bevacizumab in glioblastoma stem-like cells (GCSCs) by inhibiting ERK/AKT signalling and inhibiting MDM2 (mouse double minute 2 homolog) mediated p53 degradation. This in turn activates apoptosis and produces tumour cells death (220). Rolipram suppresses tumor progression, and apoptosis in xenograft brain tumour model by increasing the levels of cAMP/CREB (221) and by inhibiting p27 (Cip1) and p21 (Kip1) cell cycle inhibitors (232, 238). Rolipram is under investigation for its efficacy in patients with GBM.

6.10. Traumatic brain injury

Traumatic brain injury (TBI) imposes profound clinical problems such as disability, cognitive deficits (223). TBI alters glucose metabolism, increases the production of free radicals and mitochondrial dysfunction (224). TBI also increases the expression of PDE4 which results in dysfunction of the cAMP-PKA pathway (29). PDE4B2 levels increase by 10-fold within one hour after TBI. PDE4D2 is also highly expressed after TBI (225). A decrease in cAMP levels is observed in the cortex and hippocampus within 15 minutes after TBI (29,226). A decrease in the levels of cAMP triggers the release of proinflammatory mediators and affects LTP in the hippocampus. This leads to cognitive decline in an experimental model of TBI (223). Rolipram has been found to reduce the expression of inflammatory mediators like TNF-α and IL-1β. These are upregulated in microglial cells in EOC2 microglia cells and in rodent model of TBI (227,228). Rolipram also improves cognitive function in cerebral ischemic rats and is reported to prevent neuronal loss in the cortex and CA1 region of the hippocampus by increasing the expression of cAMP-PKA/CREB signalling cascade in TBI animals (229,230). It also reduces the deposition of the beta-amyloid precursor protein in traumatic axonal injury (230). Since rolipram modulates PDE4 isoforms and can effectively manage TBI symptoms, we suggest that PDE4 is a potential target in the management of TBI.

6.11. Vascular dementia

Vascular dementia (VD) is an age-related neurodegenerative condition, responsible for at least 20% of dementia cases (231). Pathophysiologically, it is characterized by reduced cerebral perfusion and causes mood disorders and attention and cognitive deficits (232). Multiple risk factors including arterial hypotension, cerebrovascular diseases, cerebral haemorrhage and infarcts causes VD (231). Furthermore, excitotoxicity, neuroinflammation, and alterations in the cyclic nucleotides levels are the pathogenetic mechanisms involved in the progression of VD (233,234). Inhibition of PDE4 results in the increase in cAMP level and is reported to play a critical role in regulating cerebral blood flow, synaptic plasticity, and learning and memory (46,235). Increased levels of cAMP are reported to dilate pial vessels and potentially inhibit platelet aggregation, which is correlated to improved brain blood flow in feline cerebral ischemia (236). Rolipram is shown to increase cortical blood flow measured via autoradiography in rats (237). Similarly, administration of roflumilast increases the survival rate, memory and reduces white matter injury in aged rats with chronic cerebral hypoperfusion, which corroborates to the increased cAMP content (238). Betulinic acid, a naturally occurring PDE4 inhibitor is shown to improve the cerebral blood flow measured by using the laser-Doppler flow meter in rats (260). Liang et al. (2020) reported that α-mangostin, a natural PDE4 inhibitor, improves memory functions in beagle dogs that are subjected to unilateral common carotid artery occlusion. Interestingly, treatment with α-mangostin does not cause emesis behaviour, as it selectively inhibits PDE4B (239). Convincingly, PDE4 inhibition improves blood flow to the brain by modulating blood vessels function indirectly in VD.

6. Clinical trials on PDE4 inhibitors for neurological disorders

Clinical trials conducted so far have strengthened the therapeutic potential of PDE4 inhibitors in the treatment of various neurological diseases like AD, PD, MS, HD, stroke, and depression. PDE4 are highly expressed in the brain and modulate a wide range of physiological processes by modulating the intracellular secondary messengers cAMP and cGMP. In general, most of PDE4 inhibitors have better blood-brain barrier penetration property and hence, they have been focused more to reposition in the treatment of brain related diseases (15). Rolipram, a cAMP specific PDE4 inhibitor, has been widely investigated in comparison to its counterparts (168). In 1992, a clinical trial with rolipram showed potent antidepressant activity (240). However, it produced dose dependent side effects like emesis, headache and increased gastric secretion (14). Inhibition of PDE4D in the postrema and nucleus of the solitary tract is emetogenic causative factor of rolipram (241). Another clinical trial was initiated by the National Institute of Health in 2006 to re-evaluate the antidepressant activity of rolipram. It was found that rolipram inhibits both PDE4B and PDE4D (which are prominently expressed in the brain) and has a potent antidepressant activity with less side effects (178). PDE4 inhibitors under clinical trials for some neurological disorders are listed in **Table 2**. The data is collected from ClinicalTrials.gov.

7. PDE4-isoform specific allosteric modulators and their advantages

Inhibition of cAMP specific PDE4 enzymes is a promising therapeutic option for airway diseases treatment (19). Albeit, the first generation PDE4 inhibitors such as roflumilast, rolipram, apremilast, RS25344, PMNPQ, etc. have shown prominent therapeutic effect in preclinical and clinical trials (242–245), the clinical acceptance is limited because of their side effects like nausea and emesis, and gastric hypersecretion (246–248). These non-specific PDE4 inhibitors tightly bind at the high affinity site (HPDE4) of the enzyme and lead to increase in the levels of cAMP, which is responsible for the side effects (249). Cilomilast, a second generation PDE4 inhibitor binds at the low affinity site (LPDE4) but still shows emesis (250). Thus, the first and second generation PDE4 inhibitors are the non-specific inhibitors of all four subtypes (PDE4A, B, C, D) and increase cAMP concentrations beyond the normal physiological need (251).

Studies in knockout mice have shown that PDE4D isoform is responsible for emesis and PDE4D-deficient mice show an amplified sympathetic drive with decrease in sleeping time under xylazine/ketamine–induced anaesthesia, a behavioural symptom that corresponds to emesis. Further, PDE4D could potentially modulates the α_2-adrenoceptor, which causes emesis and other side effects (252) and this warrants the need of development of specific PDE4 isoform inhibitors in alleviating the above reported side effects (253). X-ray crystallography techniques have helped in identifying the binding modes and the design of potent PDE4 isoform inhibitors (34). UCR2 specific allosteric modulators take advantage of an asymmetric PDE4 conformer by blocking only one active site, without affecting the second active site. UCR2-directed PDE4D allosteric modulators partially inhibit the cAMP hydrolysis and reduce emesis (251). D159687, a negative allosteric modulator of PDE4D, enhances learning and memory in TBI rats (254). Furthermore, it was also reported that D159687 does not induce emesis as predicted by the anaesthesia duration test in mice (181). D159797 is a UCR2-directed allosteric modulator of PDE4D and shows better performance in novel object recognition test with a 300 fold less emetic potential as compared to rolipram in female Cynomolgus monkeys (255). Allosteric modulation provides a big ray of hope in the clinical utility of PDE4 inhibitors in neurological disorders by improving synaptic plasticity (254), increasing the spine density and upregulating the expression of neurotrophic factors such as CREB, BDNF and VGF (256). Substantial research is underway to minimize the adverse effects of PGE4Is and to obtain a therapeutic option that has better benefit-to-risk ratio. Approaches towards the development of PDE4 isoform specific inhibitors with high binding affinity at the catalytic site are expected to have reduced emesis, due to the reduced affinity at HPDE4 site 4, whilst maintaining the potential therapeutic properties (257).

8. Conclusion

Dysregulation of cAMP signalling in brain is said to have strong connection with various neurological disorders, of which some have been found to be related to the increased expression of PDE4 enzyme. Inhibition of PDE4 is shown to improve cAMP levels and offer neuroprotective effects in AD, PD, HD, depression, MS, epilepsy, schizophrenia, and other neurological disorders. Many of the non-specific PDE4 inhibitors show neuroprotective effects in preclinical models of neurological disorders, but unfortunately majority of them have failed in clinical trials. The first and second generation PDE4 inhibitors are non-specific between other members of PDE4 families and they produce a surge in cAMP levels beyond the physiological needs and this results in side effect. Allosteric modulation on PDE4 isoform with specific inhibitors, particularly PDE4B and PDE4D inhibitors have shown to possess required therapeutic properties and reduced side effect. None-the-less, there is a need for extensive investigation on long-term toxicities, pharmacokinetics, and data on biodistribution profiles for PDE4I. Also, the role of PDE4 subtype specific inhibitors' in neurological disorders largely and their ability to cross the blood brain barrier needs investigation. Towards this end, the use of PDE4 subtype specific transgenic knockout rodent models will provide clear information on the benefit-to-risk ratio. In conclusion, PDE4 inhibition could be a worthwhile therapeutic option in the treatment of neurological disorders and the development of new subtype specific inhibitors and their efficacy and toxicity at preclinical and clinical levels needs to be investigated.

Conflict of interest

Authors declare no conflict of interest

Acknowledgments

Mr Abid Bhat acknowledges the Indian Council of Medical Research, Govt of India, New Delhi, for financial assistance as Senior Research Fellowship. Prof Guillemin is supported by the NHRMC, ARC and Macquarie University. This manuscript is professionally edited by Red Fern Communication, Australia.

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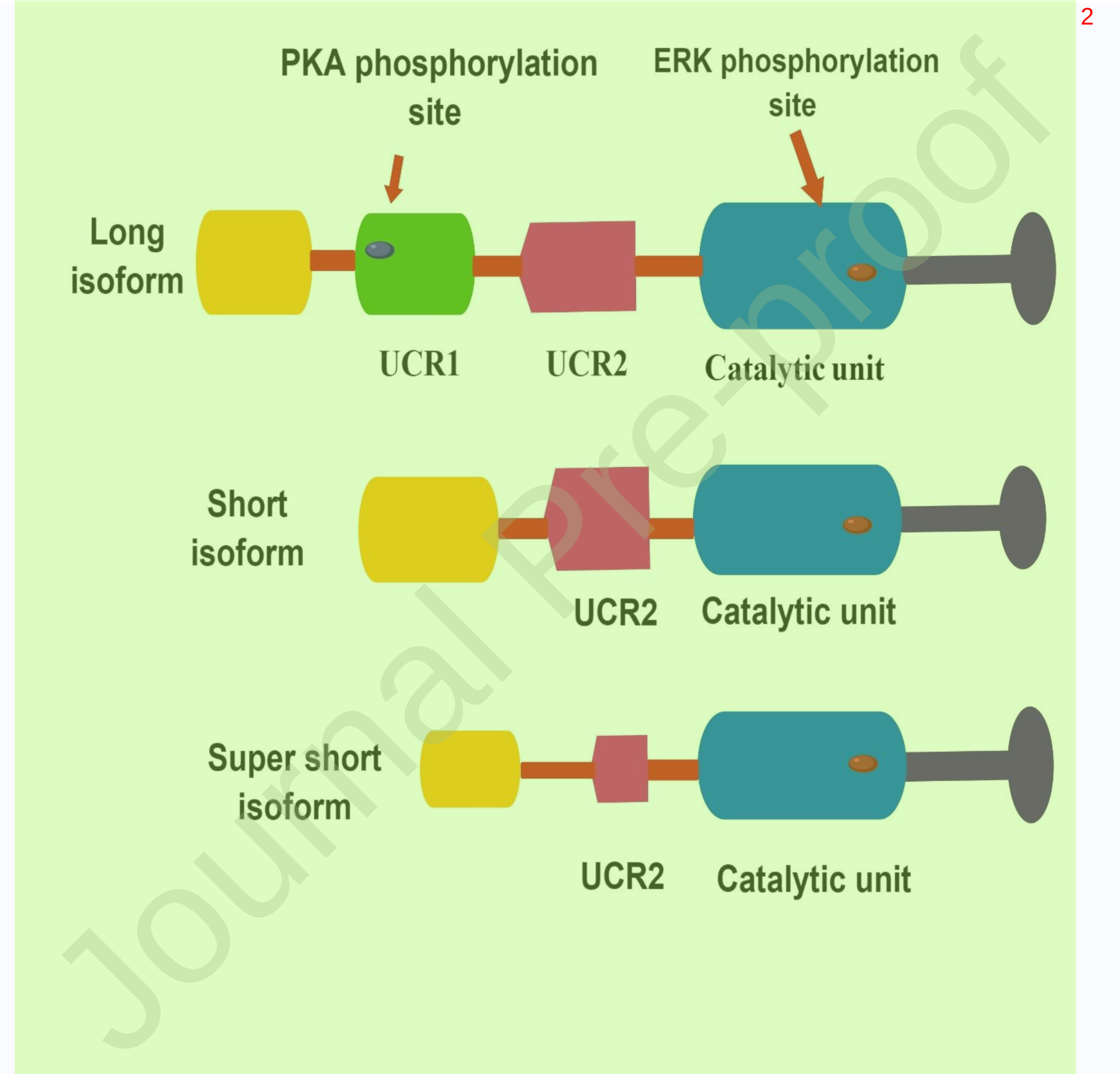


Fig.1: PDE4 isoforms and their post-translational regulation. PDE4 isoforms are classified based on the presence of their upstream conserved regions (UCR) and each isoform is differentially

regulated by PKA and ERK 1/2 phosphorylation (*Reproduced with permission / as copy right guidelines of Journal Proc. Natl. Acad. Sci.;* (Cedervall et al., 2015, p. 4)

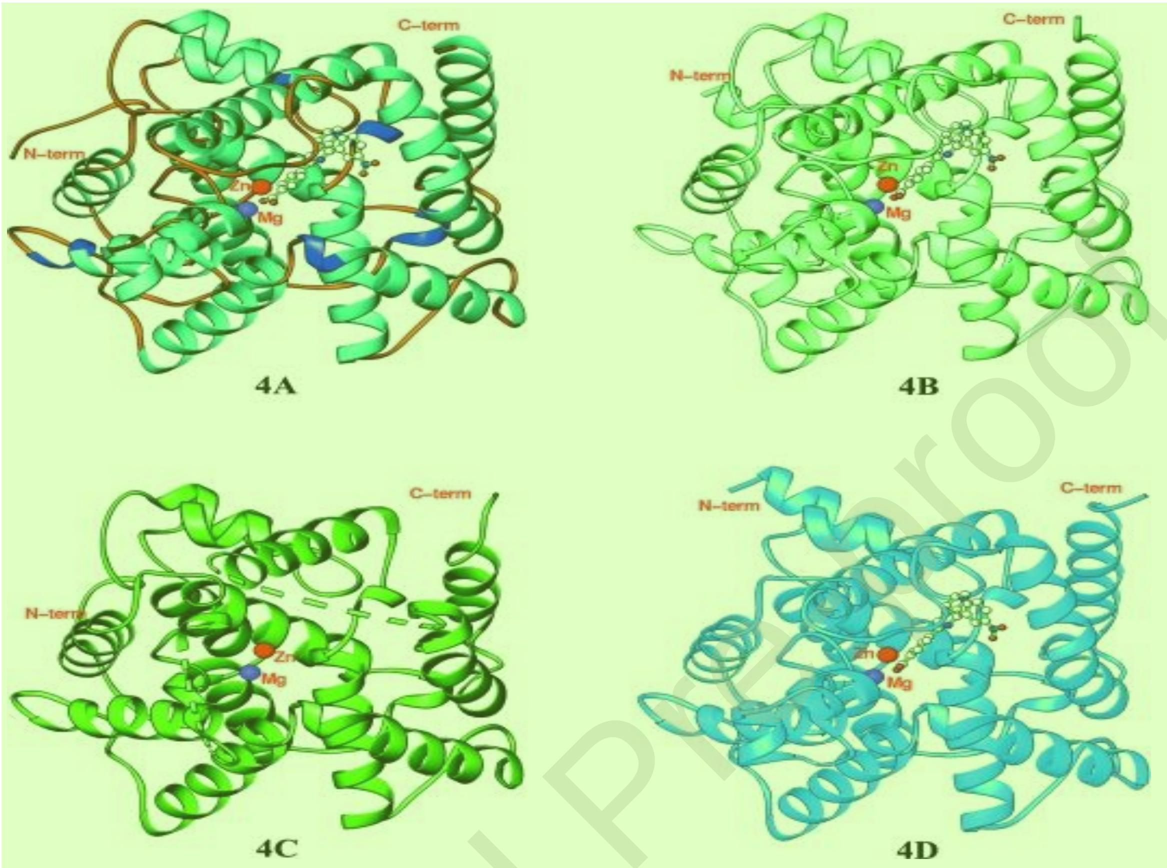


Fig 2: Ribbon diagrams of PDE4 subfamily members 4A, 4B, 4C and 4D: The broken lines in PDE4C represent the disordered residues 333–345 of the H-loop and 465–490 of the M-loop. C-term, C-terminus; N-term, N-terminus. (*Reproduced with permission / as copy right guidelines of Biochem J;* Wang et al., 2007)

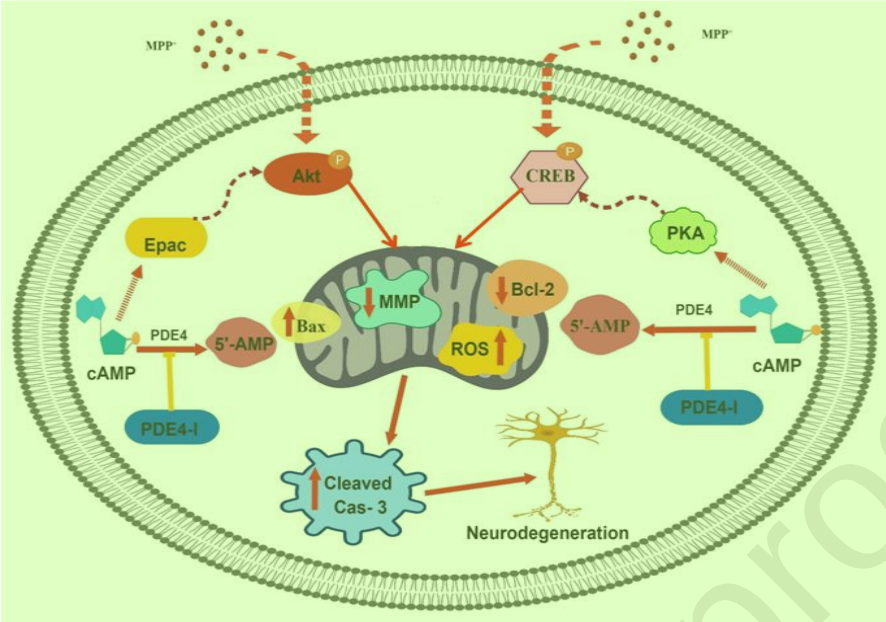


Fig. 3: 1-methyl-4-phenylpyridinium (MPP^+) triggers the accumulation of reactive oxygen species (ROS) and reduces mitochondrial membrane potential (MMP) along with an increase in expression of Bax and decrease in the level of Bcl-2. The levels of cleaved caspase 3 are also increased which leads to neurodegeneration. MPP^+ inhibits cAMP/PKA/CREB and Epac/Akt signalling pathway. PDE4 inhibitors act by increasing the level of cAMP which activates cAMP/PKA/CREB and Epac/Akt signalling pathways and prevents neurodegeneration.

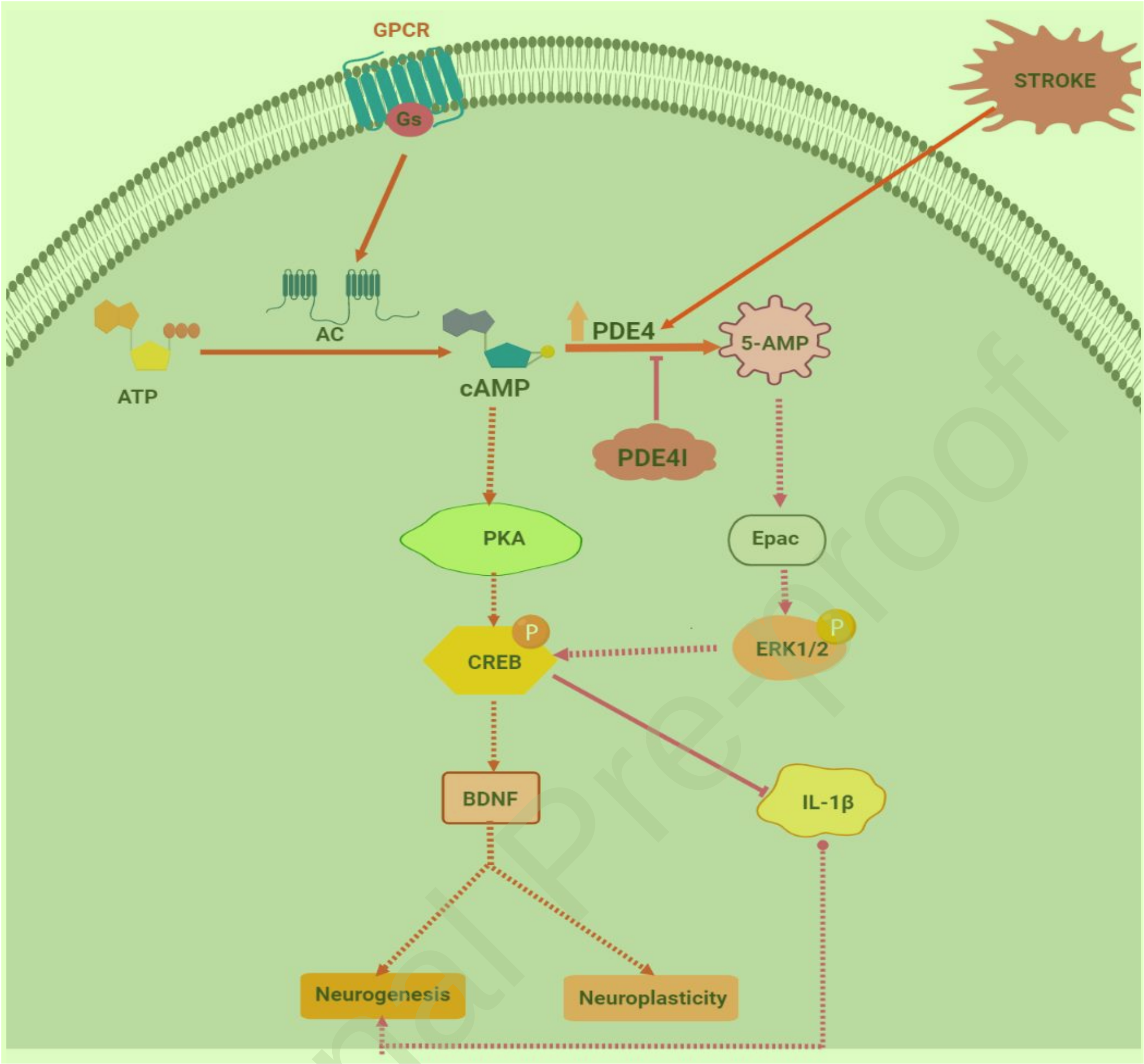


Fig. 4: Activation of GPCR activates Gsα subunit and adenylyl cyclase (AC), which subsequently catalyses the conversion of ATP to cAMP. Increase in the level of local intracellular cAMP leads to activation of protein kinase A (PKA), exchange proteins activated by cAMP (Epac) which in turn activates cAMP-responsive element-binding protein (CREB). Under stroke conditions there is an over expression of PDE4 in brain which decreases the cAMP levels which inhibits PKA/CREB and Epac/ERK1/2 signalling. Activation of cAMP/PKA/CREB is critical for the production of neurotrophic factors like BDNF while as Epac/ERK1/2 activation inhibits proinflammatory factors. PDE4 inhibitors act by increasing the levels of cAMP/BDNF and thus play a crucial role in neurogenesis and neuroplasticity

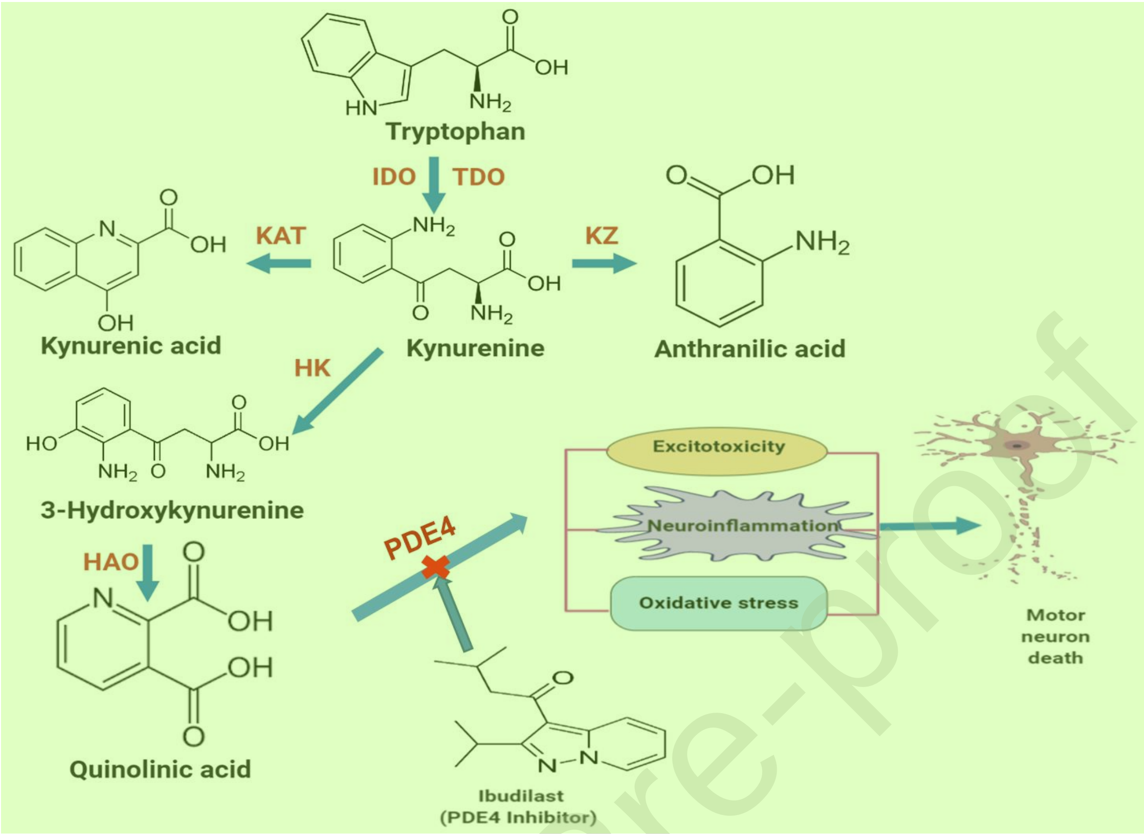


Fig. 5: Schematic representation of kynurenine pathway. TDO—tryptophan 2,3-dioxygenase, IDO—indoleamine 2,3-dioxygenase, KAT— kynurenine aminotransferase, KZ—kynureninase, HK—kynurenine 3-hydroxylase, HAO—3-hydroxyanthranilate-3,4-dioxygenase, PC— picolinic carboxylase, NC—nonenzymic cyclization. Increase in the production of Quinolinic acid by microglia increases the expression of PDE4 which leads to excitotoxicity, neuroinflammation and increase in the production of oxidative stress. PDE4 inhibitors act by blocking PDE4 expression and reducing excitotoxicity, neuroinflammation and oxidative stress, thereby inhibiting the neuronal loss in ALS.

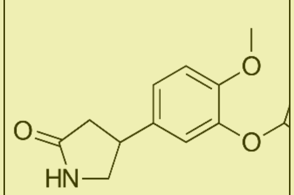
Table 1: Expression of PDE4 isoforms in different tissues

Isoform	Expression	Tissue	Reference

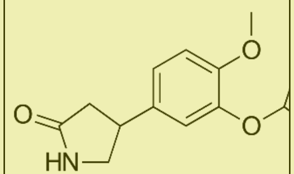
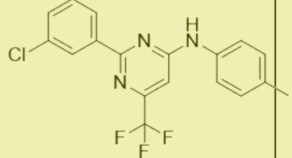
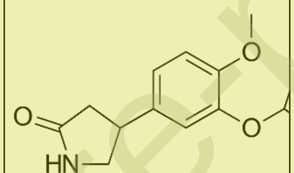
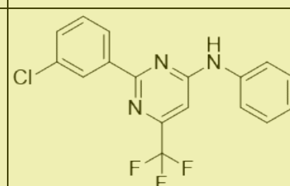
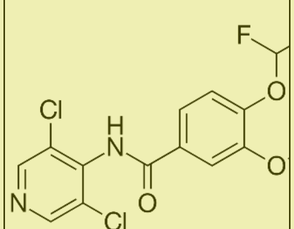
PDE4A	High	Adipose Tissue, Brain, Heart, Testis	(13,258,259)
	Moderate	Breast, Colon, Lung, Lymph Node, Skeletal Muscle, Thyroid	(8,260–263)
	Low / Very low / Absent	Adrenal, Kidney, Liver, Ovary, Prostate	(264–267)
PDE4B	High	Brain, Lungs	(261,268,269)
	Moderate	Adipose Tissue, Adrenal, Lymph Node, Prostate,	(270–273)
	Low / Very low / Absent	Breast, Colon, Heart, Kidney, Liver, Ovary, Skeletal Muscle, Testis, Thyroid	(265,268,272,274–278)
PDE4C	High	Adrenal, Colon, Prostate,	(279–281)
	Moderate	Lung, Testis	(282,283)
	Low / Very low / Absent	Adipose Tissue, Brain, Breast, Heart, Kidney, Liver, Lymph Node, Ovary, Skeletal Muscle, Thyroid	(13,40,41,272,275,284–287)
PDE4D	High	Skeletal Muscle	(4,288)
	Moderate	Ovary, Prostate, Thyroid	(10,289,290)
	Low / Very low / Absent	Adipose Tissue, Adrenal, Brain, Breast, Colon, Heart, Kidney, Liver, Lung, Lymph Node, Testis	(41,285,290–294)

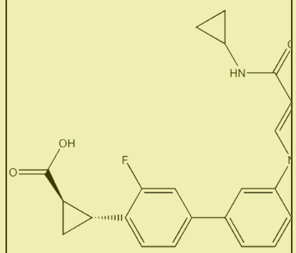
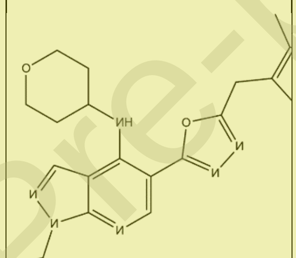
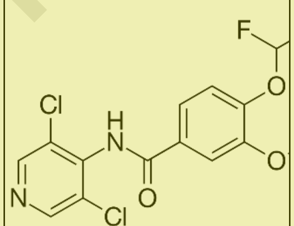
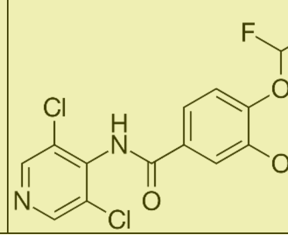
2

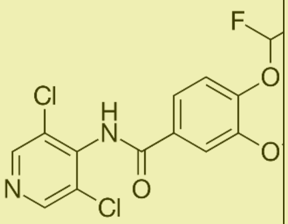
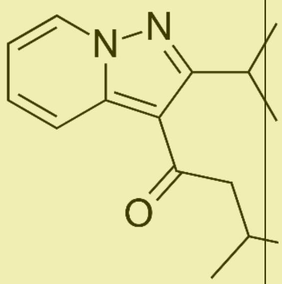
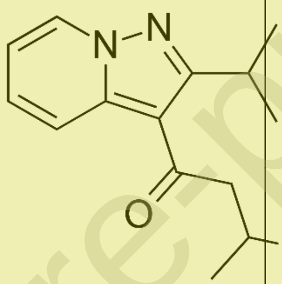
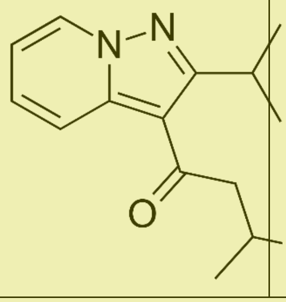
Table 2: Clinical trials on PDE4 inhibitors for different neurological disorders 1

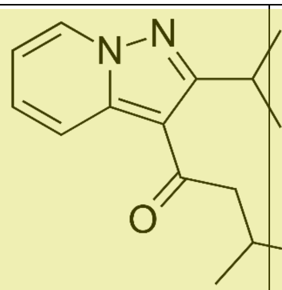
S. No.	NCT Number	Indication	Intervention	Chemical structure	Phase	Locations
1.	NCT00011375	Multiple Sclerosis	• Drug: Rolipram		Phase 2	• National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, Maryland,

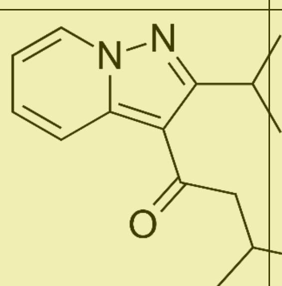
3

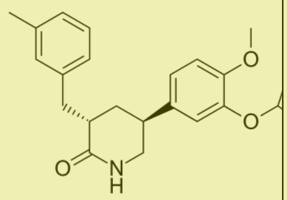
						United States
2.	NCT01602900	Huntington Disease	• Drug: GSK356278 • Drug: Rolipram		Phase 1	• GSK Investigational Site, London, United Kingdom
3.	NCT03030105	Alzheimer Disease	• Drug: BPN14770		Phase 3	• ICON Early Phase Services, LLC, Austin, Texas, United States
4.	NCT00369798	Major Depressive Disorder	• Drug: Rolipram		Phase 1	• National Institutes of Health Clinical Center, 9000 Rockville Pike, Bethesda, Maryland, United States
5.	NCT03861000	Depression	•Drug: [C-11]T-1650 rug: BPN14770		Phase 1	• National Institutes of Health Clinical Center, Bethesda, Maryland, United States
6.	NCT01433666	Dementia	• Drug: Roflumilast		Phase 2	• Maastricht University, Faculty of Psychology and Neuroscience, Maastricht,

						Limburg, Netherlands 1
7.	NCT00362024	Alzheimer's Disease	• Drug: MK0952		Phase 2	• National Institutes of Health Clinical Center, Bethesda, Maryland, United States
8.	NCT02840279	Alzheimer's Disease	• Drug: BPN14770		Phase 1	• Jasper Clinic, Kalamazoo, Michigan, United States
9.	NCT01573819	Huntington Disease	• Drug: GSK356278		Phase 1	• GSK Investigational Site, Zuidlaren, Netherlands
10	NCT02835716	Alzheimer Disease	• Drug: Roflumilast Biological: ustekinumab		Phase 1	• Millennium Magnetic Technologies, LLC, Westport, Connecticut, United States
11	NCT02079844	Schizophrenia	• Drug: Roflumilast		Phase 1	• Denmark Hill, London, United Kingdom

12	NCT02051335	Memory Impairment Alzheimer's Disease	• Drug: Roflumilast		Phase 1	• London, United Kingdom
13	NCT03782415	Glioblastoma Recurrent Glioblastoma	• Drug: MN-166		Phase 2	• Dana Farber Cancer Institute, Boston, Massachusetts, United States
14	NCT02714036	Amyotrophic Lateral Sclerosis	• Drug: ibudilast		Phase 2	• Massachusetts General Hospital, Boston, Massachusetts, United States • South Shore Neurologic Associates, P.C., Patchogue, New York, United States
15	NCT01389193	Migraine Headache	• Drug: Ibudilast		Phase 1	• School of Medical sciences, University of Adelaide, Adelaide, Australia

16	NCT01982942	Multiple Sclerosis, Primary Progressive	• Drug: ibudilast		Phase 2	• University of Alabama at Birmingham, Birmingham, Alabama, United States • University of California Davis, Davis, California, United States • University of California Los Angeles, Los Angeles, California, United States • University of Colorado Denver, Denver, Colorado, United States • University of Miami Miller School of Medicine, Miami, Florida, United States • Emory University,

						Atlanta, Georgia, United States • Northwestern University, Evanston, Illinois, United States • University of Kansas Medical Center, Kansas City, Kansas, United States • Massachusetts General Hospital, Boston, Massachusetts, United States • Brigham and Women's Hospital, Boston, Massachusetts, United States
17	NCT02238626	Amyotrophic Lateral Sclerosis	• Drug: MN-166 • Drug: riluzole		Phase 2	• Carolinas Healthcare System, Dept. of Neurology, Charlotte, North Carolina, United States

18	NCT02013310	Age-Associated Memory Impairment (AAMI)	• Drug: HT-0712		Phase 2	• Sun City, Arizona, United States • Long Beach, California, United States • Santa Monica, California, United States