Phosphodiesterase 7 as a therapeutic target – Where are we now?

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ABSTRACT

Cyclic nucleotide phosphodiesterases (PDEs) are a superfamily of enzymes that hydrolyse the intracellular second messengers cAMP and cGMP to their inactive forms 5'AMP and 5'GMP. Some members of the PDE family display specificity towards a single cyclic nucleotide messenger, and PDE4, PDE7, and PDE8 specifically hydrolyse cAMP. While the role of PDE4 and its use as a therapeutic target have been well studied, less is known about PDE7 and PDE8. This review aims to collate the present knowledge on human PDE7 and outline its potential use as a therapeutic target. Human PDE7 exists as two isoforms PDE7A and PDE7B that display different expression patterns but are predominantly found in the central nervous system, immune cells, and lymphoid tissue. As a result, PDE7 is thought to play a role in T cell activation and proliferation, inflammation, and regulate several physiological processes in the central nervous system, such as neurogenesis, synaptogenesis, and long-term memory formation. Increased expression and activity of PDE7 has been detected in several disease states, including neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington's disease, auto-immune diseases such as multiple sclerosis and COPD, and several types of cancer. Early studies have shown that administration of PDE7 inhibitors may ameliorate the clinical state of these diseases. Targeting PDE7 may therefore provide a novel therapeutic strategy for targeting a broad range of disease and possibly provide a complementary alternative to inhibitors of other cAMP-selective PDEs, such as PDE4, which are severely limited by their side-effects.

1. Introduction

Cyclic nucleotide signalling is a major intracellular signalling pathway that modulates many physiological processes [1]. Cyclic adenosine monophosphate (cAMP) is a cyclic nucleotide 2nd messenger that is generated on demand in response to external stimuli [2]. The conversion of ATP to cAMP is catalysed by adenylate cyclase (AC), and cAMP can be hydrolysed by a superfamily of phosphodiesterase (PDE) enzymes back to the inactive 5'-AMP. Out of the 11 family members of the PDE superfamily, five degrade both cAMP as well as cyclic guanosine monophosphate (cGMP), while PDE4, PDE7 and PDE8 hydrolyse cAMP specifically [3]. As abnormally low levels of cAMP have been associated with various disease states, much research has gone into the development of inhibitors of PDE4, as it is the best characterised of the cAMP-specific PDEs. However, PDE4 inhibitors are clinically limited by their broad range of adverse effects, which is why other cAMP degrading enzymes are becoming increasingly interesting drug targets [4,5]. This review will focus on the lesser studied cAMP-selective PDE7 family and discuss how its structure, expression, and physiological roles make it an

attractive therapeutic target. The current state of PDE7 drug development will also be discussed.

2. PDE7 discovery, structure and expression profile

PDE7 was first isolated from a human glioblastoma cDNA library in 1993, and shown to be a new cAMP-specific phosphodiesterase insensitive to rolipram, a potent inhibitor of the previously identified PDE4 [6,7]. Later, a second isoform, PDE7B, was isolated from human caudate nucleus [2]. Both PDE7A and PDE7B have high affinity for cAMP (K_M values between 0.1 and 0.2 μM) and do not bind cGMP [2,7]. PDE7A and PDE7B are encoded by two separate genes located on chromosomes 8 g13-q22 and 6q23-q24, respectively [8,9]. The PDE7A gene product exists as three different splice variants generating PDE7A1, PDE7A2, PDE7A3 in humans. PDE7A1 and PDE7A2 display 97% sequence identity and vary in their N-terminal regions, while PDE7A3 is a C-terminal variant of PDE7A1 but is a shorter protein that still displays 99% sequence identity with PDE7A1 (Uniprot). Less is known about potential variants of PDE7B. Three splice variants of PDE7B have been found in
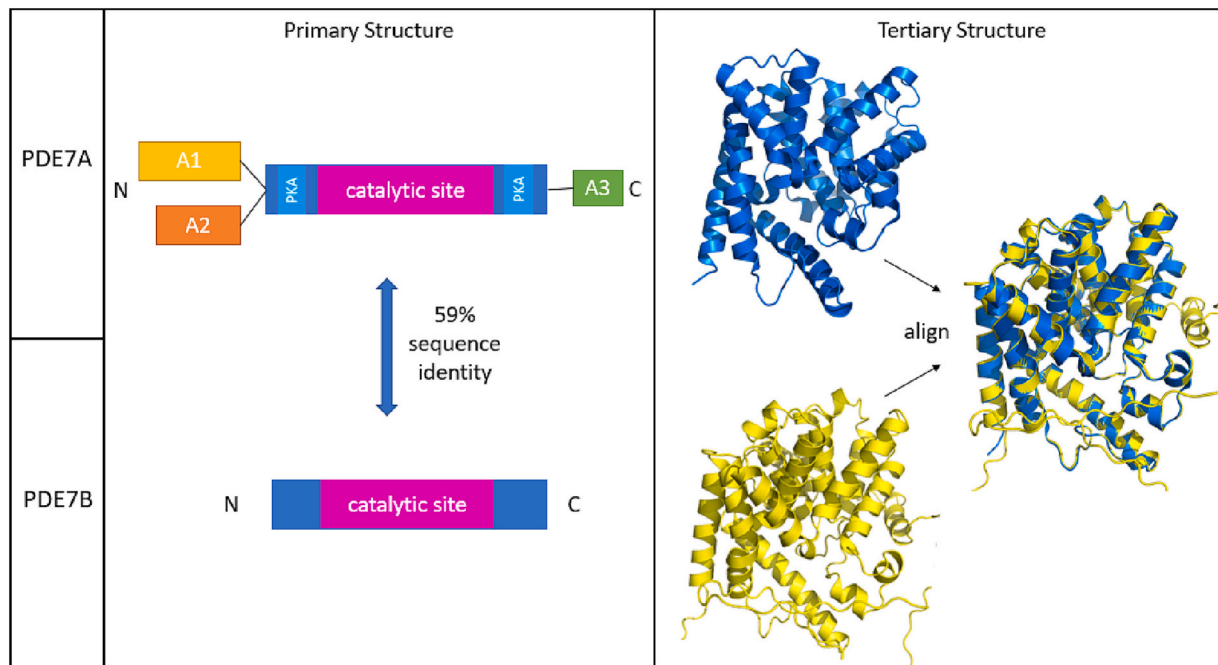
Fig. 1. Primary and tertiary structure comparison of human PDE7A and PDE7B
Primary structure (left) and tertiary structure (right) comparison of human PDE7A and PDE7B in humans. PDE7A (Uniprot ID: Q13946) and PDE7B (Uniprot ID: Q9NP56) display 59% overall sequence identity, with 70% identity in the catalytic site (Clustal Omega). Three splice variants of PDE7A have been identified in humans. Structural alignment of PDE7A (4 PM0) and PDE7B (alphafold predicted structure) in *PyMol* reveals high structural similarity between the two proteins allowing for similar functionality. **Abbreviations:** N-terminus (N), C-terminus (C).

rodents but have not yet been reported in humans [8,10].

Alignment of the primary sequences of PDE7A (Uniprot ID: Q13946) and PDE7B (Uniprot ID: Q9NP56) shows that there is only 59% amino acid sequence identity between these two PDE7 sub-families (Clustal Omega). However, the catalytic site is highly conserved between these two proteins with 70% amino acid sequence identity in the catalytic site [11], and structural alignment of PDE7A (PDB: 4PM0) and PDE7B (alphafold2 predicted structure) reveals very similar tertiary structures (Fig. 1). This allows for enzymatic activity to be carried out in a biochemically similar manner but sequence differences between PDE7A and PDE7B opens the possibility of targeting these two isoforms specifically with a small molecule drug.

The two PDE7 sub-families display varied tissue expression in humans. PDE7A is expressed in the brain (cerebellum, hippocampus, striatum), as well as inflammatory and immune tissues and cells (spleen, lymph nodes, T-lymphocytes, monocytes, neutrophils) (Fig. 2) [12,13]. It is also found in alveolar tissue, the smooth muscle of the pulmonary vasculature, and cardiomyocytes [12]. Of the various PDE7A isoforms, it is thought that PDE7A1 is expressed in the lymphoid tissues and leukocytes, while PDE7A2 is contained to the heart, skeletal muscle, and kidney. The PDE7A3 isoform is mainly found in the heart, skeletal muscle, spleen, testis and is present in T-lymphocytes following their activation [8,14,15]. In humans, PDE7B is highly expressed in the brain (substantia nigra, caudate nucleus, nucleus accumbens, striatum, hippocampus, putamen, oligodendrocyte precursor cells), peripheral blood mononuclear cells, liver, heart, kidney, small intestine and skeletal muscle (Fig. 2) [2,9,11,16–19].

3. Physiological roles of PDE7

PDE7 regulates intracellular cAMP levels, a second messenger involved in controlling many cellular functions including regulation of the inflammatory response, cellular growth and proliferation, gene transcription, memory formation and cognition [9,20–22]. Upon activation of adenylate cyclase (AC), ATP is converted to cAMP which has

five downstream targets through which its physiological role is mediated: protein kinase A (PKA) [23], exchange protein directly activated by cAMP (EPAC) [24], Popeye domain-containing proteins (POPDC) [25], hyperpolarisation-activated cyclic nucleotide-gated channels (HCN) [26], and cyclic nucleotide receptor involved in sperm function (CRIS) [27]. cAMP signalling is a balance between production by AC and local degradation by phosphodiesterases, such as PDE7.

The extent of cAMP regulation by PDE7 at a physiological level remains incompletely understood. A few papers have shown that PDE7 may be required for T cell activation and proliferation [15,28,29,76]. Administration of PDE7 inhibitors was shown to supress natural killer cell and T-cell proliferation by increasing intracellular cAMP levels and PKA signalling [28,29]. However, PDE7A-deficient mice were shown to still have functional T cells and produce pro-inflammatory cytokines, suggesting that PDE7A may contribute to, but is not essential for T cell function [30]. It has been shown that some human PDE7 isoforms are not present in unstimulated T cells, but expression is induced following T cell activation, in an attempt to reduce cAMP concentrations and promote T cell proliferation and cytokine production. For example, PDE7A3 expression was absent in unstimulated CD4+ T-cells, yet its expression increased following T cell activation and peaked around 24-48 h post-stimulation [15].

PDE7 has also been detected in several brain regions (Fig. 2) and shown to alter cAMP signalling to modulate neurogenesis, synaptogenesis and long-term memory formation [9,13]. PDE7 activity may also be required for correct functioning of cells in the central nervous system, such as astrocytes, microglia, and oligodendrocyte precursor cells, as well as T lymphocytes, and highlights the role of PDE7 involved in regulating neuroinflammation [16,21,31,32]. The PDE7A isoform has also been detected in the habenula, a brain structure found in the hypothalamus that plays a role in decision-making processes and motivational behaviour. A recent study has revealed a potential link between PDE7A polymorphisms and risk of depression, however, this hypothesis requires further investigation [33]. PDE7 has also been suggested to play a role in memory, with inhibition of PDE7A1 leading to enhanced
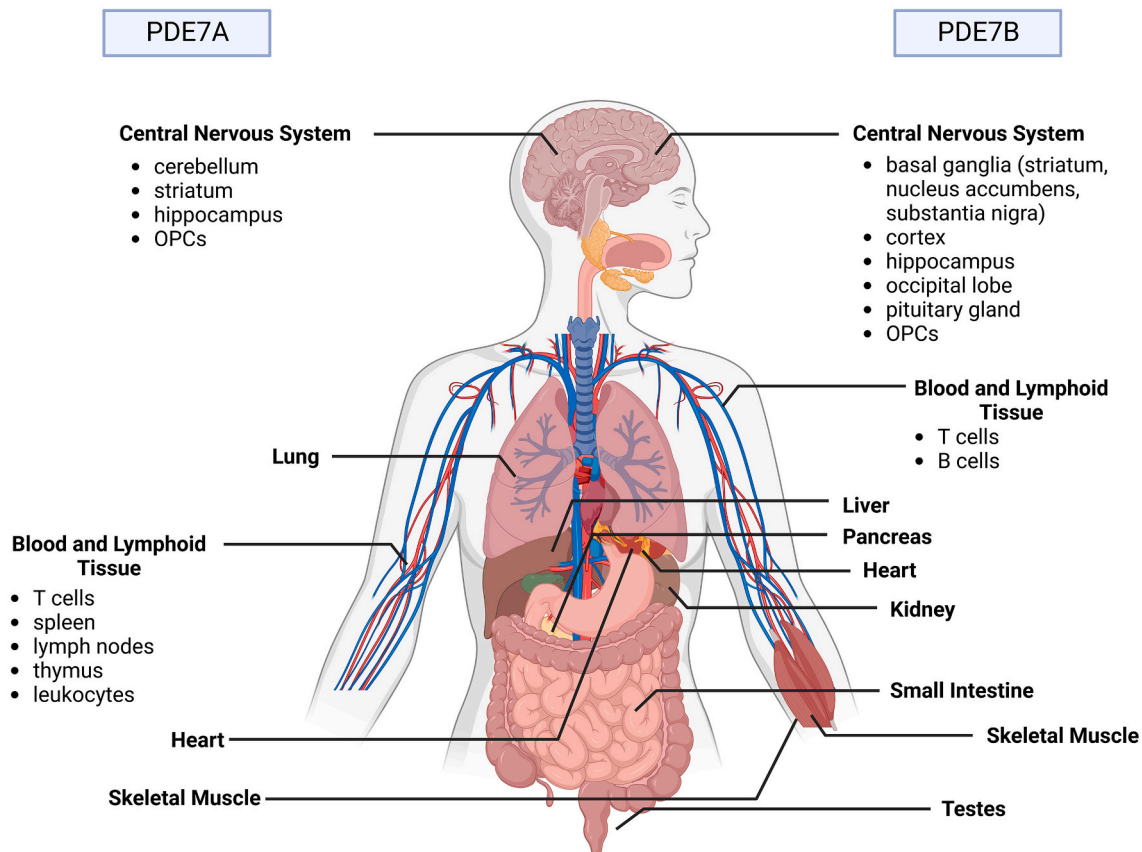
Fig. 2. Expression pattern of PDE7A and PDE7B in humans.
Expression pattern of PDE7A (left) and PDE7B (right) in humans. PDE7A is mainly expressed in the CNS, leukocytes, and the lymphatic system, but has also been found in the lung, heart, and skeletal muscle tissue. PDE7B is also widely expressed in the CNS, as well as T cells and B cells. Lower levels of PDE7B expression have been observed in the liver, pancreas, heart, kidney, small intestine, skeletal muscle, and testes. Image created with Biorender.com.

learning and memory in rodents [34]. Conversely, a recent study has shown that genetic knock-out of PDE7A causes disrupted long-term spatial memory and learning yet resulted in moderately enhanced cued fear memory. Contrary to expectations, PDE7A knock-out resulted in a reduction of intracellular cAMP levels rather than an increase [35]. The authors argue that other PDEs may compensate for PDE7A loss and increase cAMP hydrolyse, however, other experimental methods will have to confirm the observed reduction in cAMP [35]. The same study suggested that PDE7A may play a role in spatial memory formation and learning, however, the full extent to which PDE7A is involved and the underlying biochemical mechanisms remain to be fully elucidated. While not all physiological roles of the various PDE7 isoforms have been completely characterised, PDE7 is becoming an increasingly interesting therapeutic target for a myriad of different diseases which will be discussed in the following sections of this review.

4. Targeting PDE7 in disease

4.1. Neurodegenerative diseases

Inhibition of PDE7A and PDE7B signalling is thought to have potential therapeutic applications in neuroinflammation and CNS disorders, such as Parkinson's disease, Alzheimer's disease, or Huntington's disease [9,36–39]. PDE7 mRNA has been found in the cerebellum, olfactory bulb, the striatum and the hippocampus, which are all brain areas involved in cognition, learning, neurogenesis, memory and motor control, and are often affected in neurodegenerative disease (ND) [13,40]. The cAMP/PKA/CREB pathway is thought to play an important role in neurogenesis and neuroinflammation, suggesting that inhibition

of PDE7 to increase cAMP levels presents a promising treatment approach for acute brain injury and NDs. This is supported by *in vitro* and *in vivo* data showing that treatment with PDE7 inhibitors improves neurogenesis and enhances performance in memory tests [13,38,75]. In addition, application of PDE7 inhibitors has shown to have neuroprotective effects by reducing neuroinflammation in experimental models of stroke, multiple sclerosis, and Parkinson's disease [16,21,32]. Chronic neuroinflammatory processes are thought to underlie most NDs which is why PDE7 inhibitors have become attractive drug candidates for these diseases [41].

Parkinson's disease (PD) is characterised by the progressive loss of dopaminergic neurons, particularly in the substantia nigra region of the brain. Currently, PD is treated with the dopamine-replacement therapy L-DOPA, however, this treatment causes severe side-effects with chronic use [9]. Chronic neuroinflammation in PD is thought to be a massive contributing factor and cAMP signalling is known to protect against this [32]. PDE7 has been shown to be highly expressed in the striatum and substantia nigra, and inducing damage in this area using 6-hydroxydopamine (6-OHDA) or lipopolysaccharide (LPS) has been shown to increase PDE7 expression in the SH-SY5Y cell line, a cell model for dopaminergic neurons, microglia, and astrocytes [42]. Genetically silencing PDE7 has neuroprotective and anti-inflammatory effects in the SH-SY5Y cell line, suggesting that inhibition of PDE7 may be beneficial for treating neuroinflammation [9]. Proof of concept has been demonstrated on several occasions showing that administration of PDE7 inhibitors protects dopaminergic neurons following 6-OHDA or LPS-induced neuronal injury in cell and animal models of Parkinson's disease by activating the cAMP/PKA/CREB pathway [32,41]. Interestingly, some inhibitors of PDE7 appear to indirectly inhibit another key

regulator of neuroinflammation and target for the treatment of neuro-degenerative diseases; Glycogen Synthase Kinase 3β (GSK3β) [41]. Inhibition of this ubiquitously expressed serine-threonine kinase has been extensively studied for the treatment of PD and other neurodegenerative diseases to reduce inflammation, and some are already in clinical trials for the treatment of Alzheimer's disease [41,43]. Studies have shown that inhibition of PDE7, leading to an increase in cAMP levels and subsequent activation of PKA, can result in phosphorylation and inhibition of GSK3β to further reduce pro-inflammatory signalling [41]. This dual inhibitory effect makes development of PDE7 inhibitors a highly promising approach for PD and other NDs, and the first small molecules are thought to be ready to enter clinical trials [44].

Studies have also investigated the role of PDE7 in Alzheimer's disease (AD), a neurodegenerative disease characterised by progressive memory loss and the accumulation of β-Amyloid plaques and Tau protein in the brain. Inhibiting PDE7 in cellular and mouse models of AD has been shown to elevate intracellular cAMP levels and increase levels of phosphorylated CREB [37,38]. In addition, a PDE7 inhibitor used in rodent models of AD also significantly decreased β-Amyloid plaque formation in the cerebral frontal cortex and hippocampus, and reduced β-Amyloid-induced apoptotic signalling [38]. Dual inhibition of PDE7 and GSK3β either by using drug combinations or *via* indirect inhibition of GSK3β by PDE7 inhibitors has also been suggested as a potential treatment strategy for AD. The PDE7 inhibitor VP1.15 has been shown to enhance cognition in mouse models of schizophrenia which could also be beneficial in patients with AD [45].

Other neurological disorders, such as Huntington's disease (HD) have also been linked to dysregulated cAMP signalling [19,20,46,47]. HD is characterised by involuntary muscle contraction (chorea), cognitive decline and mental disorders as a result of damage to neurons in the striatum (basal ganglia) [19]. Studies in mouse models of HD have demonstrated that striatal cAMP levels progressively decrease over time and significantly reduced cAMP concentrations have also been observed in the cerebrospinal fluid of HD patients compared to healthy controls [46,47]. A paucity of cAMP resulting in reduced PKA activity and subsequent CREB phosphorylation have been shown to cause a decrease in BNDF expression which is required for maintaining neuronal health in the striatum [47]. Increasing cAMP levels *via* pharmacological inhibition of PDE4, PDE10A, and activation of AC using forskolin has been shown to improve the HD phenotype in experimental models [46,47]. Therefore, increasing human cAMP levels by inhibiting PDE7 may present a novel approach for the treatment of HD in the future.

4.2. Inflammatory disease

Diseases characterised by chronic inflammation are often associated with increased levels of PDE activity and a subsequent reduction in cAMP levels. For example, in spinal cord injury, a full recovery of the neuronal damage can often be prevented by the formation of a glial scar and sustained inflammation causing additional neuronal damage [48]. PDE7 inhibitor treatment of spinal cord injuries in mice was shown to reduce pro-inflammatory cytokine production (IL-1β and TNFα) in the spinal cord and ameliorate functional deficits. PDE7 inhibitors may also be useful for treating demyelinating diseases such as multiple sclerosis (MS). MS is an autoimmune disease leading to progressive loss of myelin and breakdown of the blood-brain barrier, which results in subsequent infiltration of immune cells into the CNS causing microglial activation, chronic inflammation, further demyelination and axonal damage [31,49]. In cultured microglial cells, PDE7 inhibitors were shown to increase intracellular cAMP levels and inhibit neuronal cell death at micromolar concentrations. Using a mouse model of the disease, administration of PDE7 inhibitors improved motor function, reduced spinal cord demyelination and reduced overall disease pathology in the treated mice compared to the control [4,31,49–51]. The reduced immune cell infiltration and improved motor function observed following inhibition with PDE7 inhibitor VP3.15 is thought to result from co-inhibition of GSK3β *via* the same mechanism described previously [51]. Reduction in disease pathology was also observed in MS mice treated with inhibitors of PDE4, however as previously stated, the clinical use of PDE4 inhibitors is severely limited by their numerous side-effects [4]. Therefore, targeting PDE7could be a novel route to enhance cAMP levels while minimising adverse drug reactions due to more localised expression pattern of PDE7.

Germane to this review, PDE7 is also implicated in other chronic inflammatory diseases such as chronic obstructive pulmonary disease (COPD) and asthma [12]. PDE4 inhibitors used to treat this disease such as rolipram or cilomilast again have limited utility because of their side-effects, so targeting PDE7 to reduce airway inflammation may be a useful avenue [52]. PDE7 inhibitors have also been tested in models of stroke, where they have shown to reduce the inflammatory response and reduce nitrite production in astrocyte cultures, and reduce infarct volume and neurological deficits in a mouse model [21].
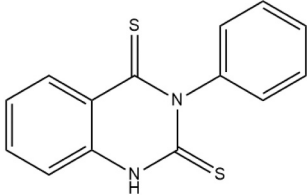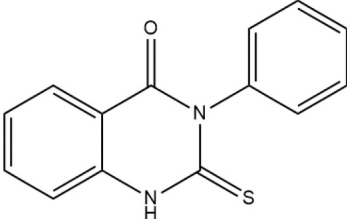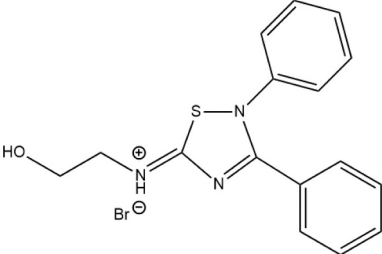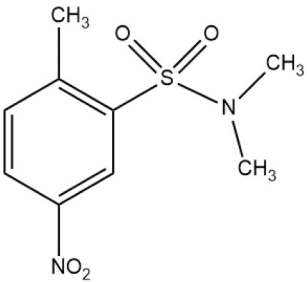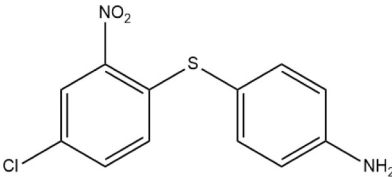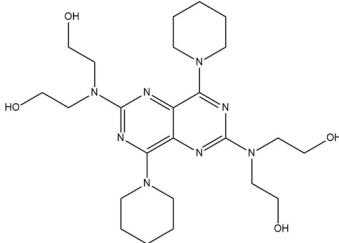
4.3. Cancer

A reduction in cAMP levels and subsequent loss of PKA and CREB activation is a feature of some malignant diseases, suggesting that PDEs may play an important role in the progression of cancer [53]. In addition to other PDEs, dysregulated PDE7 activity has been reported in several types of cancer. Patients with mantle cell lymphoma (MCL) exhibited increased PDE7B mRNA compared to healthy controls, and higher PDE7B mRNA expression correlated with reduced overall survival time [54]. In addition, PDE7 expression has been detected in multiple subtypes of leukaemia and has been associated with unfavourable outcomes. Increased expression of the PDE7B isoform was revealed to be a poor prognostic marker in cytogenetically normal acute myeloid leukaemia (CN-AML), as overall patient survival was significantly lower in patients with increased PDE7 expression levels [55]. Further studies revealed that PDE7B expression was also increased at the mRNA and protein level in chronic lymphatic leukaemia (CLL) malignant B cells compared to control [56]. Increased PDE7B mRNA expression was also shown to be a poor prognostic marker in CLL [57]. A SNP in the 5′ non-coding region of the PDE7B gene has since been identified, yet it is observed in healthy and CLL patients in equal measure so is not likely to be causative to CLL onset. However, treatment with PDE7 inhibitors increased cAMP levels and induce apoptosis in CLL cells, suggesting that this may be a favourable therapeutic route for the treatment of this cancer [56].

In addition to lymphatic and blood cancers, a SNP in PDE7B in BRCA1/2-negative high-risk breast cancers has been identified in Asian patients that seems to be implicated in disease progression [58]. High PDE7 expression has also been correlated with a higher tumour grade in triple negative breast cancer (TNBC) and shown to drive tumour growth in TNBC cell lines [53].

5. Development of PDE7 Inhibitors

Proof of concept that increasing cAMP signalling can be a useful therapeutic approach for many inflammatory diseases has been demonstrated by marketed PDE4 inhibitors, such as roflumilast and apremilast. However, their therapeutic application is limited by their side-effects as a result of PDE4 inhibition in off-target tissues, causing nausea, emesis, diarrhoea, weight loss and headaches [5,52]. While second-generation PDE4 inhibitors and alternative routes of administration are being considered (*e.g.* inhaled *vs.* systemic), inhibiting cAMP degradation by inhibiting PDE7 proves an additional alternative approach [48,52]. It is thought, that PDE7 inhibitors may display a reduced side-effect profile compared to PDE4 inhibitors, due to the more restricted expression of PDE7 isoforms. This has been tested in experiments directly comparing the side-effect profile of PDE4 against PDE7 inhibitors in mice and revealed that those treated with PDE7 compounds did not have any emetic side-effects compared to those treated with

Table 1
PDE7 Inhibitors.

Compound	Features	Therapeutic indication	References
TC3.6	• Quinazoline derivative • Targets both PDE7 isoforms • Can cross the BBB • Potential dual inhibitor of GSK3β	Multiple sclerosis	[4]; [16]; [31]; [49]; [51]
S14	• Quinazoline derivative • Targets both PDE7 isoforms • Can cross the BBB	Alzheimer's disease, Parkinson's disease, spinal cord injury	[32,38,48,74]
VP1.15	• 5-imino-1,2,4-thiadiazole derivative • Targets both PDE7 isoforms • Can cross the BBB • Potential dual inhibitor of GSK3β	Spinal cord injury, schizophrenia, multiple sclerosis	[48]; [45]; [16]
BRL 50481	• Benzene/sulphonamide derivative • PDE7A selective	Chronic lymphocytic leukaemia, neurodegeneration and long-term memory deficits, Parkinson's disease	[18,32,56,71,75]
	• Sulphide-like inhibitor evaluated against PDE7A1 • Anti-inflammatory in experimental model	Experimental use	[59]
Dipyridamole	• Inhibits PDE7B, but also binds other PDEs including PDE4, PDE5, PDE6, PDE8 and PDE10	Experimental use	[17,76]

Structures of some experimentally used PDE7 inhibitors and their potential therapeutic applications. Chemical structures created in *ChemDraw*.

PDE4 inhibitor rolipram [59].

While no marketed inhibitor of PDE7 exists to date, the last ten years have seen rapid advances in the development of novel PDE7 inhibitors. Some of these have been extensively tested *in vitro* and *in vivo* and are thought to be ready for clinical development [44]. Several chemically diverse groups of PDE7 inhibitors have been developed thus far, examples of which are shown in Table 1. These include 5-imino-1,2,4-thiadiazoles (ITDZ) and other thiazole derivatives [49–51], benzyl derivatives [60,61], sulphide-like compounds [59], quinazoline derivatives (*e.g.* thioquinazolines, spiroquinazolinones) [62–65], and dihydronaphthyridinedione derivatives [66]. In order to improve the potency of these compounds towards PDE7, various derivatives of these molecular scaffolds have been identified based on structure-activity-relationship studies, virtual screening, molecular modelling, and docking analyses based on structural similarity [48,65–67].

Early PDE7 inhibitors, such as dipyridamole and SCH51866, often displayed cross-reactivity with other PDEs limiting their application [10,12,17,68,69], but virtual screening and molecular modelling studies have helped to improve selectivity of PDE7 inhibitors both over other PDEs (such as PDE4), but also towards PDE7A and PDE7B isoforms. To improve selectivity of PDE7 inhibitors over other PDEs, molecular modelling studies have been used to study pharmacophores that will interact exclusively with residues in the PDE7 binding pocket, and how PDE7 inhibitors interact with the active site binding pocket to prevent cAMP binding [39]. Studies have shown that thiadiazine and quinazoline scaffolds with non-substituted phenyl and ortho-halogens are most biologically active [67], while the best pharmacophores of heterocyclic PDE7 inhibitors include one hydrogen bond acceptor, one aromatic ring, and two hydrophobic aliphatic points [39]. In addition, molecular modelling has also lead to the identification of two additional allosteric binding cavities on the PDE7A1 enzyme [70]. Allosteric modulators may have several benefits, further increasing PDE7 isoform selectivity and reducing the possibility of side-effects, while not having to compete with cAMP for the active site [70]. For example, smaller quinazoline derivatives missing alkyl groups can fit into the smaller allosteric pockets of PDE7A1 and could function as allosteric modulators [70]. While most experimentally used PDE7 inhibitors are highly selective for this PDE family over others, PDE7 isoform and splice variant-selective inhibitors are still scarce. More success has been achieved for PDE7A, with BRL50481 being an established PDE7A-selective PDE7 inhibitor [71]. This is likely the result of most structure-based screening and docking-based analyses are performed using crystal structures of PDE7A isoforms, and no structure for PDE7B exists to date [65,70]. A greater understanding of how splice variants of the two PDE7 isoforms are expressed and contribute to disease, as well as improved molecular models, will be required to inform further development of PDE7 isoform and splice-variant-selective inhibitors in future.

Biological studies of promising compounds have demonstrated their anti-inflammatory abilities by reducing nitrite production, inhibiting astrocyte and microglial activation, and inhibiting release of pro-inflammatory mediators such as IL-6 and COX-2 [21,28,31,48,72]. Neuroregenerative effects, neuroprotective effects, and enhanced cognition following treatment with PDE7 inhibitors has been demonstrated in several studies indicating clinical utility for the treatment of NDs [13,32,37,73]. Pharmacokinetic studies of these compounds have also been performed to determine if they have sufficient drug-like properties, such as adhering to Lipinski's rule of 5 or their binding ratio with plasma binding proteins such as human serum albumin to determine volume of distribution and inform dosing regimens [62]. More importantly, since PDE7 inhibitors show potential for the treatment of NDs, these compounds have also been investigated in their ability to cross the blood-brain barrier (BBB) [13,21,62]. Novel drug delivery systems to improve the pharmacokinetic profile of drugs have also been tested for the promising PDE7 inhibitor S14 in order to advance it to clinical trials. S14 has recently been loaded into poly-lactic-*co*-glycolic acid (PGLA) nanoparticles to improve release and BBB penetration, which demonstrated safety and efficacy *in vitro* and *in vivo* studies allowing for potential clinical translation [74].

Interestingly, many PDE7 inhibitors are now being investigated for their dual inhibitory function of GSK3β. As outlined previously, studies demonstrated that PDE7 inhibition leading to subsequent increase in cAMP levels and activation of PKA, can result in phosphorylation of GSK3β. GSK3β is a well-established target in neuroinflammation and is being investigated for the treatment of many NDs [41]. Phosphorylation of GSK3β by PKA leads to reduction of pro-inflammatory signalling and could further potentiate the effect of PDE7 inhibitors [51]. This creates an exciting new focus for the development of PDE7 inhibitors with dual functionality: 1) direct inhibition of PDE7 to increase intracellular cAMP levels, and 2) indirect inhibition of GSK3β through activation of the cAMP/PKA pathway.

6. Concluding remarks

cAMP was the first second messenger to be discovered and it is the most studied. Much attention has been given to the mechanism and function of PDE4 family members in order to provide rational and context for the inhibition of cAMP hydrolysis as a therapeutic strategy [3]. Much less is known about other cAMP-specific PDEs such as PDE7. Here we have provided an extensive review that brings together some of the pertinent literature surrounding PDE7 to allow the reader to grasp the current state of play concerning this enzyme family. From the review it is evident that PDE7 is an important regulator of cAMP signalling involved in physiological processes such as T-cell activation, inflammation, and signalling in the CNS. Enhanced PDE7 activity and subsequently low levels of cAMP have been associated with several disease states, including neurodegenerative diseases, inflammatory diseases and cancers. Most promise has been shown for the treatment of Parkinson's disease using PDE7 inhibitors, yet further work is required to fully characterise the role of PDE7 and its therapeutic use in other diseases. Several inhibitors of PDE7 have been designed and tested in experimental models to demonstrate their therapeutic potential, with the first compounds thought to be ready for clinical testing. The next big step will involve the development of PDE7 isoform/splice-variant selective compounds, and the advancement of these to clinical trials.

CRediT authorship contribution statement

Alina Zorn: Conceptualization, Investigation, Visualization, Writing – original draft. **George Baillie:** Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Alina Zorn reports financial support was provided by Medical Research Council. Professor George Baillie is the Editor in Chief of Cellular Signalling.

Data availability

No data was used for the research described in the article.

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