REVIEW ARTICLE

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cAMP/PKA-CREB-BDNF Signaling Cascade and Phosphodiesterase 4 Inhibition: A Possible Neuroprotective Approach in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common cause of age-related dementia worldwide. It is a neurodegenerative disease characterized by cerebral plaques containing amyloid-β (Aβ) peptide aggregates, intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated tau proteins, and neuroinflammation with subsequent death of neurons and brain tissue damage. There is currently no treatment available for the disease or even to halt its progress. Therefore, targeting the etiologic pathologies to find new agents is a crucial requirement. It is speculated that Aβ-induced downregulation of cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) protein, a biological component essential for learning and memory, causes cognitive impairments in AD. Phosphodiesterase (PDE4) inhibitors have been shown to improve AD manifestations by restoring synaptic function through the activation of the cAMP/PKA-CREB-BDNF signaling cascade. Cilomilast (CILO) is a potent selective inhibitor of PDE4 with anti-inflammatory effect that is currently tested in phase III clinical trials as a possible treatment for chronic obstructive pulmonary disease (COPD). Chlorogenic acid (CGA), is a major polyphenol in Coffea that possesses neuroprotective, anti-inflammatory, and anti-oxidative properties. Augmented PDE4 inhibition may be demonstrated through the co-administration of CGA and CILO, which implies that PDE4 inhibitors may serve as potential neuroprotective molecules.

Keywords: Alzheimer's; phosphodiesterase 4; CREB.

1. Background

Alzheimer's disease (AD) is a neurodegenerative condition that affects elderly people **(Schachter & Davis, 2022)**. It is the most frequent cause of dementia, accounting for 60–70% of cases **(Błaszczyk, 2022)**. It is clinically identified by memory loss, cognitive problems, increased

dependency, and altered behavior in elders. Additionally, various nonclassical characteristics (not based on memory), such as visuospatial difficulties, dyspraxia, and anomia are frequently noted, particularly in younger patients **(Xi et al., 2022)**.

The World Health Organization (WHO) estimates that the number of individuals with dementia worldwide is approximately 55 million, with this number expected to reach approximately 78 million by 2030 and 139 million by 2050. The global financial burden of dementia was estimated to be US$ 1.3 trillion in 2019 and may rise to US$ 2.8 trillion by 2030 **(Shin, 2022)**.

The primary pathologic characteristics of AD include neuroinflammation, extracellular amyloid β-(Aβ) peptide accumulation, intracellular neurofibrillary tangles, tau protein degeneration, and neuronal loss with progressively declining cognitive function **(Falsetti et al., 2022)**. The downregulation of CREB is implicated in the pathogenesis of age-related diseases, including Alzheimer's disease (AD) (Ye et al., 2020). In the context of Alzheimer's disease (AD), the protein kinase A (PKA), which is a primary regulator of the (CREB), experiences disruption in AD patients due to the action of Aβ **(Girotra et al., 2022)**. As the disease progresses, the brain-derived neurotrophic factor (BDNF) is depleted due to various pathological processes, including tau phosphorylation, buildup of amyloid-beta (Aβ), neuroinflammation, and neuronal apoptosis **(Gao et al., 2022)**. Selective inhibitors that target PDE4 may present new therapeutic approaches for AD and age-related cognitive impairment **(Xiang et al., 2024)**. This is because the PDE4 isoenzyme, which is highly expressed in the frontal cortex and the hippocampus, is an essential regulator of intracellular cyclic adenosine monophosphate (cAMP) **(Bhat et al., 2020)**. PDE4 inhibition-induced intracellular cAMP accumulation causes protein kinase (PKA) to phosphorylate CREB, which in turn causes an increase in brain-derived neurotrophic factor (BDNF) (**Feng et al., 2019)**.

Cilomilast (CILO), a selective phosphodiesterase-4 inhibitor among the second generation as roflumilast, has demonstrated significant anti-inflammatory, antidepressant immunomodulatory, and cognitive enhancement effects both in vitro and *in vivo* **(Fan et al., 2024)**. Its mechanism of action is similar to that of roflumilast, but its more selectivity towards PDE4 results in a more potent anti-inflammatory action with fewer adverse effects **(Peng et al., 2014)**. Inhibition of PDE4, which leads to the sequential activation of cAMP/PKA signaling and, ultimately, an increase in the expression of phosphorylated CREB and BDNF, is responsible for roflumilast's neuroprotective action **(Sugin et al., 2020)**. Chlorogenic acid, also known as 3-O-caffeoylquinic acid (CGA), is a prominent polyphenolic compound found in several plants and green coffee beans. It has been shown to possess antioxidant and neuroprotective properties in experimental models of neurological and pathological conditions **(Wang et al., 2018)**. There is mounting evidence that CGA can protect the brain from the risk of AD, as several meta-analyses have shown that long-term coffee drinkers have a significantly lower risk of AD compared to non-coffee drinkers **(Shi et al., 2023)**.

2. Molecular CREB signaling pathway

The CREB signaling pathway is The CREB signaling pathway is a well-researched phosphorylation-dependent transcription factor that provides evolutionary conserved ways for vertebrates and invertebrates to express genes differently. The stimulation of CREB is controlled by a number of cellular protein kinases that work after specific cell surface receptors (**Chowdhury et al., 2023)**. It makes signal-dependent gene expression easier when active CREB pairs up with cis-acting cAMP-responsive elements in target gene promoters. Finding CREB, which is expressed everywhere, led to the finding that it controls the expression of many target genes and is involved in many cellular processes, such as cell growth, adaptation, survival, differentiation, and physiology **(Steven et al., 2020)**.

2.1. The role of CREB in the nervous system

Numerous studies have shown that CREB affects adult hippocampal neurogenesis, which increases the survival of neurons and improves memory formation and a number of cognitive processes, such as recognition memory, synaptic plasticity, fear conditioning, memory consolidation, neurite outgrowth, and neuroprotection **(Belgacem & Borodinsky, 2017)**. This is why CREB-modulated disease is used to describe a variety of brain diseases, such as AD, Huntington’s disease (HD), Rubinstein–Taybi syndrome (RTS), Coffin-Lowry

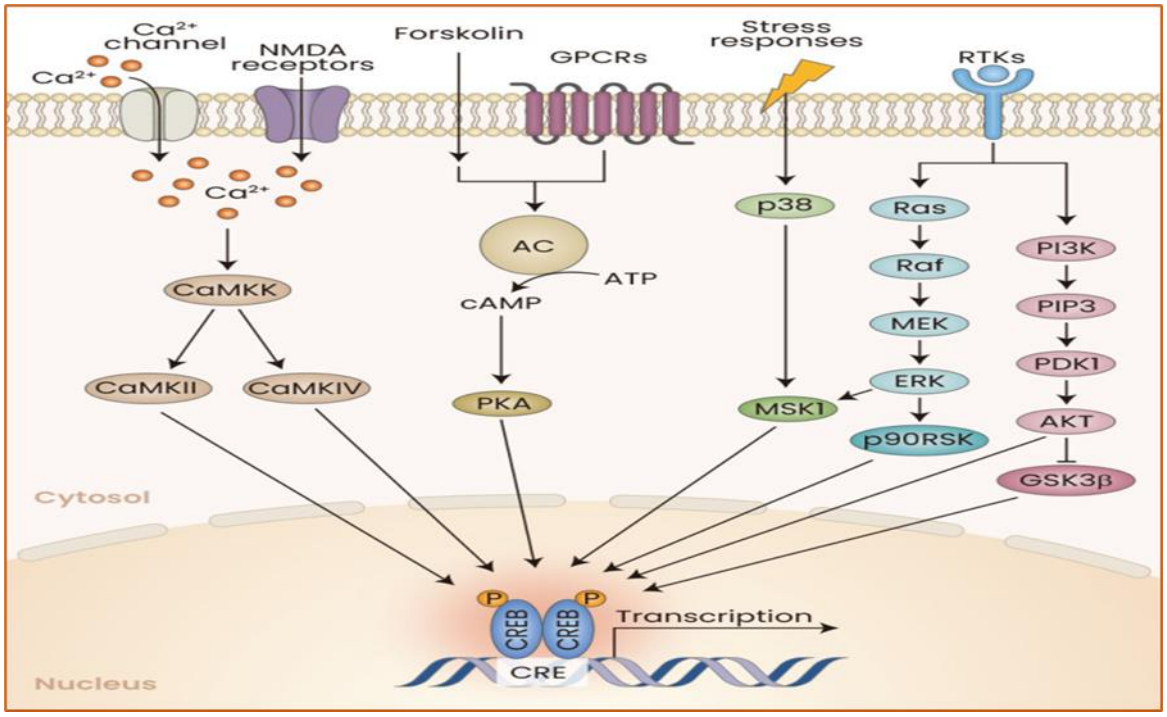

Figure (1): Signaling cascades that trigger CREB activation. When GPCRs bind to ligands, they can turn on adenylyl cyclase (AC), which converts ATP to cAMP and then turns on protein kinase A (PKA). When PKA phosphorylates CREB, it can increase the production of a target gene by connecting to the cAMP response element (CRE). Adenylyl cyclase is also stimulated by forskolin, which makes CREB much more active. Growth factors attach to receptor tyrosine kinases (RTKs), which turn on several protein kinases, such as MSK1, p90RSK, and AKT. Subsequently, CREB is phosphorylated and activated. Alternatively, CREB can be rendered inactive through GSK3β-mediated phosphorylation. Inducers of stress can also activate CREB through p38 and MSK1. In addition, calcium entering through calcium channels and NMDA receptors turns on Ca2+/CaMKs like CaMKII and CaMKIV as well as PKA, which increases the production of CREB-target genes. CREB: cAMP response element-binding protein **(Chowdhury et al., 2023)**.

syndrome (CLS), and Parkinson's disease (PD) **(Chowdhury et al., 2023)**.

2.1.1. CREB and Neuroprotection

Ample research showed that CREB controls neuroprotection by increasing neurotrophins and anti-apoptotic genes and removing reactive oxygen species from neurons. CREB regulates immediate-early genes such as c-Fos, BDNF, insulin-like growth factor 1 (IGF-1), and B cell lymphoma-2 (Bcl-2). All of them have been discovered to exert an influence on the survival of neurons and the growth of the nervous system. BDNF is a well-known gene that is targeted by CREB and plays a significant role in the formation of neural circuits and the survival of already existing neurons **(Ortega-Martínez, 2015)**. According to several studies, decreased BDNF levels may cause neuronal dysfunction in AD, which causes synapse loss and cognitive decline **(Tanila, 2017)**.

2.1.2. CREB and memory formation

CREB, the master memory gene, regulates memory genes essential for neuron growth, synaptic plasticity, and survival. CREB phosphorylation at Ser133 activates cAMP- and Ca^{2+}/calmodulin-dependent kinases, which activate CREB signaling and transcription, which are essential for gene transcription during synaptic plasticity (Tokumitsu & Sakagami, 2022). Multiple kinase pathways, including protein kinase A (PKA), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and protein kinase C (PKC), phosphorylate and activate CREB. In contrast, GSK3β phosphorylation at serine-129 inactivates CREB. Degradation of cAMP-dependent protein kinase (PKA) regulatory subunits by the ubiquitin-proteasome system (UPS) and dissociation of its catalytic subunits regulate its activity (Amidfar et al., 2020). A cAMP-specific phosphodiesterase, PDE4, which is abundantly expressed in the hippocampal CA1 subregion regulates intracellular cAMP levels and induces long-term potentiation

(LTP). Therefore, PDE4 in the hippocampus which likely plays a critical role in cAMP signaling-mediated memory processes and stimulation of the cAMP-PKA-CREB pathway boosts memory and generates permanent LTP **(Guo et al., 2017)**.

2.2. CREB and Alzheimer's disease

Amyloid beta 42 (Aβ42) peptides, generated by the sequential breakdown of the amyloid precursor protein (APP) by β-secretase and γ-secretase enzymes, are prominent insoluble constituents of neuritic plaques observed in individuals with AD **(Volloch & Rits, 2018)**. Aβ toxicity reduces the function of CREB through two mechanisms: i) by deactivation of PKA, with consequent interference with the activity-dependent production of BDNF, and ii) by activating GSK3β **(Rosa & Fahnestock, 2015)**. The lower expression of CREB-target genes and CREB binding proteins (CBP) in the absence of wild-type presenilins indicates a clear pathophysiological link with AD **(Chowdhury et al., 2023)**. Moreover, the detrimental impact of Aβ on the expression of BDNF may lead to the loss of synapses and the degeneration of neurons. BDNF, an important component for brain plasticity and memory, can potentially decrease the amyloidogenic cleavage of the amyloid precursor protein and protect against apoptotic neuronal death by activating its particular trkB receptors **(Amidfar et al., 2020)**.

2.3. Phosphodiesterases and signal transduction

PDEs are a large family of enzymes that have a significant impact on cell signaling by breaking down the second messenger's cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP) in many parts of the body and brain. Phosphodiesterase inhibitors (PDE-Is) decrease the breakdown of cAMP and/or cGMP, resulting in elevated levels of cAMP and/or cGMP. Subsequently, these signals will have a protracted impact on the signaling cascades within neurons **(Tibbo & Baillie, 2020)**. There are more than 100 distinct human PDEs in all, according to estimates. At present, 11 gene-related families of isozymes make up PDEs. PDE1, PDE2, PDE3, PDE10, and PDE11 are examples of dual-substrate PDEs that exhibit an affinity for both cyclic nucleotides. PDE4, PDE7, and PDE8 are enzymes that specifically target cAMP, while PDE5, PDE6, and PDE9 are enzymes that specifically target cGMP **(Heckman et al., 2015)**.

2.4. Phosphodiesterase inhibitor's role in neuroplasticity and neuroprotection

A PDE-I is a drug that inhibits one or more PDE subtypes. Thus, PDE-Is may impact neural communication by affecting presynaptic neurotransmitter release and postsynaptic intracellular pathways after external binding **(Heckman et al., 2016)**. Neuroplasticity is the primary mechanism by which PDE-Is influence cognitive function. The cAMP/PKA/CREB and cGMP/PKG/CREB pathways are linked to long-term potentiation (LTP), a neurophysiological marker of memory. The cAMP/PKA/CREB and cGMP/PKG/CREB pathways also target BDNF, which plays a role in synaptogenesis, neurogenesis, and the proliferation, survival, and differentiation of new neurons in the brain **(Sheng et al., 2022)**.

Cyclic nucleotides can inhibit the release of inflammatory cytokines (e.g. TNF-α, NF-κB) through downstream signaling cascades. Additionally, they stimulate BDNF production and TrkB receptor recruitment (Sharma et al., 2020). This activates MAPK and PI3K/Akt cascades, which promote neuronal growth and survival by activating anti-apoptotic proteins like Bcl-2 and inactivating pro-apoptotic factors. Neuroprotection is an additional mechanism through which PDE-Is can cause pro-cognitive benefits **(Donders et al., 2024)**.

2.5. Specific phosphodiesterase 4 inhibition

The phosphodiesterase type 4 (PDE4) family is one that influences the dynamics of cyclic AMP in glial cells and neurons. In mammals, four genes (A, B, C, and D) code for different subfamilies of PDE4. The upstream exons of all four genes are subject to splicing, which results in several PDE4 isoforms (about 25) through the activation of distinct promoters. Each isoform has its own distinct N-terminal targeting domain, conserved catalytic area, and sub-family-specific C-terminal region. Upstream Conserved Regions (UCR1 and UCR2) work together to modify enzyme function after PDE4 post-translational modification or dimerization, adding complexity **(Paes et al., 2021)**. PDE4A and D are primarily found in the brain stem, hippocampus, olfactory bulb, and cerebral cortex. The white matter of the brain has only one PDE4, PDE4B, which is present in the striatum, amygdala, hypothalamus, thalamus, frontal cortex, and olfactory bulb. In neurons,

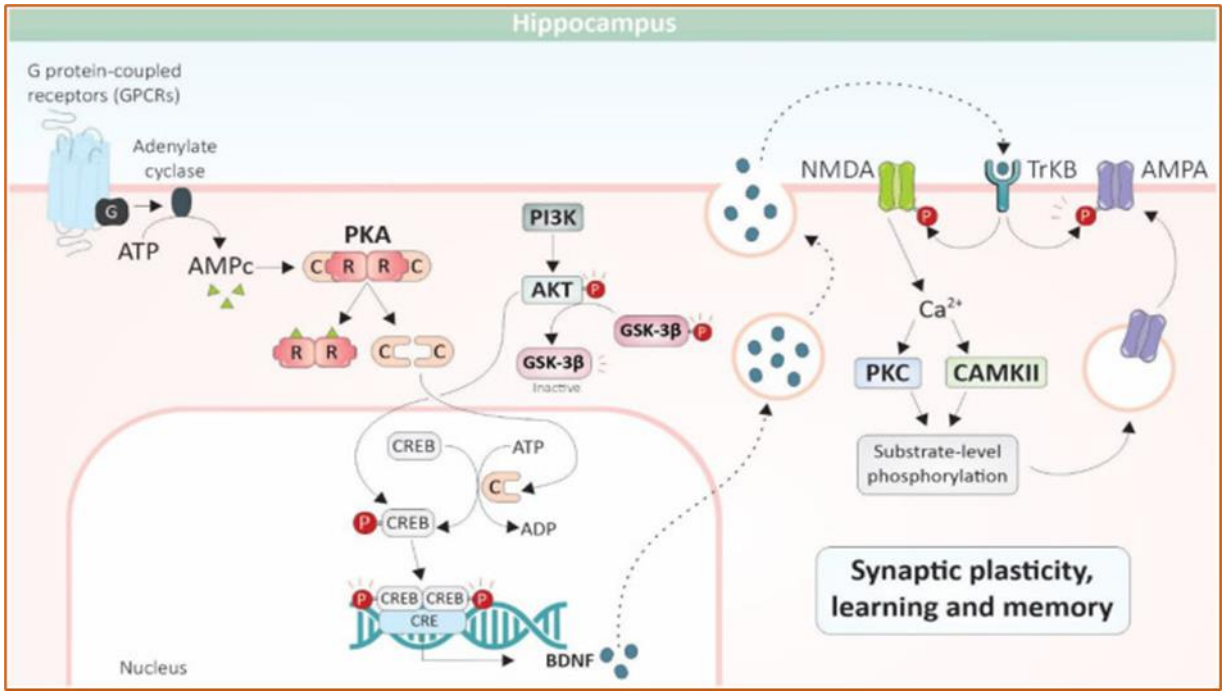

Figure (2): Molecular mechanisms through the PKA/CREB/BDNF and PI3K/Akt/CREB/BDNF pathways, whereby BDNF increases hippocampal neuron proliferation and survival as well as synaptic plasticity. cAMP activates PKA, resulting in the phosphorylation of CREB and its signaling and transcriptional activity. After PI3K activation, Akt phosphorylates and inactivates GSK3. Akt also phosphorylates CREB. CREB stimulates BDNF transcription and translation, which then binds to TrKB and phosphorylates AMPA and NMDA ionotropic glutamate receptors. Memory, learning, and synaptic plasticity depend on PKC and CAMKII receptors **(Amidfar et al., 2020)**.

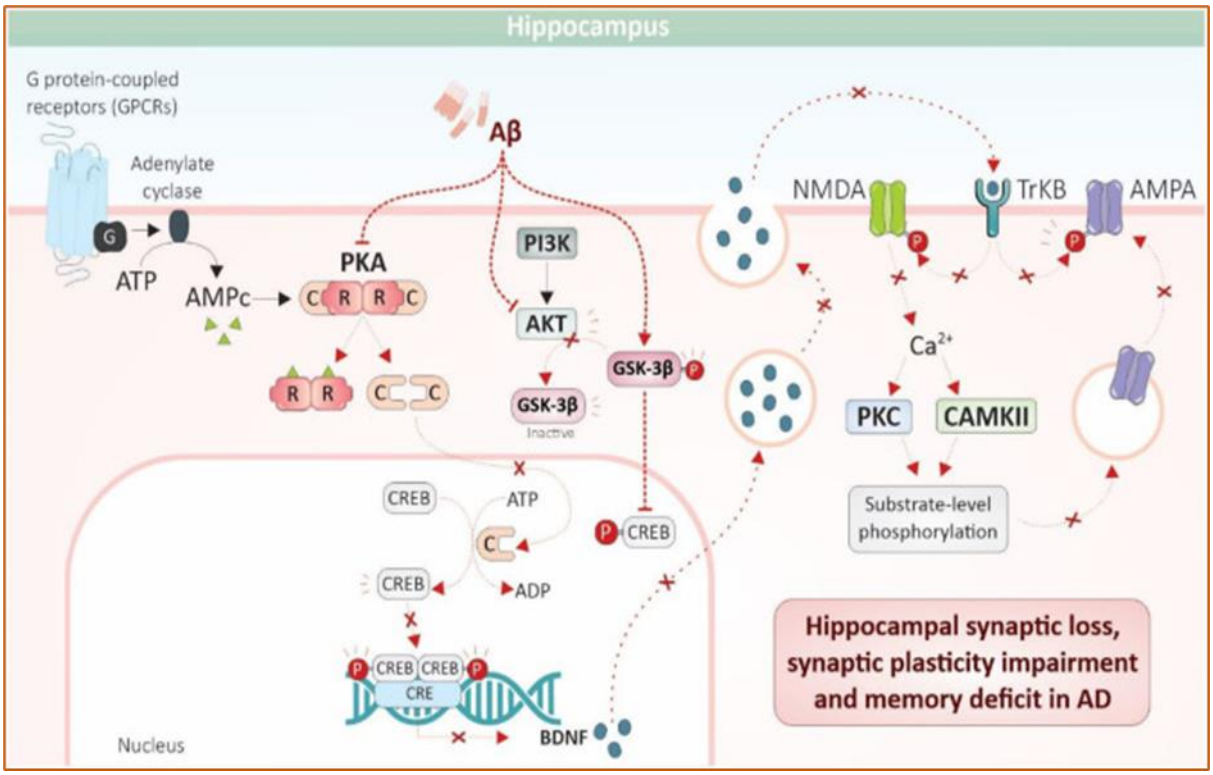

Figure (3): Molecular pathways of Aβ toxicity in the CREB/BDNF cascade. Aβ inhibits PKA, dephosphorylates Akt, and activates GSK3β. These pathways inactivate CREB, causing BDNF pathway deficits, hippocampal synaptic loss, plasticity impairment, and memory loss dis AD **(Amidfar et al., 2020)**.

PDE4A, B, and C are present, while PDE4C is only detected in peripheral tissue. PDE4A and D are crucial for antidepressant effects and memory function, while PDE4B supports stress- and dopamine-related processes like anxiety, schizophrenia, and psychosis **(Schick & Schlegel, 2022)**.

2.6. PDE4 enzymes orchestrate signaling via CREB

The achievement of cognition enhancement in people is rare, but it has been observed in various preclinical trials using the PDE4 inhibitor roflumilast. This provides evidence that PDE4 is a viable target for therapeutic intervention in AD. The potential impacts of these inhibitors are ascribed to the widely acknowledged influence of cAMP on the process of memory creation and cognitive abilities **(Possemis et al., 2024)**. The ways these processes work are based on increases in cAMP inside brain cells that turn on PKA and the cAMP response element binding (CREB) protein. PKA activation of CREB is important for synaptic plasticity and the formation of long-term memory. Because of this, there is a lot of interest in drugs that increase phosphorylated CREB as possible treatments for AD. Stopping PDE4 from working in neurons with drugs has been shown to boost CREB signaling in a way that is consistently protective **(Teich et al., 2015)**.

2.7. PDE-4 Inhibitors classification

Six families of PDE-4 inhibitors exist including xanthine (theophylline), catechol diethers (rolipram), benzamides (roflumilast), quinazoline diketone (nitr-aquazone), benzofurans, and others. There are three generations of PDE4 inhibitors. First-generation (rolipram) has limited clinical application due to severe side effects (emesis). Second-generation inhibitors (cilomilast, roflumilast) have fewer and less severe side effects due to their increased PDE-4 selectivity. Most importantly, these inhibitors preserve effective anti-inflammatory effects. EPPA-1, a new third-generation inhibitor, displays an enhanced therapeutic index **(Peng et al., 2014)**.

3. Cilomilast (CILO)

Cilomilast also is an orally administered, highly effective, specific inhibitor of phosphodiesterase type IV, specifically designed for the management of chronic obstructive pulmonary disease (COPD) **(Chong et al., 2017)**. Cilomilast exhibits significant specificity for cAMP-specific PDE4, which is an isoenzyme that is mostly found in pro-inflammatory and immunological cells. It is 10 times more selective for PDE4D compared to PDE4A, PDE4B, or PDE4C **(Wishart et al., 2018)**.

3.1. The anti-inflammatory properties of cilomilast

Cilomilast effectively inhibits the activity of various pro-inflammatory and immune cells that play a role in the development of COPD. It has demonstrated significant efficacy in animal models. For instance, cilomilast effectively suppresses neutrophil degranulation, which includes the release of neutrophil elastase, matrylisin, and myeloperoxidase **(Jones et al., 2005)**.

Additionally, cilomilast decreased neutrophil adherence to human umbilical vein endothelial cells. Cilomilast also reduces antigen-driven IL-5 production, endothelial cell adhesion, and chemotaxis. Furthermore, cilomilast inhibits TNF-α release in LPS-stimulated murine, human, or healthy person blood in vitro. Cilomilast also reduces LPS-stimulated TNF-α production in COPD patients' blood. It also reduces TNF-α and GM-CSF secretion in COPD patients' bronchial epithelial and sputum cells **(Kroegel & Foerster, 2007)**.

4. Chlorogenic acid (CGA)

Polyphenolic substances have demonstrated the ability to regulate several molecular processes, reduce oxidative stress, and improve neuroinflammation **(Singh et al., 2020)**. Chlorogenic acid (CGA), often referred to as coffee tannic acid and 3-caffeoylquinic acid (3-CQA), is a polyphenolic phenyl acrylate molecule that is soluble in water. It is synthesized by plants using the shikimic acid pathway during aerobic respiration. CGA is abundant in fruits, vegetables, coffee, and tea. The concentration in green coffee is high, with 5-CQA accounting for 50% of the total CGA (based on dry weight) **(Wang et al., 2022)**. At present, mounting research has shown that CGA possesses neuroprotective effects concerning AD **(Gao et al., 2020)**.

4.1. The antioxidant and anti-inflammatory properties of CGA

According to several studies, CGAs are free radical scavengers, anti-inflammatory, and antioxidants,

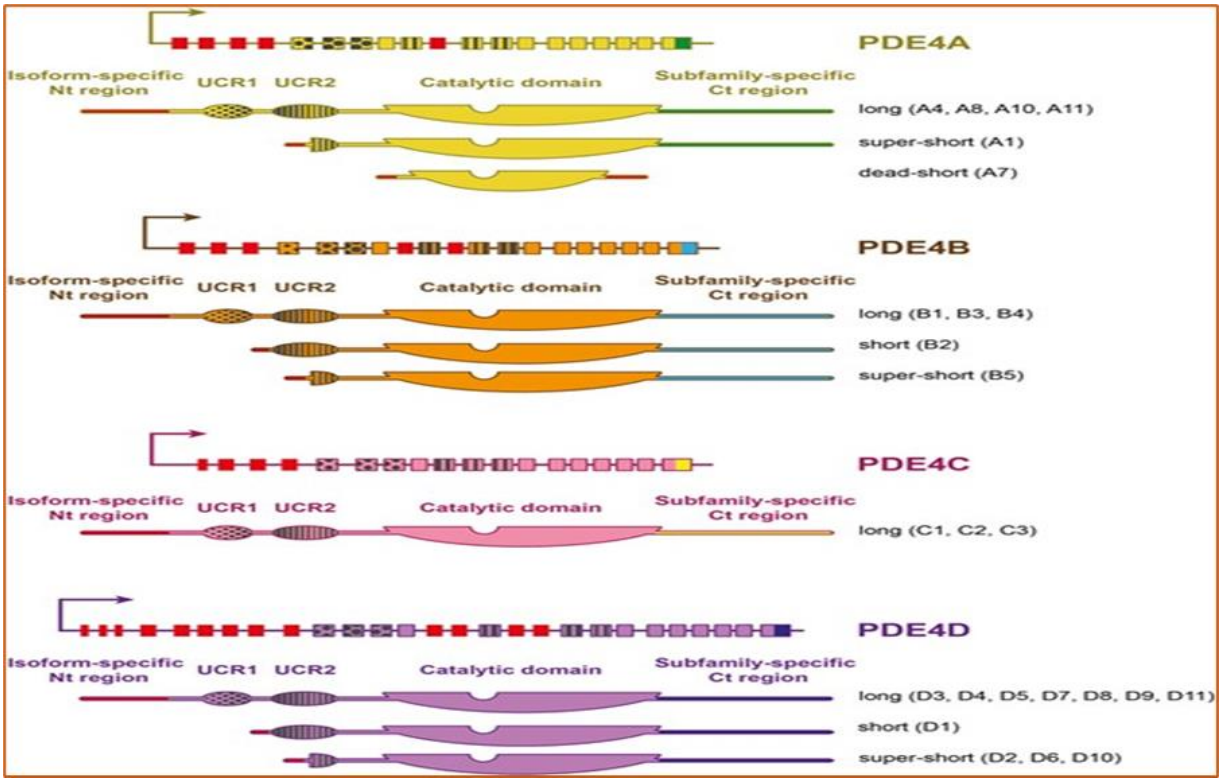

Figure (4): The PDE4 family's four genes. Each gene makes several isoform versions, each with its own N-terminal (Nt) regions that are coded for by a different set of exons (shown in red). Differences between PDE4 isoforms are based on their UCR1 (dots pattern) and UCR2 (line pattern) regulatory regions. Other than the inactive PDE4A7, all proteins in the same PDE4 subfamily have the same C-terminal (Ct) regions **(Tibbo et al., 2019)**.

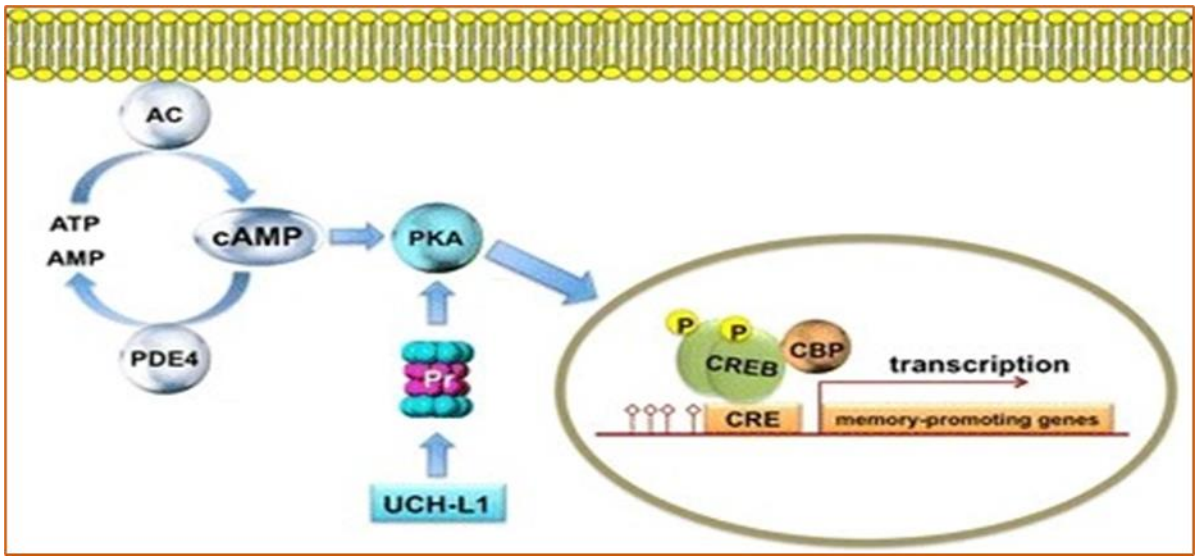

Figure (5): Diagram illustrating the cAMP signaling cascade. ATP is converted to cAMP by adenylyl cyclase (AC). AMP cAMP is degraded by PDE4. CREB is phosphorylated by PKA after cAMP activation. CREB phosphorylation stimulates transcription. DNA (red line) is used for transcription. CREB phosphorylation is promoted by PKA activation and proteasomal (Pr) degradation of the PKA regulatory subunit by Uch-L1. CRE = cAMP response element; CBP = CREB binding protein; p = phospho group **(Teich et al., 2015)**.

which may explain coffee's disease-prevention benefits. The full antioxidant mechanism of CGA can be stated as follows: (1) The polyhydroxyl structure immediately eliminates free radicals; (2) It triggers the antioxidant signaling pathway, controls the production of relevant genes, and boosts the body's antioxidant capability; (3) It directly controls the action of the internal oxidase system and its associated proteins **(Wang et al., 2022)**.

4.2. The anti-inflammatory effects of CGA

Most natural compounds containing CGAs showed anti-inflammatory properties and suggested that CGA may be a notable anti-inflammatory agent **(Naveed et al., 2018)**. CGA regulate the expression of pro- and anti-inflammatory factors by directly affecting the NF-κB signaling pathway. Research suggests that chlorogenic acids can reduce IL-8 production in human intestinal Caco-2 cells when stimulated with TNF-α and H_2O_2. Chemo attractive IL-8 is related to platelet factor 4. IL-8 is produced by phagocytes and mesenchymal cells in response to inflammation, activating neutrophils for chemotaxis **(Murai & Matsuda, 2023)**.

4.3. Protective effect of CGA on the brain

Research has demonstrated that consuming coffee on a daily basis is a significant dietary practice for controlling brain function and promoting neurological health. CGA, a crucial functional compound found in coffee, has been found to have direct or indirect effects on the central nervous system. It can pass the blood-brain barrier and has several neuroprotective benefits **(Kumar et al., 2019)**.

CGA has been shown to ameliorate cognitive decline, reduce Aβ deposition, and prevent neuronal death through the Aβ clearance pathway in a clinical crossover experiment **(Ishida et al., 2020)**. Moreover, CGA and its derivatives inhibit Aβ formation by degrading β-secretase in the proteasomal pathway, improving memory and cognition in mice **(Fukuyama et al., 2018)**. CGA also reduces microglia-induced oxidative damage by inactivating c-Src tyrosine kinase, additionally, it may regulate aberrant microglia function by suppressing the NF-kB/p38 MAPK inflammatory pathway and inflammatory molecules like TNF-α and IL-1β. In BV2 microglia, CGA dose-dependently suppresses NOS and COX-2 expression and NO production **(Kim et al., 2015)**.

5. Conclusion

CREB is a crucial molecular target that plays a fundamental role in learning and memory. Agents with potential therapeutic value for AD have been shown to enhance the cAMP/PKA/CREB pathway.

BDNF and CREB downregulation are proposed as significant downstream consequences of the signaling pathways through which Aβ negatively affects cognition and memory in Alzheimer's disease. Targeting CREB and BDNF signaling could be a therapeutic strategy for memory deficits in Alzheimer's disease due to their significant role in synaptic plasticity and memory formation at a molecular level.

Natural plant extracts have been proposed to enhance learning and memory impairments related to aging in animals by increasing normal levels of phosphorylated CREB and its kinases. To enhance cognitive function, it is crucial to identify the specific PDE4 isoforms and conformational states that should be focused on when developing PDE4 inhibitors. Additionally, understanding PDE4 signaling complexes, targeted drug delivery, and combination therapy could serve as alternative approaches to advance the development of next-generation PDE4 inhibitors for treating CNS disorders linked to cognitive impairments.

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