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REVIEW

Physiological function of cyclic nucleotide phosphodiesterases in atrial myocytes and their potential as therapeutic targets for atrial fibrillation

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Abstract

Cyclic nucleotide hydrolyzing phosphodiesterases (PDEs) are key regulators of cyclic nucleotide (e.g., cAMP and cGMP) signaling. Here, we examine the role of PDEs in the physiology of atrial myocytes (AMs), the pathogenesis of atrial fibrillation (AF), and the potential of PDEs as therapeutic targets for AF. PDE1–5 and 8 are present and functional in AMs. PDE2-4 are important regulators of AM contraction but their role beyond atrial contractility is unclear. The role of PDE1,5 and 8 in healthy AMs is unknown but of interest because of their roles in ventricular myocytes. We propose that PDE2-5 and PDE8 are potential targets to prevent the triggering of AF considering their effects on Ca^{2+} handling and/or electrical activity. PDE1–5 are possible targets to treat patients with paroxysmal or persistent AF caused by pulmonary vein automaticity. PDE8B2 is a possible target for patients with persistent AF due to its altered expression. Research should aim to identify the presence, localization, and function of specific PDE isoforms in human atria. Ultimately, the paucity of PDE isoform-specific small molecule modulators and the difficulty of delivering PDE-targeted medications or therapies to particular cell types limit current research and its application.

arrhythmias; atria; cAMP; cGMP; phosphodiesterase

INTRODUCTION

Cyclic nucleotide phosphodiesterases (PDEs) are cornerstones to the biology of almost every known living organism. They are key regulators of cyclic nucleotide signaling, which occurs almost ubiquitously in living organisms (1). This cyclic nucleotide signaling itself is of critical importance to allow cells (eukaryotes, prokaryotes, and archaea), multicellular organisms, and ecosystems (intraspecies and interspecies) to respond to signals from their internal and external environment, explaining to an extent how living organisms work. Thus, PDEs are crucial for the physiology of almost every cell type, regulating a bewildering array of different cellular processes and functions. PDEs are therefore one of the most intensely and widely researched areas of biology. At the time of writing, 77,348 results containing "phosphodiesterase" or "phosphodiesterases" in the title or abstract were returned by PubMed between 1945 and January 2024. This is a total of ~0.2% of all articles on the PubMed database. There has been an average of 1,897 publications/yr between 2013 and 2023, clearly indicating that PDEs are currently a highly researched area.

PDE research has led to and has the potential to treat diseases (2). PDEs are current drug targets for a broad range of conditions from respiratory [e.g., asthma (3)], cardiovascular [e.g., heart failure (4, 5) or claudication (6)], and urological conditions [e.g., erectile dysfunction (7, 8) or the symptoms of benign prostate hyperplasia (9)] to autoimmune [e.g., psoriasis (10, 11)] and psychiatric conditions [e.g., anxiety (12)] (please see Ref. 2 for more examples). PDE-targeting drugs are currently under development for a further broader variety of different conditions such as neurodegenerative diseases [e.g., Alzheimer's (13)], metabolic diseases [e.g., type 2 diabetes (14, 15)], rare genetic disorders [e.g., fragile X syndrome (16) or sickle cell anemia (17)], certain types of cancer [e.g., head and neck squamous cell carcinomas (18)], and hypertension (19, 20) [see Baillie et al. (2) for more examples]. Furthermore, PDEs are implicated as potential key mediators and regulators of other pathologies such as atrial fibrillation (AF) (21–24) and pulmonary hypertension (25, 26). PDEs are thus also potential biomarkers, if not drug targets, for a variety of different pathologies (2). Understanding PDEs is therefore of interest to multiple fields of medical research. This review article will focus on the role of PDEs in the cardiac atria and on their potential as treatment targets in AF.

There are, however, major risks associated with PDE-targeted treatments when the role of specific PDEs is not fully understood. This is best exemplified by the case of milrinone. Milrinone is a PDE3 inhibitor that has beneficial short-term effects on patients with chronic heart failure (27), however, causes excessive mortality in patients treated for a long

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time (28). This unexpected chronic effect of milrinone was due to a lack of understanding of the diversity of PDE3s and the variety of different PDE3-containing signalosomes in cardiac myocytes (29). It was understood that inhibiting PDE3 would increase the strength of contraction, explaining the short-term beneficial effect of milrinone (27, 28). This increase in strength of contraction is caused by inhibition of PDE3s' regulation of the cAMP domains regulating excitation-contraction coupling (30–32). However, it was not known or even considered that the activity of PDE3A1 and PDE3A2 in different signalosomes may protect cardiac myocytes from apoptosis (33, 34) and hypertrophy (29). It was therefore not predicted that milrinone would trigger cardiac myocyte apoptosis and exacerbate cardiac hypertrophy leading to excessive patient mortality in the long-term (28). This highlights that there are dangers with developing PDE-targeted treatments for AF or any other conditions without a comprehensive understanding of the PDEs being targeted and their various signalosomes.

THE ROLE OF PHOSPHODIESTERASES IN CARDIOVASCULAR PHYSIOLOGY AND PATHOPHYSIOLOGY

PDEs are key players in cardiovascular physiology and pathophysiology. At a systemic level, PDEs influence key cardiovascular functions such as both short-term (4) and long-term systemic blood pressure (19, 35). This is via the influence of PDEs on renal pressure - natriuresis (19, 35), cardiac output (36), and perfusion of specific tissues (37–39). The role of PDEs in specific cardiovascular cell types has been previously well reviewed for the sino-atrial node (SAN) (40, 41), ventricular myocytes (VMs) (42–47), and vasculature (43, 48–51) but to our knowledge not yet in atrial myocytes (AMs). Overall, PDEs appear to be key regulators of multiple functions by mediating the intracellular responses to various hormones, neurotransmitters [e.g., noradrenaline (52, 53), acetylcholine (54, 55), natriuretic peptides (56–61)], and intracellular signals. This regulation of intracellular responses to stimuli leads to the modulation of electrical (62) and Ca^{2+} signaling (41, 63–65), contractility (66), gene expression (29, 67, 68), cell growth (29, 67, 69), and more in cardiac myocytes. The disruption and alteration of cyclic nucleotide signaling is linked to multiple cardiovascular diseases including hypertension (70), heart failure (43, 46, 47), and AF (21, 24, 71).

ATRIAL FIBRILLATION

AF is an irregular rhythm of the top chambers of the heart (i.e., the atria). There are four types of AF. *1*) Paroxysmal AF - AF that comes and goes by itself; *2*) persistent AF - AF that begins spontaneously but lasts at least 7 days before it ceases (with or without medical treatment); *3*) chronic AF (sometimes referred to as long-standing persistent AF) - AF that lasts at least a year without interruption but that is being currently treated; and *4*) permanent AF - chronic AF that has proven untreatable. Patients with AF suffer debilitating symptoms greatly reducing their quality of life (72) and have increased risk of developing and/or a deterioration of many comorbidities such as stroke (73), heart failure (74, 75), myocardial infarction (76), and chronic kidney disease (77, 78). Patients with AF hence have a 3.7-fold increase in their risk of death by all causes compared with an age- and sex-matched general population (79).

AF is a major increasing burden, globally (80, 81). In 2017, 38 million people globally (0.51% of the global population) were estimated to suffer AF and by 2050, this number is expected to almost double to 68 million people (82) [0.70% of the predicted global population of 9.7 billion (83)]. AF treatments aim to either reduce the rate of atrial electrical activity (i.e., rate control) or restore sinus rhythm (i.e., rhythm control) alongside anticoagulant therapy. These current pharmacological treatments are inadequate and safe novel therapies are needed (80, 84). The cardiac autonomic nervous system (85–95), SAN (96, 97), and atrial fibrosis (98) all play important roles in AF pathology, alongside inflammation (99). However, there are only a few studies looking at the role of PDEs in the cardiac autonomic nervous system (100–102) and cardiac fibrosis (103–105), let alone studies looking at the role PDEs in autonomic neurons or fibroblasts play in atrial physiology or pathology. Similarly, there are only two studies we know of looking at the role of PDEs in sinus node dysfunction in patients with AF (106, 107) and there are good reviews on the role of PDEs in the healthy SAN (40, 41). In contrast, multiple research papers have been published on the presence and role of PDEs in cardiac atrial myocytes and AF and a review collating this information is much needed. Here, we aim to discuss the physiological function of PDEs within atrial myocytes and their therapeutic potential in patients with AF with a focus on their potential as targets for rhythm control.

BASICS OF CYCLIC NUCLEOTIDE SIGNALING

The family of cyclic nucleotide molecules includes multiple members such as cyclic adenosine 3′,5′-monophosphate (cAMP) (108, 109) cyclic guanosine 3′,5′-monophosphate (cGMP) (110), cyclic inosine 3′,5′-monophosphate (cIMP) (111), cyclic uridine 3′,5′-monophosphate (cUMP) (1, 112), and cyclic cytidine 3′,5′-monophosphate (1, 112, 113). In addition to these classical 3′-5′-cAMP/GMP/IMP/UMP versions, 2′-5′ versions also exist (114, 115) along with cyclic dinucleotides. Of these molecules, 3′-5′ cAMP and cGMP are the most established, extensively studied, and understood and will be the focus of the remainder of this article. However, cCMP, cUMP (112, 116), and cIMP (111) have also been proposed as intracellular messenger molecules (112, 116, 117). Based on published literature, we present a model of the key concepts and basics of cGMP and cAMP signaling in Fig. 1.

The Crucial Importance of Phosphodiesterases in Cyclic Nucleotide Signaling

PDEs are key regulators of multiple different aspects of cyclic nucleotide signaling. They are crucial for retaining the specificity of cyclic nucleotide signals. This is achieved through control of the diffusion of cAMP and cGMP by PDEs resulting in the compartmentalization of cAMP and/or cGMP signals. PDEs are also essential controllers of the size of cyclic nucleotide signaling triggering effector responses.

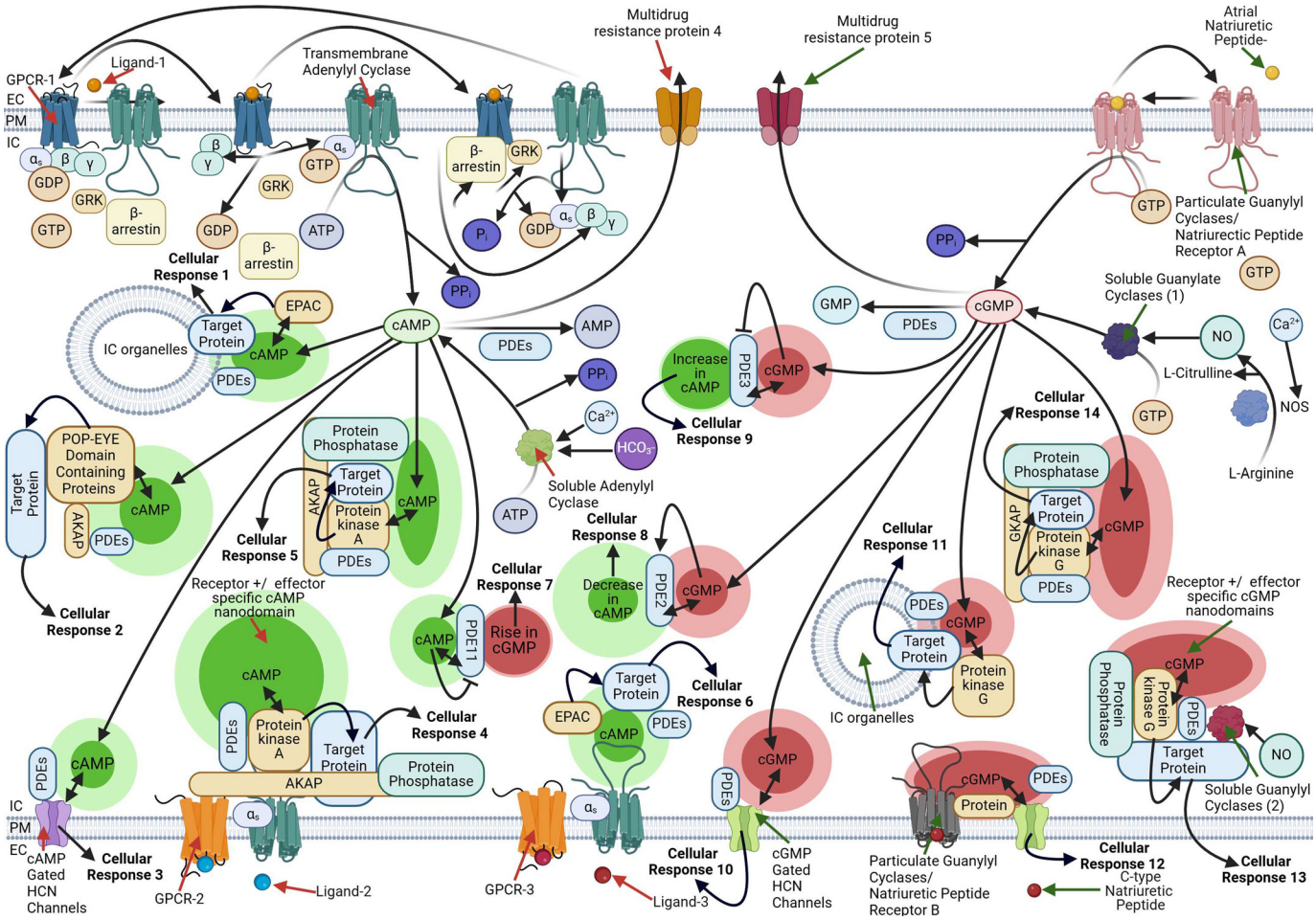

Figure 1. Model of the key concepts and basics of cAMP and cGMP signaling. Under basal condition (i.e., the absence of activators of adenylyl cyclases), there is no net cAMP production. The binding of specific ligands to specific GPCRs leads to the release of G_s that binds to transmembrane adenylyl cyclases and activates them. High [Ca^{2+}] or [HCO_3^-] around soluble adenylyl cyclases leads to their activation. Activated adenylyl cyclases produce cAMP from ATP. Each GPCR/ligand leads to a rise in cAMP in spatially distinct nanodomains. cAMP can then stimulate its effector proteins (EPAC, PKA, or POP-EYE domains containing proteins, PDE11 or HCN channels) ultimately leading to cellular responses. cAMP effector molecules are tethered to AKAPs or localized to distinct domains containing the target proteins to generate a cellular response. These distinct domains or signalosomes also contain PDEs and sometimes protein phosphatases if PKA is present. This arrangement allows cAMP to regulate a range of different cellular responses (in our model, cellular responses 1–9) but retains specificity to different signals such as different EC ligands (in our model, 3 different EC ligands). To turn off the cAMP signal and return the cells to basal conditions, GPCR signaling is inactivated and cAMP is hydrolyzed by PDEs or exported via multidrug resistance protein 4. Under basal condition (i.e., the absence of activators of guanylyl cyclases), there also is no net cGMP production. cGMP is produced from GTP by the binding of specific ligands directly to specific particulate guanylyl cyclases or activation of soluble guanylyl cyclase by NO. Activation of different particulate guanylyl cyclases by different ligands or soluble guanylyl cyclases by different pools of NO lead to rises in [cGMP] in distinct spatial domains. cGMP can then alter the activity of its effector proteins (PKG, HCN channels, PDE2, PDE3) leading to cellular responses. cGMP effector molecules are tethered to GKAPs or localized to distinct domains containing the target proteins to generate a specific cellular response. These distinct domains or signalosomes also contain PDEs and sometimes protein phosphatases if PKG is present. This arrangement allows cGMP to regulate a range of different cellular responses (cellular responses 7–14 in our model) but still retain specificity to different signals such as different EC ligands. To turn off the cGMP signal and return the cells to basal conditions, guanylyl cyclases are inactivated and cGMP is hydrolyzed by PDEs or exported by multidrug resistance protein 5. AKAP, A Kinase Anchoring Protein; AMP, adenosine 5′ monophosphate; ATP, adenosine 5′ trisphosphate; EC, extracellular; EPAC, Exchange Protein Activated directly by cAMP; GDP, guanosine 5′ diphosphate; GPCR, G-protein coupled receptor; GRK, GPCR kinase; GTP, guanosine 5′ trisphosphate; HCN, hyperpolarizing cyclic nucleotide gated; IC, intracellular; NO, nitric oxide; NOS, nitric oxide synthase; Pi, phosphate; PM, plasma membrane; PPi, diphosphate; α_s, G-protein stimulatory alpha subunit; β, G-protein beta subunit; ϒ, G-protein gamma subunit. Created in BioRender. Burton, R. (2025) https://BioRender.com/c52x119.

This is because PDEs regulate the number of effector proteins activated, the degree of activation of each effector protein, and the duration over which they are activated. This is through PDE-mediated control of the spatial dimension, cyclic nucleotide concentration, and temporal dynamics of compartmentalized pools of cAMP or cGMP (i.e., cAMP or cGMP signals). The sensitivity of PDEs to multiple different signaling molecules such as Ca^{2+} [directly via calmodulin -CaM- (118) or indirectly via calmodulin-activated kinases (CaMK) (119), cAMP (120–122), or cGMP (123–126)] makes PDEs crucial nodes for the integration of cAMP or cGMP signals with many other different signals (see Table 1), allowing cells to respond appropriately to multiple simultaneous internal and external signals.

Having discussed the basics of cAMP and cGMP signaling and the key importance of PDEs, we will now dive into the molecular biology and pharmacology of PDEs. This information is needed to understand the role of

Table 1. *Different mammalian cyclic nucleotide hydrolysing PDEs and their physiological and pharmacological regulation*

Family	Key Features	K_m cAMP, μM	K_m cGMP, μM	Physiological Activators	Physiological Inhibitors	Pharmacological Modulators*	References K_m Values
PDE1 (1A, 1B, 1C)	Ca^{2+}/calmodulin-stimulated dual-specific Heterotetrametric	PDE1A: 50–100 PDE1B: 7–24 PDE1C: 1	PDE1A: 5 PDE1B: 3 PDE1C: 1	$4Ca^{2+}$-CaM (127)	PKA (128) CaMKII (129)	IBMX vardenafil vinpocetine MMPX PF-05085727 ITI-214	(130–134)
PDE2 (2A)	cGMP-stimulated dual-specific	30	10	cGMP		IBMX PF-05180999 EHNA	(125)
PDE3 (3A, 3B)	cGMP-inhibited dual-specific	0.2–0.5	0.02–0.2	PKA (135) PI3K (136) PKB (137) PKC (PDE3A only) (138)	cGMP	IBMX milrinone cilostamide cilostazol enoximone olprinone	(126)
PDE4 (4A, 4B, 4C, 4D)	Low-affinity, high-capacity cAMP specific	1–4	∼0	PKA (139) ERK (140) SIK1 (141) AMPK (142) CaMKII (119) PA (143) Phosphatidyl serine (144) Lysophosphatidic acids (144) Calcineurin (145) mAKAP/AKAP6 (163) SUMO E3 Ligase PIASy (146)	ERK (140) DISC1 (147, 148) PHD2 (149)	IBMX rolipram roflumilast Ro 20–1724 piclamilast A 33 (selective PDE4B) D159687 (selective PDE4D) GEBR-3a (selective PDE4D) MR-L2 (activator of long-isoform variants of PDE4 only)	(150, 151)
PDE5	cGMP-specific	∼0	1–5	cGMPPKG (123, 124)		IBMX sildenafil tadafil vardenafil avanafil udenafil UK 357903	(123, 124, 152–154)
PDE6	cGMP-specific Heterotetrametric	∼0	20	cGMP (155–157)		IBMX Vardenafil sildenafil	(158)
PDE7	cAMP specific	0.03–0.2	0∼			IBMXBRL-50481	(159–164)
PDE8	High-affinity, low-capacity cAMP specific	0.04–0.15	0∼	PKA (165) I-κ B proteins (166)		PF-04957325 PF-04671536	(167–170)
PDE9	cGMP-specific	∼0	0.07–0.26			PF-04449613	(168, 171)
PDE10	cAMP-inhibited dual-specific	0.05–0.26	3–9		cAMP	IBMX TP-10 balipodect	(172–175)
PDE11	Dual-specific	1–6	0.5–4			IBMX Tadafil BC11-38	(176–180)

Adapted from Epstein et al. (181). *Inhibitor unless stated otherwise.

PDEs within AMs and PDEs' potential as therapeutic targets in AF.

BRIEF OVERVIEW OF PHOSPHODIESTERASES' MOLECULAR BIOLOGY AND PHARMACOLOGY

Cyclic nucleotide phosphodiesterases (PDEs) are a super family of enzymes, which typically form homodimers. There are 11 families of mammalian cyclic nucleotide PDE (PDE1–11) made up of 21 PDE genes. These genes are grouped into families based on their products' affinity for and efficacy to hydrolyze the high-energy 3′-5′ phosphate bond in cAMP and cGMP to yield adenosine monophosphate or guanosine monophosphate (182), along with how their activity is regulated. All families have the same basic molecular blueprint. Towards the C-terminal tail is a catalytic domain that contains multiple highly conserved residues (182). The sequence of a nucleotide recognition pocket determines whether the phosphodiesterase is cAMP-specific, cGMP-specific, or exhibits dual specificity (183, 184) (see Table 1). Regulators of the catalytic site are found generally towards the N-terminal (182). Crucially, the amino acid sequences and structure outside of the conserved catalytic domain can differ greatly between variants of the same PDE gene. This is due to the presence of multiple promoters and nontranscriptional regulatory domains within PDE genes along with a multitude of splice variants of the same nascent messenger RNA (185, 186). In total, there are more than 100 PDE isoforms (187). For a more comprehensive review please see Ref. 182.

The structural biology of PDEs has important implications for their pharmacology and applications in medicine. The diversity of PDE proteins from the same gene allows each different PDE isoforms to localize to specific regions of a cell and to regulate specific cAMP or cGMP pools (188, 189). This specificity of function of individual PDE isoforms may offer the opportunity to develop more precise therapeutics with improved efficacy and reduced side-effects (190). Targeting specific PDE isoform-protein interactions could enable therapies to target the activity of specific PDEs in specific signalosomes, as the same PDE isoform can interact with multiple proteins (191). The differences in the structure of PDEs in nonconserved regions in the catalytic domain has allowed the discovery and development of PDE inhibitors for specific families (192, 193), except for PDE6 and PDE11. Furthermore, the large differences in regulatory regions outside of the highly conserved catalytic site, which is normally the structure targeted by PDE inhibitors (192, 193), has facilitated the development of PDE4 subtype-specific inhibitors (194, 195) [e.g., A33 (196), GEBR-32a (197)] and activators [e.g., MR-L2 (198)]. Moreover, there is a large field working to develop various strategies to finely modulate the function of PDEs (2), such as small molecular activators, small molecular modulators of the location of PDEs via targeting their protein-protein interaction, or posttranslational modifications (2). In addition, there are efforts to develop gene therapies to either knockout, knock-down, mutate, or insert PDE genes into cells [see Baillie et al. for a summary (2)].

THE PRESENCE AND LOCALIZATION OF PHOSPHODIESTERASES IN ATRIAL MYOCYTES

PDE1–4 and 8 Are Present in Human Atrial Myocytes

PDE1–4 and 8 have been identified to be present and functional in AMs and will be discussed further here. PDE1–4 proteins are expressed and present in AMs of multiple different species (199–205) including humans (71) (see Table 2) and matured human induced-pluripotent stem-cell derived AMs (hiPSC-AMs) developed by Axol Bioscience (Company, UK) (Table 3). In detergent extracts from human atria, Molina et al. (71) investigated the relative proportion of 1 μmol cAMP hydrolyzed by PDE1–4. They showed that PDE3 accounts for most of the cAMP hydrolysis in human AMs followed by PDE4, PDE2, and PDE1, respectively (see Table 3). In their experiments, 15% of cAMP hydrolysis was not accounted for by PDE1–4. However, PDE8A and 8B have also been identified to be expressed in human AMs by qPCR, Western blot, immunohistochemistry and have been shown to be functional using Förster resonance energy transfer (FRET)-based cAMP sensors (24). Therefore, PDE8s may account for the remaining cAMP hydrolysis in human AMs.

We are not aware of any studies that have identified the other cAMP hydrolyzing PDEs - 7, 10, 11 - in AMs of any species. Thus, it is worth considering the observations made in ventricular myocytes (VMs) to investigate the potential role of PDEs in AMs. PDE7 is mainly thought to be expressed in immune cells. PDE7A has been observed in human atrial tissue samples (225), guinea pig (204), and human VMs (204) (see Table 2) and Axol's hIPSC-AMs (Table 3). However, PDE7A has not yet been identified in the human (221) or rat myocardium (204). PDE10A2 is present in mouse and human VMs (224), therefore, PDE10s' presence in human AMs is feasible though remains to be confirmed. PDE11 expression in the cardiac atria to our knowledge has not been found.

The Localization of PDE4 and 8 in Human Atrial Myocytes is Incompletely Understood

Only the localization of PDE4 and 8 has been investigated in human AMs. In human AMs, PDE4 colocalizes with the Z-line marker α-actinin in immunohistochemistry analysis (71), while PDE8A shows a cytosolic distribution, and PDE8B is mainly distributed at or near the membrane (24). In human AMs, within the cytosol both PDE8s are expressed in a modest striated pattern, and this likely represents a localization at either the t-tubules or Z-lines (24). PDE8B also appears in peripheral puncta either at or underneath the membrane in human AMs (24).

There Maybe Differences in the Activity of Different cAMP Hydrolyzing PDEs between Human Atrial and Ventricular Myocytes

The differences in the relative importance of different cAMP hydrolyzing PDEs in regulating global cAMP levels between human AMs and VMs are unclear. Although studies have measured the relative importance of different cAMP hydrolyzing PDEs in regulating global cAMP levels in human AMs (71) or VMs (204), glaring differences in the

Table 2. *PDEs present in cardiac tissue across different species*

PDE Family	Mice	Rat	Guinea Pig	Rabbit	Dogs	Pigs	Human
PDE1	1A and 1C present VMs (206, 207)	Present SANCs (208), AMs (208), and VMs (204) (1A and IC)	Present VMs (204)	1A, B, C present SANCs (203), AMs (203), VMs (203), and PVCMs (209)	Not known	Not known	1C Present AMs (71) and VMs (204)
PDE2	Present SANCs (205), AMs (205), VMs (207, 210)	2A present AMs (208) and VMs (204)	Present AMs (211), VMs (204)	Present SANCs (212)	Not known	Not known	Present AMs (71) and VMs (204)
PDE3	Present SANCs (205), AMs (205), VMs (34) (207)	3A and 3B present AMs (208) and VMs (204)	Present SANCs (213, 214), AMs (215), VMs (204)	Present SANCs (216) and PVCMs (216)	Not known	Present SANCs (202, 217), AMs (202, 217) and VMs (202, 217)	Present AMs (71) and VMs (204)
PDE4	Present SANCs (205), AMs (205) and VMs (207)	4A, B, D present SANCs (208), AMs (208), and VMs (204)	Present AMs and VMs (204)	Present PVCMs (216) and SANCs (216)	Present VMs (199)	Present SANCs (202), VMs (202) andAMs (202)	Present in AMs (71) and VMs (204)
PDE5	Present SANCs (218) and VMs (219, 220)	5A present AMs (208) and VMs (204)	Present VMs (204)	Present SANCs (216) and PVCMs (216)	Not known	Not known	Present in VMs (204)
PDE6	Not known	Not known	Not known	Not known	Not known	Not known	Not known
PDE7	Not known	Absent VMs (204)	7A present VMs (204)	Not known	Not known	Not known	VMs: unclear; found in Ref. 204 and absent in Ref. 221
PDE8	8A present VMs (222)	Not known	Not known	Not known	Not known	Not known	Present AMs. 8A, but not 8B, present VMs (24)
PDE9	9A present VMs (223)	Not known	Not known	Not known	Not known	Not known	Not known
PDE10	10A Present VMs (224)	Not known	Not known	Not known	Not known	Not known	10A present in VMs (224)
PDE11	Not known	Not known	Not known	Not known	Not known	Not known	Not known

Presence identified either by molecular biology and/or functional pharmacological or genetic modulations experiments. AMs, atrial myocytes; PVCMs, pulmonary vein cardiac myocytes; SANCs, sino-atrial node cells; VMs, ventricular myocytes.

Table 3. *Expression of PDE-RNAs in hiPSC-derived cardiomyocytes (Axol Bioscience, UK)*

Gene/ Protein Name	RNA Expression in iPSC-AMs Divided by the Expression in iPSC-VMs	Normalized RNA Expression in iPSC Derived AMs (Transcripts per Kilobase Million)
PDE1A	2.66	0.05
PDE1B	1.60	1.09
PDE1C	2.31	0.17
PDE2A	2.80	0.14
PDE3A	6.37	1.01
PDE3B	1.21	0.64
PDE4A	2.29	0.17
PDE4B	0.28	0.10
PDE4C	5.06	0.41
PDE4D	0.91	0.29
PDE5A	1.32	2.18
PDE6A	4.09	0.37
PDE6B	1.41	6.74
PDE6C	3.77	0.23
PDE6D	1.39	4.23
PDE6G	3.22	0.50
PDE6H	1.19	0.04
PDE7A	1.11	2.63
PDE7B	2.20	0.07
PDE8A	1.66	1.28
PDE8B	11.38	0.94
PDE9A	4.76	0.75
PDE10A	0.59	0.55
PDE11A	1.29	0.04

These data were provided or calculated from data provided by Axol Bioscience, UK (see Supplemental Table S1 for the raw data provided) and are freely available on request from Axol Bioscience, UK.

experimental methods and conditions unfortunately make it impossible to draw any definitive conclusion from such comparisons. Experiments looking for differences in the relative importance of different PDEs in AMs versus VMs using the same experimental conditions and methods are needed.

There may be an increased importance of PDE1 in AMs versus VMs. In rats, there is an increased expression of PDE1 in AMs versus VMs (208). In combination with there being no reported differences in the cytosolic [Ca^{2+}] (226) (the major regulator of PDE1 activity) in rat AMs versus VMs, this suggests that there is also increased PDE1 activity. However, whether this increased PDE1 activity results in increased cAMP and or cGMP hydrolysis is unknown. As the expression of PDE1 has only been investigated in one single animal study, rats (208), we analyzed Axol's hiPSC cardiomyocyte transcriptomic data as well (See Table 3 for analyzed data or Supplemental Table S1 for raw data). We found that *PDE1s* are expressed more in Axol's matured hiPSC-AMs than in their matured hiPSC-VMs.

The suggested higher basal cAMP levels in rabbit (227), guinea pig (228), and mice (229) AMs, particularly in mice AMs subsarcolemmal and axial tubule junction domains (229) may increase the reliance on low-affinity high-capacity cAMP-hydrolyzing PDEs like PDE3 or PDE4. However, animal studies comparing PDE3 and PDE4 expression between AMs and VMs yield conflicting results, potentially due to the use of either whole tissue or isolated myocytes. In mice, PDE3A and 4A expression is lower but PDE4B and D expression is higher in right atria than in right ventricles, while PDE2A mRNA expression does not differ (205). However, in rats, PDE3A and PDE4A protein expression is higher, while PDE4D and PDE2A expression is lower with no difference in the expression of PDE3B and PDE4Bs in AMs compared with VMs (208).

The Presence and Importance of cGMP Hydrolyzing PDE in Human Atrial Myocytes Has Not Been Specifically Investigated

PDE1-3 are known to be present in human adult AMs, but the presence of PDE5,6,9,10,11 has not yet been investigated. However, as PDE5 is crucial for t-tubule formation and function in sheep and neonatal rat VMs (230) and as human AMs also have t-tubules (230), it is likely that PDE5A is also active in human AMs. Several other lines of evidence in different models support this hypothesis. PDE5A shows higher expression levels in rat AMs than in VMs (208) and is present and functional in the SAN and VMs of multiple species including humans (204, 218–220). Crucially, PDE5 appears to be functional in rabbit pulmonary vein cardiomyocytes (216), which are thought to be very similar to AMs. Finally, *PDE5A* shows higher expression levels in hiPSC-AMs than in hiPSC-VMs (Table 3). This supports the likely presence of PDE5A in human AMs. However, this hypothesis needs to be tested experimentally. In contrast, *PDE6* isoforms appear to be expressed in hiPSC-AMs and hiPSC-VMs (Table 3) but the existence of functional PDE6 has never been reported in cardiomyocytes, so this may be a feature distinct to iPSC cardiomyocytes. PDE9A is present in VMs from mice and human VMs and is found near SERCA2a, regulating phospholamban and NHE1's phosphorylation (223). PDE9A negatively regulates the cGMP signals produced by natriuretic peptides in VMs inhibiting hypertrophy (223), and in the atria, natriuretic peptides alter contraction-relaxation cycling, electrical signaling, and β-adrenergic signaling (61, 223, 231–233). This supports the possible presence of PDE9A in AMs, but this hypothesis needs to be tested experimentally.

Different Models Express Different Levels of PDEs and Results from Different Models Should be Interpreted with Caution

Johnson et al. (204) found that PDEs in the VMs of mice and rats differed from guinea pig and human VMs (in terms of the expression and activity of PDEs). This difference in PDE expression between mice and rats compared with humans may also be true in AMs. Our analysis of transcriptomic data provided by Axol has identified that *PDE2A, 3A, 4A*, and *PDE4C* are expressed more in hiPSC-AMs than in hiPSC-VMs, while *PDE4B* and *PDE4D* are expressed less (See Table 3 for analyzed data or Supplemental Table S1 for raw data and ESM File 1). These findings in hiPSC-AMs are the opposite of what is seen in mice (205), for *PDE2A*, *3A* and all *PDE4s*. Similarly, the findings of *PDE4* expression in hiPSC-AMs conflict with those in adult human AMs (71). It was found that the majority of PDE4 activity in adult human AMs could be accounted for by PDE4D (D3, D8, D9) with PDE4A and B also detected but PDE4C was not found present (71). However, in Axol's hiPSC-AMs, *PDE4C* is the predominant

PDE4 isoform followed by *PDE4D, A and B*. This difference in expression of *PDE2A, 3A,* and *PDE4s* in these hiPSC-AMs from adult mice and or human AMs (71) may be a specific feature of these hiPSC-AMs line or hiPSC-AMs in general. However, in the case of *PDE8A* and *PDE8B* expression, Axol's hiPSC-AMs seem to replicate much higher expression of *PDE8B* found in human adult AMs versus VMs (24). Further comparison of the expression of different PDE isoforms in mice AMs and human iPSC-derived AMs with the expression of PDE isoforms in human adult AMs is needed to verify the relevance of these different models to human hearts.

Summary of the Presence of Phosphodiesterases in Human Atrial Myocytes

In summary, PDE1–4 and 8 are present in human AMs and it is suspected that PDE5,9 and 10 also are present. Before exploring the role of PDEs in AMs, it should be recognized that differences in the relative expression of PDEs between animal models, hiPSC models, and human adult cardiomyocytes exist, as well as possible differences in PDE expression between ventricles and atria. This will allow a more nuanced understanding of the findings below. We will next focus on the role and potential roles of those PDEs (PDE 1–5,8) in regulating the key function of AMs—contraction and electrical conduction. Although it is recognized that PDE1-5 and PDE8 likely play crucial roles in multiple different cellular functions in AMs beyond just regulating their contraction and electrical activity.

THE ROLE OF PHOSPHODIESTERASES IN ATRIAL MYOCYTES

Phosphodiesterase 2 and 3 Negatively Regulate Basal Atrial Contractility

PDE2 inhibition with erythro-9-(2-Hydroxy-3-nonyl) adenine hydrochloride (EHNA) was positively inotropic in guinea pigs atrial tissue preparations (211). Similarly, PDE3 inhibition in humans (71, 234) and guinea pigs (215) AMs was also positively inotropic but not in mice AMs (205). This control of basal atrial contractility (defined here and in the rest of the article as the contractility in the absence of neurotransmitter or hormonal stimulation or inhibition) in AMs by PDE2 and 3 was also observed in human and rodent VMs and SAN (40, 204, 205, 235), suggesting that both PDE2 and PDE3 regulate the basal contractility of human AMs.

These positive inotropic effects may in part be explained by both PDE2 (236) and PDE3 inhibition increasing the basal (defined as in the absence of neurotransmitter or hormonal stimulation or inhibition) L-type Ca^{2+} current ($I_{Ca,L}$) in human and rabbit AMs (71, 237). This reveals that the activity of PDE2 and PDE3 inhibits the basal $I_{Ca,L}$ physiologically. $I_{Ca,L}$ plays a crucial role of coupling the atrial action potential to intracellular Ca^{2+} release and thus contraction (see Fig. 2). PDE2 and PDE3's negative regulation of the basal $I_{Ca,L}$ may be either via their hydrolysis of cAMP or cGMP as both PKA (71) and PKG (237) can stimulate basal $I_{Ca,L}$ in human and rabbit AMs, respectively (71, 237). Considering the low-affinity high-capacity nature of both PDE2 and PDE3, it seems likely the effect of their inhibition is in part through control of the high [cAMP] domains in junctional axial tubules that positively regulates the $I_{Ca,L}$ and subsequently Ca^{2+} transient (CaT) peaks and intracellular CaT's propagation (229) (see Figs. 2 and 3).

Further research is needed regarding the other cAMP domains potentially regulated by PDE2 and PDE3 in human AMs that regulate contractility. Ahmad et al. (244) found that PDE3A (tethered via AKAP18delta) negatively regulates sarcoplasmic endoplasmic reticulum Ca^{2+} ATPse 2a (SERCA2a) activity via inhibiting the phosphorylation of phospholamban (a negative regulator of SERCA2a activity) by PKA in human VMs, speeding up lusitropy and Ca^{2+} reuptake into the sarcoplasmic endoplasmic reticulum (SR) (244). In addition, in rat VMs, PDE3 regulates troponin I phosphorylation (235), while PDE2 negatively regulates basal troponin I and myosin-binding protein C phosphorylation in rat VMs (235). This reduces the Ca^{2+} affinity of the myofilament and increases cross-bridge kinetics, leading to positive lusitropy in rat VMs (235). Notably, neither PDE2 or 3 alter the basal phosphorylation or open probability of type 2 ryanodine receptors (RyR2s) in rat VMs (235).

Phosphodiesterase 4, 5, and 8 Do Not Regulate Basal Atrial Contractility

Inhibition of PDE4 [humans (71), guinea pig (245, 246)] or PDE5 [humans and dogs (247)]) in human or other mammalian atrial tissue does not increase basal inotropy. This is like what is seen in human VMs for PDE4 (204) and mice VMs for PDE8A (222). In human AMs, PDE8 inhibition did not lead to an increase in the peak amplitude of $I_{Ca,L}$ or phosphorylation of the L-type calcium channel (LTCC) under basal conditions, despite PDE8B2 and PKA coimmunoprecipitating with LTCC and PDE8 inhibition leading to a statistically significant rise in subsarcolemmal [cAMP] (24). This does not mean that PDE4,5 and 8 do not basally regulate cyclic nucleotide domains involved in atrial contractility, as PDE4,5 and 8 possibly regulate multiple antagonistic domains as will be discussed for PDE4.

PDE4 inhibition leads to a rise in global cAMP, an increase in the basal $I_{Ca,L}$ and an increase in the basal Ca^{2+} spark frequency in human AMs (71). PDE4 therefore appears to negatively regulate [cAMP] in specific domains, stimulating sarcolemmal Ca^{2+} influx and SR Ca^{2+} release/content. The role of PDE4 isoforms detected in human AMs is therefore consistent with the following localization and roles of the same PDE4 isoforms in VMs. *1*) PDE4B (248) and PDE4D8 (249) are tethered to the LTCC in mice VMs, PDE4D8 via SAP97 (249). *2*) PDE4B negatively regulates the LTCC in mouse VMs (248) via preventing PKA-mediated phosphorylation and inhibition of the tonic inhibition of the LTCC by the Ras-related protein Rad (250–252). *3*) PDE4D3 is tethered via mAKAP to RyR2 and negatively regulates the phosphorylation and thus activity of RyR2 (253) in rat VMs. Although in mice, PDE4B not PDE4D regulates RyR2 phosphorylation (254). *4*) PDE4D is tethered to SERCA2a via AKAP18 delta and inhibits SERCA2a activity via inhibiting PKA-mediated phosphorylation of phospholamban and the subsequent suppression of phospholamban's inhibition of SERCA2a and thus SR Ca^{2+} reuptake in mice VMs (30, 254, 255). It is unknown if the same signalosomes exist in AMs as in

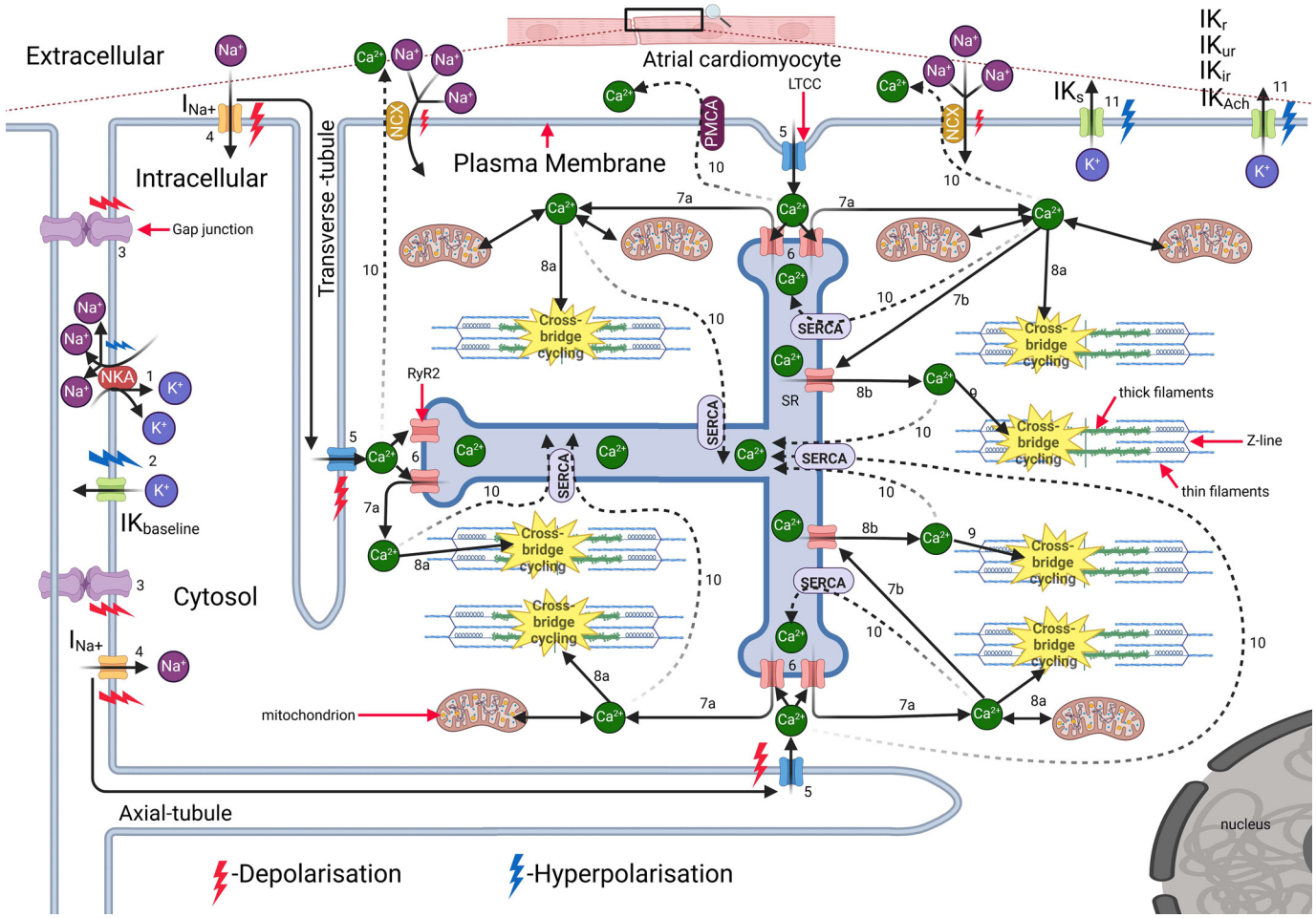

Figure 2. Schematic model of excitation-contraction coupling in human atrial myocytes. This is a mixed model of excitation-contraction coupling. This model combines the different models of excitation-contraction coupling proposed following work on rodent atrial myocytes (AM) that lack transverse tubules (238, 239) but have axial tubules (240) and the model proposed follows findings for the presence (241) and function (242, 243) of sparser transverse tubules in AMs of large mammals including humans (241). However, it is recognized that excitation-contraction coupling in human atrial myocytes is incompletely understood, including the role of axial and transverse tubules. Excitation-contraction coupling (1–11): *1*) the action of NKA that maintains an outward K^+ and inwards Na^+ concentration gradient. *2*) K^+ efflux causes hyperpolarization of the plasma membrane. *3* and *4*) A depolarizing current originating from the sino-atrial node causes the opening of voltage-gated Na^+ channel. *5*, *6*, *7a*) This depolarizes the cell's PM including its intracellular projections (i.e., transverse and axial tubules) leading to an excitation-induced Ca^{2+} transient through the opening of L-type calcium channels (LTCC) and Ca^{2+}-induced Ca^{2+} release. *7b* and *8b*) In human AMs, the Ca^{2+} transient is propagated deeper into the cell from the PM through a process involving Ca^{2+} diffusion from subsarcolemma or axial junction RyR2s to RyR2s clusters deeper into the cell and subsequent Ca^{2+}-induced Ca^{2+} release. The Ca^{2+} transient, propagated or not, triggers cross-bridge cycling between the thin filament (actin) and thick filament (myosin) leading to AM contraction. *10*) Contraction is then stopped by the removal of Ca^{2+} from the cytosol by various Ca^{2+} transporter proteins including SERCA and NCX and consequently the cessation of cross-bridge cycling. *11*) AMs are then repolarized via a range of voltage-gated or ligand-gated K^+ channels. AKAP, A Kinase Anchoring Protein; EC, extracellular; GPCR, G-protein coupled receptor; IC, intracellular; IKAch, acetylcholine-activated K^+ current; $IK_{baseline}$, baseline K^+ current; I_{Na+}, inward Na^+ current; IK_r, delayed rectifier K^+ current; IK_s, slowly activating delayed rectifier K^+ current; IK_{ur}, ultrarapid delayed rectifier K^+ current; LTCC, L-type calcium channels; NCX, $3Na^+$- $1Ca^{2+}$ exchanger; NKA, sodium potassium ATPase; NO, nitric oxide; PM, plasma membrane; PMCA, plasma membrane Ca^{2+} ATPase; RyR2, ryanodine type 2 receptor; SERCA, sarcoplasmic endoplasmic reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum. Created in BioRender. Burton, R. (2024) https://BioRender.com/y52o552.

VMs. In AMs, PDE4's low-affinity and high-capacity cAMP hydrolysis characteristics may mean that, like PDE2 and 3, PDE4 regulates the high [cAMP] in axial tubule junction domains specific to AMs. These high [cAMP] domains regulate the LTCC, RyR2 phosphorylation, the CaT amplitude, and CaT decay rate in mice AMs (229). Overall, this supports the idea that basal PDE4 activity is important for regulating the basal activity of RyR2 and LTCC and potentially SERCA2a in AMs.

How does PDE4 inhibition not have a positive inotropic effect in AMs despite apparently increasing Ca^{2+} influx or release? This could be explained by PDE4 regulating domains in AMs that positively regulate either: a) the sensitivity of myofilaments to Ca^{2+}; b) the inward propagation of the CaT; c) net cytosolic Ca^{2+} extrusion; or d) SR Ca^{2+} reuptake. In support of hypothesis (a), in human AMs, PDE4 does colocalize at the Z-line (71), potentially via association with myomegalin/PDE4DIP. The Z-line is a key site of thin filament regulation in human and rodent VMs (256). PDE4D activity does positively regulate the sensitivity of troponin C to Ca^{2+} via troponin I and creates a smaller rise in cAMP in this domain in response to β-adrenergic signaling, which is

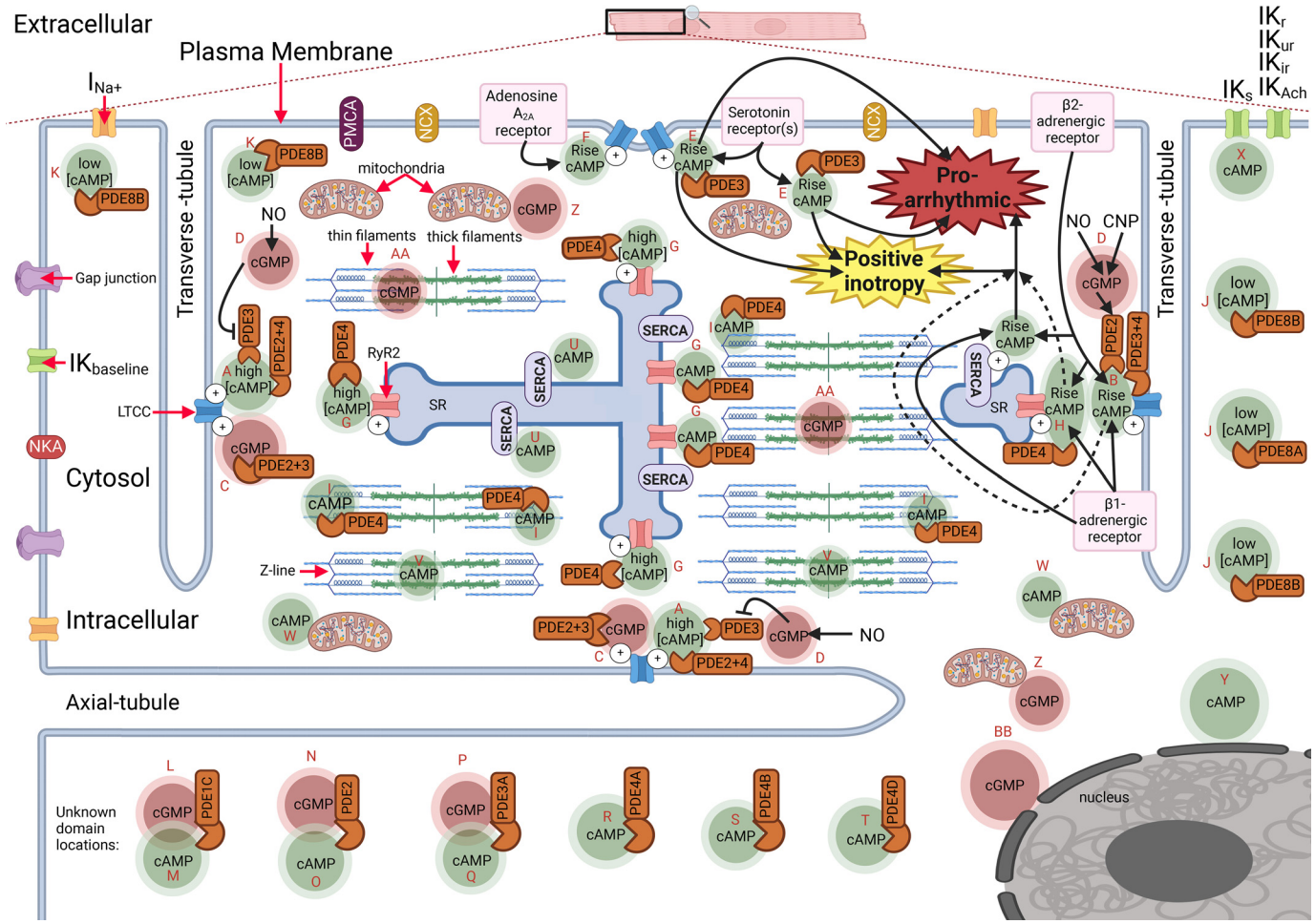

Figure 3. Schematic model of the role of PDEs in cGMP and cAMP signaling in human atrial myocytes. Role of PDEs in human AMs cGMP and cAMP signaling (*A*–*X*). Within human AMs, several distinct cAMP and cGMP signaling domains exist. The cAMP domain that regulates the LTCC under baseline conditions (*A*) or β-adrenergic receptor signaling (*B*) is modulated by PDE2,3,4. The concentration of cAMP in junctional cAMP domains around the LTCC is high. The cGMP domain that regulates LTCC directly (*C*) or indirectly (*D*) via the cAMP domain is regulated by PDE2 and PDE3. Serotonin and adenosine regulate cAMP domains around LTCC (*E* and *F*, respectively) but not RyR2s. The cAMP domain induced by serotonin is regulated by PDE3 (*E*). The cAMP domain that regulates the RyR2 under baseline conditions (*G*) or β-adrenergic receptor signaling (*H*) is regulated by PDE4. PDE4 regulates a cAMP domain near or on the Z-line of thin filaments in human AMs (*I*). PDE8A and B regulate cAMP domains in a transverse striated pattern in human AMs (*J*). PDE8B regulates a subsarcolemma or junctional SR cAMP domain (*K*), but the exact location is not yet known. PDE1C (*L* and *M*), PDE2 (*N* and *O*), PDE3A (*P* and *Q*), PDE4A, B, D (*R, S*, and *T*, respectively) are present in AMs but the location of cAMP or cGMP domains they regulate in human AMs is unknown. It is also not known which PDEs regulate the cAMP domains around SERCA (*U*), cardiac myofilaments (*V*), mitochondria (*W*), or the channels conducting IK_s (*X*) or around the nucleus (*Y*) in human AMs but the existence of such domains is suspected. Separate cGMP domains also likely regulate mitochondria (*Z*), the cardiac myofilaments (*AA*), and the nucleus (*BB*). AKAP, A Kinase Anchoring Protein; EC, extracellular; GPCR, G-protein-coupled receptor; IKAch, acetylcholine-activated K^+ current; IC, intracellular; $IK_{baseline}$, baseline K^+ current; I_{Na+}, inward Na^+ current; IK_r, delayed rectifier K^+ current; IK_s, slowly activating delayed rectifier K^+ current; IK_{ur}, ultrarapid delayed rectifier K^+ current; LTCC, L-type calcium channels; NCX, $3Na^+$-$1Ca^{2+}$ exchanger; NKA, sodium potassium ATPase; NO, nitric oxide; PM, plasma membrane; PMCA, plasma membrane Ca^{2+} ATPase; RyR2, ryanodine type 2 receptor; SERCA, sarcoplasmic endoplasmic reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum. Created in BioRender. Burton, R. (2024) https://BioRender.com/p08n759.

crucial to allow the positive inotropic effect of β-adrenergic signaling in adult rat VMs (257). Thus, PDE4 inhibition may cause a large rise in cAMP in this domain that outweighs the effects on Ca^{2+} handling. In support of hypothesis (b), cAMP and PKA signaling in rat VMs leads to RyR2 cluster dispersion, and this was associated with a reduced Ca^{2+} spark propagation speed (258). cAMP signaling at RyR2s in AMs may in part impair the inward propagation of the CaT in AMs, which is thought to rely on Ca^{2+} sparks inwards propagation between RyR2 clusters (259). Thus, PDE4 activity around RyR2 may protect against slowed inward propagation of the Ca^{2+} transients. In support of hypothesis (c), PDE4's can negatively regulate hyperpolarizing K^+ currents in rodent VMs (260–263), as will be discussed in more detail below, and thus PDE4 may feasibly positively regulate depolarizing I_{NCX} Ca^{2+} extrusion. In support of hypothesis (d), the reported inhibition of SR leak by PDE4 during diastole would increase the systolic SR Ca^{2+} release. Conversely, PDE4D activity inhibits SERCA2a activity in mice VMs, which would inhibit SR Ca^{2+} reuptake (255).

The Role of Phosphodiesterase 2, 3, and 4 in Regulating the Positive Inotropic Response to Several Cyclic Adenosine 3′,5′ Monophosphate-Producing Stimuli

PDE3 and 4 often work together to negatively regulate the positive inotropic response to cAMP-producing stimuli in human AMs. It has been reported that PDE3 and/or PDE4 inhibition increased the β-adrenergic receptor-induced cAMP signal and potentiation of the $I_{Ca,L}$ in human AMs (71) and β-adrenergic receptors-positive inotropic effects on human atrial strips (71, 234). Similarly, the positive inotropic response to forskolin or β-adrenergic stimulation in guinea pig atrial strips is increased by PDE3 and/or PDE4 inhibition (245, 246, 264).

The molecular mechanisms of most of these effects have not been specifically investigated in human AMs except for the effects on the LTCC. The modulation of the positive inotropic response potentially involves PDE3 and 4-dependent regulations of the cAMP signals generated by external stimuli around the molecular targets discussed in the previous section. In addition, PDE4D8 and PDE4D9, the isoforms identified in human AMs also dynamically associate and dissociate with β-1 and 2 adrenergic receptors acting to prevent their basal phosphorylation and desensitization and also negatively regulate the cAMP signal and response to β-1 and 2 adrenergic signaling in neonatal rat VMs (265, 266).

The role of PDE3 and 4 in regulating the positive inotropic response in AMs depends on the cAMP-producing agonist. Berk et al. (267) found that PDE3 inhibition, but not PDE4 inhibition, increased the positive inotropic effect of 5-hydroxytryptophan or serotonin (5-HT) in human atrial trabeculae (267). This suggests that PDE4 does not influence these 5-HT cAMP signals. The exact mechanism explaining why PDE4 is not an important regulator of this 5-HT response in human trabeculae (268) but is an important regulator of the β-adrenergic response (71) has not been elucidated. However, the difference in the role of PDE4 between 5-HT and β-adrenergic signaling is probably due to the compartmentalization of cAMP pools for different receptors signaling cascades in separate micro/nanodomains.

Role of Phosphodiesterase 2 and 3 in the L-Type Calcium Channel and Contractile Response of Atrial Myocytes to Guanosine Cyclic 3′,5′ Monophosphate cGMP

PDE2 mediates the inhibitory effects of cGMP- or cGMP-producing agonists like nitric oxide (NO) on the LTCC in human AMs. In mice AMs, C-type natriuretic peptide application is associated with a natriuretic peptide receptor B-dependent rise in cGMP, increased PDE2-mediated hydrolysis of cAMP, and a subsequent reduction in the cAMP response to β-adrenergic receptor stimulation (269). In particular, inhibition of PDE2 abolished the ability of C-type natriuretic peptide to decrease the increase in the $I_{Ca,L}$ caused by isoprenaline in both mouse and human AMs (269), showing that PDE2 most probably mediates the inhibition of β-adrenergic signaling by C-type natriuretic peptides in AMs. In healthy human AMs, pretreated with β-adrenergic stimulation or PDE3 inhibition, the NO donor SNAP leads to a decrease in the $I_{Ca,L}$, likely mediated via PDE2 (270). This negative feedback by NO on β-1/2 adrenergic signaling in human AMs does not occur through β-3-eNOS stimulation, as seen in neonatal rat VMs (271). This is because in human AMs, β-3 adrenergic receptors stimulate a rise in cAMP and increase in the $I_{Ca,L}$ positive inotropy (272). This suggests that when the [cAMP] is high around LTCC, a NO-sGC-cGMP domain negatively regulates the $I_{Ca,L}$ via stimulation of PDE2-dependent cAMP hydrolysis. PDE5 may also regulate this cGMP domain in human AMs (270).

PDE3 mediates the positive effects of cGMP and cGMP-producing agonists on $I_{Ca,L}$ (270) and positive inotropy (71). SNAP as a NO donor leads to sGC-dependent and PKA-dependent increase in the $I_{Ca,L}$ in the absence of any additional stimuli in human AMs (270). This is replicated by PDE3 inhibition in human AMs (71, 270). NO also leads to an increase in the $I_{Ca,L}$ via the cGMP-PDE3-cAMP pathway in human AMs (273). Wang et al. (274) found in adult cat AMs that the positively inotropic α-1 adrenergic receptor activation causes an eNOS- and sGC-dependent increase in the $I_{Ca,L}$ and that NO leads to an sGC- and PDE3-dependent increase in the $I_{Ca,L}$ (274). Similarly, in human AMs, cGMP analogs stimulate $I_{Ca,L}$ via PDE3 (275). These data support the existence of a NO-sGC-cGMP domain that positively regulates the $I_{Ca,L}$ and contractility in human AMs, via inhibiting PDE3-mediated cAMP hydrolysis around the LTCC.

The Role of Phosphodiesterases in Regulating the Electrical Activity in Human Atrial Myocytes

The role of PDEs in regulating AM electrical activity in humans is poorly understood but has been explored in mice (205). Only the effect of PDE8 inhibition has been studied directly on the electrical activity of healthy human AMs and no effects on the resting membrane potential, action potential duration (APD), or action potential plateau were observed (24). PDE2 inhibition does not appear to alter the increase in $I_{Ca,L}$ caused by isoprenaline in mouse (205) or human AMs (269). The effect of PDE3 inhibition on atrial electrical activity has been investigated in patients with severe heart failure (276) or idiopathic-dilated cardiomyopathies (277). PDE3 inhibition with enoximone was found to increase the atrial conduction speed (276) and reduce the atrial refractory period in human patients (277). It is not clear whether these were direct effects on AMs or not. PDE3 and 4 inhibition in humans AMs, if this only potentiates the basal $I_{Ca,L}$, would be expected to increase the APD and possibly increase the conduction velocity. However, in mice AMs, PDE3 inhibition did not affect the APD (205). This is not due to the absence of PDE3 in mice AMs but is explained by the lack of effect of PDE3 inhibition on the $I_{Ca,L}$ in mice AMs (205). This lack of effect of PDE3 inhibition on the $I_{Ca,L}$ is unlike the increase in $I_{Ca,L}$ seen in human AMs (71). In contrast to the lack of effect of PDE3 inhibition, PDE2 or PDE4 inhibition increased the APD without affecting the action potential amplitude or upstroke velocity in mice AMs (205). Pertinently, PDE4 inhibition in mice and humans AMs (71) increased the $I_{Ca,L}$ (205), which interestingly is not seen in rabbit AMs (64). In VMs, PDE4 inhibition caused an increase in APD in mice and guinea pigs (204, 278). These observations support the hypothesis that PDE4 inhibition may increase the APD also in human AMs like reported in mice.

However, PDE4 inhibition might also affect hyperpolarizing K^+ currents and thus the APD, as in rodent VMs, PDE4D3 inhibits the increase in the slowly rectifying K^+ current (I_{Ks}) and shortening of the APD following β-adrenergic stimulation (260, 261, 279, 280). This is through PDE4D3 presence in a signaling complex containing adenylyl cyclase 9, Yotiao, and KCNQ channels. In human AMs, like in VMs, PDE4D3 is also present and PDE4s appear present in their sarcolemma (71), supporting the hypothesis that in human AMs, PDE4 activity may inhibit the increase in I_{Ks} following β-adrenergic stimulation. Contrastingly, PDE4s anchored near POP-EYE DC1 proteins protect against the inhibition of TREK currents by cAMP in mouse SANCs (262, 263) meaning PDE4 activity can also inhibit a decrease in a K^+ current following β-adrenergic stimulation. These TREK K^+ currents via TREK channels are also present in rat AMs (281). We hypothesize that PDE4 may protect against the observed inhibition of TREK currents by noradrenaline and the prolongation of the APD in rat AMs (282). Overall, further experiments in combination with computer modeling are needed to work out the role of PDE2, 3, and 4 in the human AMs' action potentials and the mechanism of any effects of these PDEs on AMs' action potentials.

Potential Function of Phosphodiesterase 8 in Healthy Atrial Myocytes

The function of PDE8 in healthy AMs is unknown but may be physiologically important. PDE8 might act as an important regulator of the effect of β-adrenergic signaling on the LTCC and CaT in human AMs. This is because of PDE8B's physical association and visual colocalization with the LTCC and PDE8B's regulation of the basal [cAMP] close to the plasma membranes in human AMs (24). Moreover, PDE8As negatively regulate the increase in the CaT and $I_{Ca,L}$ by β-adrenergic stimulation in mice VMs (222). Alternatively, PDE8B's high cAMP affinity, presence, and basal hydrolysis of cAMP at or near the sarcolemma and PDE8B's association with the LTCC potentially means that PDE8B regulates low [cAMP] regions near the LTCC. The LTCC in AMs is present in caveolae at the surface of AMs and axial and transverse tubules. Thus, PDE8B2 may modulate the activity of some of the multiple different proteins present in the axial and transverse tubules, caveolae, or the closely associated SR (24). In mice VMs, PDE8A activity inhibits basal SR Ca^{2+} reuptake and Ca^{2+} spark frequency without affecting basal inotropy (222), providing further support for this hypothesis. Junctophilin tethers LTCC close to RyR2s (283), indicating that the components of the LTCC complexes could be in close proximity with RyR2, which would strengthen the hypothesis that these components can functionally interact with RyR2s and regulate them. Therefore, PDE8B potentially could modulate SR Ca^{2+} handling in AMs.

Summary of the Role of Phosphodiesterases in Atrial Myocytes

In summary, PDEs2–4 are established as important in regulating basal Ca^{2+} signaling, contractility, the LTCC in human AMs, and the physiological responses of AMs to a variety of cGMP- and cAMP-generating stimuli (Fig. 3). PDE2–4 also potentially alter electrical signaling in human AMs. PDE1 and PDE8 are present but their physiological function in AMs is unknown. As cardiac arrhythmias involve the interplay between Ca^{2+} and electrical signaling, PDE2–4, and maybe also PDE1 and PDE8, potentially play important roles in atrial arrhythmias and thus they may be good therapeutic targets. This will therefore be discussed next.

THE ROLE OF PHOSPHODIESTERASES IN PAROXYSMAL ATRIAL FIBRILLATION AND THEIR POTENTIAL AS THERAPEUTIC TARGETS

Limited Clinical Data are Available on the Therapeutic Potential of PDE-Targeted Therapies

There is a lack of clinical trials' data available on the effectiveness of PDE inhibitors on the prevention of paroxysmal AF. A comprehensive search of a publicly available clinical trial database (clinicaltrails.gov) and PubMed, at the time of writing, revealed that there are no on-going and only a few completed clinical trials using a phosphodiesterase inhibitor that investigated or reported an effect of specific phosphodiesterase inhibitors on the incidence of AF (276, 284–288) (see Supplementary discussion for details of the search performed and results obtained). These clinical trials or retrospective analyses are of limited scope because they all focused on the effect of PDE3 inhibitors (276, 284–288). In addition, most of these studies only investigated the incidence of AF in patients with severe heart failure and these are only a subset of all patients at risk of developing AF (276, 284–286). One of these studies investigated the incidence of postoperative AF in patients with heart failure (286). Most of these studies found that AF or supraventricular arrhythmias are a commonly reported event after use of a PDE3 inhibitor (284–286). Nevertheless, these are not placebo-controlled studies (284–286) and the development of AF in patients with heart failure is a common occurrence (74, 75). In fact, a similar study found that the inducibility of atrial arrhythmias or AF was not increased by treatment with a PDE3 inhibitor (276). It is therefore unclear if PDE3 inhibitors cause AF in patients with heart failure. Another study retrospectively found an increased incidence of postoperative AF in cardiac surgery patients who took a PDE3 inhibitor (287). However, as it was a retrospective study (287), it is unclear if there was an unknown or unreported difference between the patients who were treated or not treated, with the PDE3 inhibitor, that can explain the different incidence of AF between the groups. The only placebo-controlled study we have identified found that the PDE3 inhibitor olprinone reduced the incidence of postoperative AF in patients undergoing pulmonary resection for lung cancer (288). The location of the PDE3 activity that is responsible for the pro arrhythmic role of PDE3 in these patients remains unclear. Overall, there is little robust clinical data on the effectiveness of PDE inhibitors to prevent paroxysmal AF. The rest of this section will therefore focus on the experimental versus clinical data.

Phosphodiesterase 2, 3, and 4 are Targets for the Inhibition of Ectopic Automaticity in Atrial Myocytes

Reduced PDE2 cAMP hydrolysis in mice, caused by reduced expression of natriuretic peptide receptor B, is associated with

increased susceptibility to burst pacing or isoprenaline-induced atrial fibrillation (269). The response to β-adrenergic stimulation in these mice with reduced PDE2 cAMP hydrolysis is also associated with increased proarrhythmic alterations in AMs' electrophysiology (e.g., increased dispersion of action potential durations) and Ca^{2+} handling (e.g., increased spontaneous Ca^{2+} events) (269). This suggests PDE2 may protect against atrial arrhythmias in mice through effects on both Ca^{2+} handling and electrical activity. However, this needs to be investigated directly.

PDE3 and PDE4 activity negatively regulates basal ectopic activity and β-1 adrenergic and 5-HT-stimulated arrhythmias in the atrial trabeculae of patients with sinus rhythm and those with paroxysmal AF (22, 71). PDE4 inhibition with rolipram increases the frequency of Ca^{2+} sparks, Ca^{2+} waves, and spontaneous depolarizations in human AMs, suggesting that PDE4 plays an antiarrhythmic role. PDE3 or PDE4 inhibition also increased the maximal frequency and potency of β-1 adrenergic receptor-stimulated arrhythmias in human atrial trabeculae, while only PDE4 increased β-2 adrenergic-stimulated arrhythmias (71). Similarly, PDE3 or PDE4 inhibition increases the propensity for 5-HT-induced atrial arrhythmias in the atrial trabeculae from patients with sinus rhythm or with paroxysmal AF (22). These functional studies support a role for PDE3 and 4 in protecting against atrial arrhythmias. However, it is unclear whether a decrease in PDE3 or 4 activity is involved in the triggering of AF in human patients.

Interestingly, Genome wide association studies (GWAS) have identified 10 SNPs associated with AF, which mapped to introns of the AKAP6 gene (289, 290). The functional effect of these SNPs and validation that these SNPs alter AKAP6 gene expression has to our knowledge not been investigated. However, AKAP6 encodes mAKAP, which tethers and so restricts PDE4D3 and PKA activity to around the RyR2, at least in rodent VMs (253, 291–294). mAKAP is also reported to bind to the Na^{+}-Ca^{2+} exchanger (NCX) (295). Through mAKAP's binding to NCX, PDE4D3 may play a role in regulating NCX, although the regulation of NCX by cAMP is unclear (296–299). Therefore, these SNPs could feasibly lead to alterations in PDE4D3 localization or regulation around two key players in ectopic cardiac action potentials.

The major site of ectopic activity triggering paroxysmal and persistent AF in humans is the pulmonary vein myocardium (300, 301), but the experiments mentioned above were performed on isolated human AMs or atrial trabeculae that, although very similar, are not the pulmonary vein cardiomyocytes or myocardium. Whether these arrhythmogenicity-modifying roles for PDE3 and 4 are also seen in the pulmonary vein myocardium is discussed in the next section.

Phosphodiesterase 1,3,4, and 5 are Target for Controlling Pulmonary Vein Myocardium Automaticity

Specifically targeting spontaneous pacemaking in the pulmonary vein myocardium pharmacologically is a potential new therapeutic strategy for AF. Only the role of PDE1,3,4, and 5 has been investigated in pulmonary vein automaticity so far. Most promisingly, Yugo et al. (209) found that PDE1 inhibition with ITI-214 reduced the spontaneous electrical activity in rabbit pulmonary vein myocardial tissue and this was associated with a reduction in the late sodium current, $I_{Ca,L}$, and NCX current (209). In addition, Lin et al. (216) found that the PDE5 inhibitor, sildenafil, reduced the spontaneous activity and the isoprenaline-stimulated increase in rabbit pulmonary vein cardiomyocytes spontaneous activity (216). Moreover, sildenafil also can potently inhibit PDE6, another cGMP-hydrolyzing PDE with a similar catalytic site (302). Therefore, it remains to be proven by using genetic manipulations of PDE5 and PDE6, which PDE may be a good target for preventing AF.

Although PDE3 or PDE4 inhibition increases the basal spontaneous activity of pulmonary vein myocytes (216), PDE3 inhibition did not affect the response to isoprenaline (216). The exact mechanisms of this effect are unclear and basal activity of the pulmonary vein myocardium is poorly understood. The authors reported that the effects of PDE3 inhibition were dependent on PKA and PKG, suggesting other cAMP- and cGMP-hydrolyzing PDEs like PDE1 and 2 that negatively regulate SAN automaticity may also be important. cGMP plays a complicated role with cGMP being able to both stimulate (in PDE3-regulated domains) and inhibit (in PDE5- or 6-regulated domains) pulmonary vein automaticity. Either way, PDE3-activating drugs or sildenafil may be viable treatment options for the early stages of AF. However, just because inhibition of PDE3 or PDE4 appears proarrhythmic, this does not mean that activation of PDE3 would necessarily be antiarrhythmic. This is because each aspect of atrial Ca^{2+} and electrical signaling is in a delicate equilibrium, and increases or decreases of a single part of Ca^{2+} or electrical signaling can trigger arrhythmias. For example, both hyperphosphorylation or hypophosphorylation of RyR2 at the PKA phosphorylation sites increases SR Ca^{2+} leak (303, 304), suggesting that if PDE activity is too high or too low around RyR2 then this might promote arrhythmias.

Phosphodiesterase Remodelling is Different in Paroxysmal Atrial Fibrillation and is Potentially Protective against Arrhythmias

In contrast to observations in chronic AF, patients with paroxysmal AF show increased activity and expression of PDE8A with increased localization at the membrane/subsarcolemmal space in AMs. There is no change in the fraction of IBMX-sensitive PDEs in regulating cAMP in subsarcolemmal domains (24). Inhibition of PDE8 in human AMs does not lead to changes in the resting membrane potential, APD, plateau potential, or $I_{Ca,L}$ (24). This increase in PDE8A expression and its distribution at/or just under the membrane in paroxysmal AF without affecting the LTCC activity or action potential may be a mechanism to protect against basal automaticity and/or the triggering of arrhythmias by cAMP-producing agonists. This is because in patients with paroxysmal AF there is a lack of hyperphosphorylated RyR2s at PKA or CaMKII phosphorylation sites (305), while PDE8A activity in mouse VMs protects against basal Ca^{2+} sparks and negatively regulates the increase in the LTCC and CaT in response to β-adrenergic stimulation (222). Increased PDE8A expression in human AMs may therefore represent an antiarrhythmic response to the reported increased SR Ca^{2+} leak [caused by

increased RyR2 expression (305), reduced phosphorylation via striated preferentially expressed protein kinase (SPEG) (306)], increased SR Ca^{2+} uptake [via increased phospholamban phosphorylation (305)], and delayed after depolarizations (DADs) in patients with paroxysmal AF (305).

Summary of the Role of Phosphodiesterases in Paroxysmal Atrial Fibrillation and Their Potential as Therapeutic Targets

Overall PDE2-5 and PDE8 are potential targets for preventing the triggering of atrial arrhythmias via either ectopic automaticity in AMs or the pulmonary vein myocardium (Fig. 4). However, the exact PDE isoforms or signalosomes responsible for the antiarrhythmic or proarrhythmic roles of these PDEs are unknown. Furthermore, there is not much known about whether PDE expression and activity changes in patients with paroxysmal AF. Patients with paroxysmal AF would be the main patients who could benefit from PDE-targeting drugs to prevent the triggering of AF. Thus, whether such treatment targets would be efficacious is unclear. Changes in PDEs in patients with chronic or persistent AF are much better documented.

THE ROLE OF PHOSPHODIESTERASES IN PERSISTENT AND CHRONIC ATRIAL FIBRILLATION AND THEIR POTENTIAL AS THERAPEUTIC TARGETS

Only Two Clinical Studies Have Investigated the Influence of PDE Inhibitors in Patients with Chronic Atrial Fibrillation

The effect of phosphodiesterase inhibitors on patients with chronic AF (cAF) has to our knowledge only been investigated twice (106, 107). These studies (106, 107) were returned by our search on PubMed (see Supplemental discussion). One paper found that treatment with the PDE3 inhibitor cilostazol for 6 mo improved bradycardia in bradycardic cAF patients with

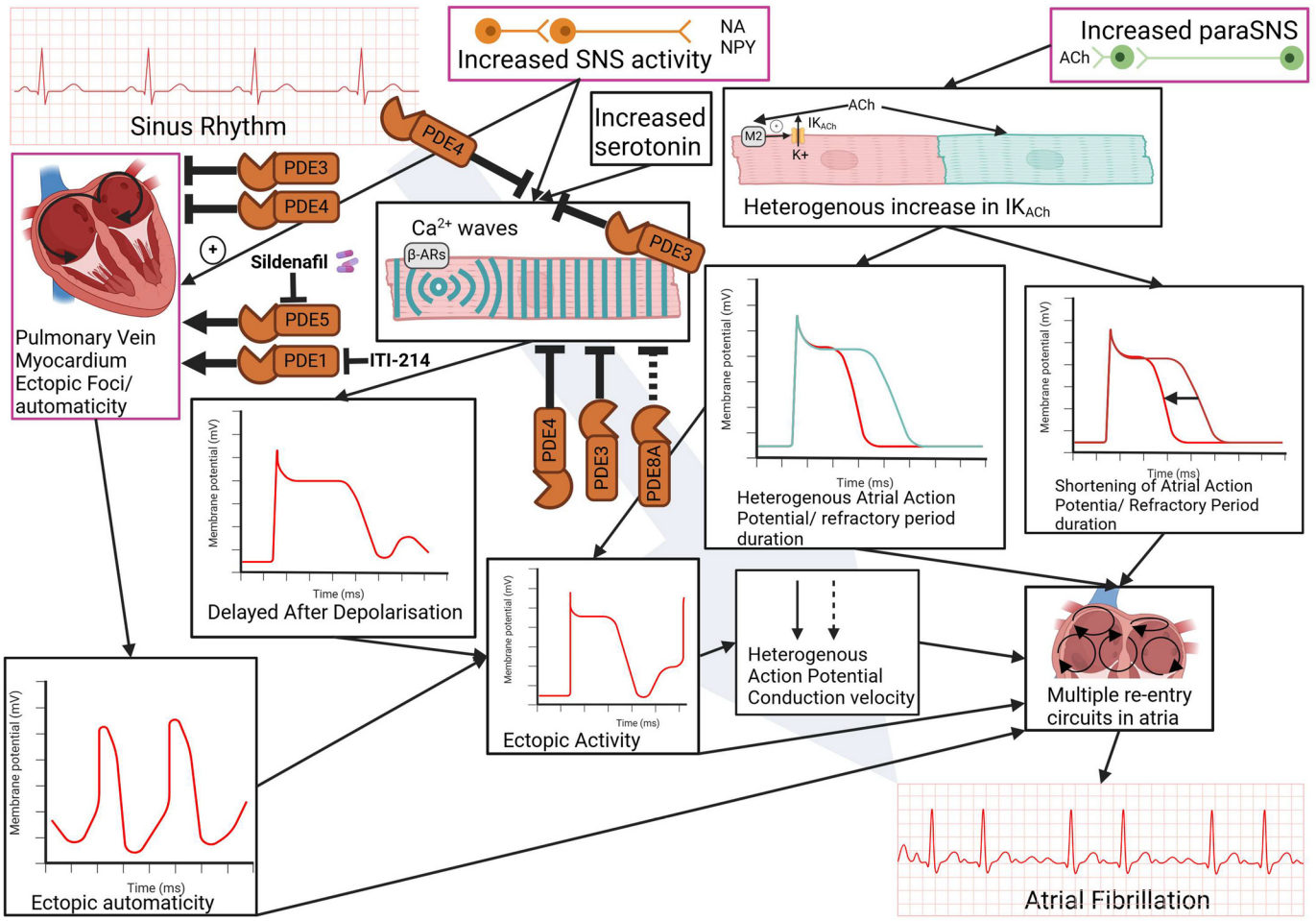

Figure 4. Roles of PDEs in paroxysmal atrial fibrillation. Increased activity of the sympathetic nervous system (SNS), the parasympathetic nervous system (paraSNS), or increased pulmonary vein ectopic activity are all thought to be able to cause atrial fibrillation. They do this by promoting ectopic atrial electrical activity (i.e., an arrhythmia trigger) and/or promoting the creation of electrical substrates (heterogeneous refractory periods, action potential velocities, shortened atrial action potentials), therefore allowing ectopic electrical activity to lead the generation of multiple self-sustaining re-entry circuits within the atria and thus atrial fibrillation. PDE1,3,4,5 may modulate pulmonary vein ectopic automaticity and thus paroxysmal AF. PDE3,4 and maybe PDE8A may modulate the proarrhythmic effects of increased SNS and thus also paroxysmal AF. Solid lines represent roles with strong evidence. Dotted lines represent potential roles with inconclusive supporting evidence. ACh, acetylcholine; NA, noradrenaline; NPY, neuropeptide Y; paraSNS, parasympathetic nervous system; SNS, sympathetic nervous system. Created in BioRender. Burton, R. (2025) https://BioRender.com/u57p885.

heart failure, and this was compared with before treatment with cilostazol, not placebo (106). The second paper found that cilostazol, after at least 2 mo, increased the minimal heart rate, decreased the number of pauses, and mean heart rate was increased in patients with cAF associated with bradycardia episodes (107). In both studies, cardiac function improved, the levels of natriuretic peptides decreased, and no deterioration of cAF was reported (106, 107). Unfortunately, it is unclear whether the beneficial effects of PDE3inhibition on these clinical measures involved effects on AMs or were solely mediated via the more obvious mechanisms of increasing SAN or atrioventricular node automaticity directly or indirectly via increasing sympathetic tone. The rest of this section will therefore focus on experimental data where the mechanisms of action are easier to work out.

Phosphodiesterase Remodeling in Patients with Persistent or Chronic Atrial Fibrillation

There are marked decreases in PDE3 and PDE4 (21, 71, 225, 307), and some evidence suggests decreased PDE2 activity (308) in patients with cAF (See Table 4). Total atrial PDE activity assays in tissue homogenates also indicated decreased PDE activity in patients with chronic AF (71). However, direct in vitro FRET-based cAMP measurements in human AMs from patients with cAF reveal that total PDE activity in sarcolemmal and RyR2 domains is increased and cytosolic PDE activity is unchanged (309). These data imply that PDE activity is decreased in other cell types or that in vitro assays altered the activity of PDEs. Doll et al. (308) reported a decrease in PDE2A expression in human atrial tissue samples (308), while others have reported no change (21). These studies did not look specifically at AMs in their tissue samples, so differences in tissue collection and/or the cell types present in samples along with variable patient populations and characteristics may explain such differences. PDE3A and PDE4B expression (21, 225, 307), and PDE3 (23) and PDE4 (71) activity is decreased in AMs from humans with cAF compared with those in sinus rhythm.

The cytosolic rise in cAMP caused by complete PDE3 or PDE4 inhibition is reported to be smaller in AMs from patients with cAF versus patients with sinus rhythm (23, 268). This suggests there is reduced PDE3 and PDE4 presence and activity in cytosolic domains (or a domain regulating the cAMP flux from sarcolemmal to cytosolic domains). This explanation is supported by the finding that complete PDE inhibition had the same effect on cytosolic [cAMP] in AMs from patients in sinus rhythm or cAF (309), meaning that the reduced response to PDE3 or PDE4 inhibition could not be caused by reduced basal cAMP production. Despite decreased PDE3 and PDE4 activity in cytosolic domains, the same effect of complete PDE inhibition in patients with sinus rhythm and cAF suggests that there must be a compensatory increase in the activity of a cAMP-hydrolyzing PDEs other than PDE3 or 4 that regulates cytosolic cAMP to account for the lack of difference in total cytosolic PDE-mediated cAMP hydrolysis between patients with sinus rhythm versus cAF (309). Supportingly, in patients with cAF, there is a paradoxical decrease in the rise in cytosolic cAMP caused by β-adrenergic stimulation (309). These results could be explained by the increased activity of other cAMP-hydrolyzing PDE families that regulate cytosolic cAMP levels. However, other changes in β-adrenergic receptor signaling may also reduce the isoprenaline-stimulated cytosolic cAMP signal.

The effect of PDE3 or 4 inhibition on sarcolemmal cAMP levels is the same in AMs from both patients with cAF and sinus rhythm (23), despite a greater rise in [cAMP] caused by complete PDE inhibition (23, 309). This suggests PDE3 and PDE4 activity is sustained in subsarcolemmal domains in cAF but that there is increased activity of other cAMP-hydrolyzing PDE families. In patients with cAF, the β-adrenergic receptor-stimulated rise in cAMP around RyR2 and the LTCC is the same as in patients in sinus rhythm (309). This supports the idea that the activity of cAMP-hydrolyzing PDEs is capable of hydrolyzing large amounts of cAMP rapidly, like PDE3 and 4, is sustained if cAMP production is not altered in AMs from patients with cAF.

Increased PDE8 activity explains the increased PDE activity observed in, at least, sarcolemmal domains in AMs of patients with cAF (24). PDE8B expression and PDE8 activity are both increased in AMs from humans with cAF (24). In contrast, the amount of cAMP hydrolysis by PDE8 in cytosolic domains is unchanged but its hydrolysis of subsarcolemmal cAMP is vastly increased in AMs from patients with cAF versus sinus rhythm (24). PDE8 activity increases in subsarcolemmal cAMP domains in human AMs (24). Subsarcolemmal domains also contain RyR2 and LTCCs so PDE8 potentially increasingly regulates LTCC and RyR2s in AMs from patients with cAF. In patients with cAF, there is a decreased rise in cytosolic cAMP caused by β-adrenergic stimulation but a normal rise in cAMP around RyR2s and the LTCC (268, 309). This suggests the increase in PDE8 activity around the sarcolemma and RyR2s does not affect the cAMP response to β-adrenergic signaling at RyR2s or LTCC but may inhibit the cytosolic cAMP signal. Interestingly, this retention of cAMP signals around the LTCC and RyR2 but the loss of cytosolic cAMP signals reflects what is seen in the VMs of patients with heart failure (257).

The consequences of the changes in the expression of these PDEs on arrhythmias are unclear. However, patients with cAF do have an increased frequency of inward transient currents driven by increased PKA activity but similar sensitivity to β-adrenergic-induced increases in transient inward currents (309). It may be that PDE remodeling does not predispose patients with cAF to β-adrenergic-induced arrhythmias, but it may contribute to the observed higher basal propensity to transient inward currents and ectopic activity (309). Potential mechanisms and the rationale behind the changes will be discussed next.

Mechanism by Which Reduced Cytosolic Phosphodiesterase 3 and 4 in Chronic Atrial Fibrillation Might be Proarrhythmic

PDE3- and PDE4-regulated cAMP nanodomains can respond differently to the net global cytosolic cAMP response. Therefore, despite a normal global cytosolic [cAMP] or reduced global cytosolic rise in [cAMP] in response to β-adrenergic stimulation, cAMP signaling may be higher in specific nanodomains. Thus, reduced cytosolic PDE3 and PDE4 activity could lead to the loss of their negative regulation of

Table 4. *Changes in PDEs and AKAPs expression in atrial samples from human patients with atrial fibrillation (evidence mostly from transcriptomics or proteomics data)*

Protein Name	Net Change in Chronic AF	Evidenced by	Sample Location and Type of AF	Control Patients	References
PDE1C	No change	Transcriptomics	Human right and left atrial appendage paroxysmal and long-standing persistent AF	Sinus rhythm with or without atrial dilation but undergoing open heart surgery	(21)
PDE2A	No change	Transcriptomics	Human right and left atrial appendage paroxysmal and long-standing persistent AF	Sinus rhythm with or without atrial dilation but undergoing open heart surgery	(21)
	Down	Proteomics	Human left atria, three patients left atria persistent or permanent AF	Three hearts from young men with no detected cardiac abnormalities	(308)
PDE3A	Down	Transcriptomics	Human right atrial appendage,permanent AF + coronary artery disease requiring bypass or mitral valve disease	Coronary artery disease requiring bypass or mitral valve disease	(307)
			Human left atrial appendage persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)
			Human right and left atrial appendage paroxysmal and long-standing persistent AF + require open heart surgery	Sinus rhythm with or without atrial dilation but undergoing open heart surgery	(21)
PDE3B	No change	Transcriptomics	Human right and left atrial appendage paroxysmal and long-standing persistent AF + require open heart surgery	Sinus rhythm with or without atrial dilation but undergoing open heart surgery	(21)
PDE4B	Down	Transcriptomics	Human right and left atrial appendage paroxysmal and long-standing persistent AF + require open heart surgery	Sinus rhythm with or without atrial dilation but undergoing open heart surgery	(21)
			Human left and right atria with persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)
PDE7A	Down	Transcriptomics	Human pulmonary vein-left atrial appendage, persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)
PDE8B	Up	Transcriptomics	Human right atrial appendage, left atrial appendage, persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)
		Western blot + single myocyte immunofluorescence	Right atrial tissue patient with chronic AF under open-heart surgery	Sinus rhythm patient undergoing open-heart surgery	(24)
AKAP1	Down	Transcriptomics	Human left atrial appendage persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)
			Human right atrial appendage,permanent AF + coronary artery disease requiring bypass or mitral valve disease	Coronary artery disease requiring bypass or mitral valve disease	(307)
AKAP2	Up	Proteomics	Left atria, three patients, persistent or permanent AF	Three hearts from young men with no detected cardiac abnormalities	(308)
AKAP3	Down	Transcriptomics	Human AF right atrial appendage persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)
AKAP8 (AKAP95)	Up	Transcriptomics	Human pulmonary vein-left atrial appendage with persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)
AKAP9 (Yotiao)	Down	Transcriptomics	Right and left atrial appendage paroxysmal and long-standing persistent AF + require open heart surgery	Sinus rhythm with or without atrial dilation but undergoing open heart surgery	(21)
AKAP12 (gravin)	Up	Proteomics	Left atria, three patients, persistent or permanent AF	Three hearts from young men with no detected cardiac abnormalities	(308)
	Down	Transcriptomics	Human right atrial appendage, permanent AF + coronary artery disease requiring bypass or mitral valve disease	Coronary artery disease requiring bypass or mitral valve disease	(307)

Continued

Table 4.— *Continued*

Protein Name	Net Change in Chronic AF	Evidenced by	Sample Location and Type of AF	Control Patients	References
AKAP13	Up	Proteomics	Left atria, three patients, persistent or permanent AF	Three hearts from young men with no detected cardiac abnormalities	(308)
PI3K-γ	Up	Transcriptomics	Right and left atrial appendage paroxysmal and long-standing persistent AF + require open heart surgery	Sinus rhythm with or without atrial dilation but undergoing open heart surgery	(21)
			Human left atrial appendage, pulmonary vein-left atrial appendage with persistent AF (>7 days) + mitral valve disease	Mitral valve disease + sinus rhythm	(225)

At the level of transcription, there are no reported differences in the expression of PDE1C or PDE3B but a decrease in PDE3A, 4B, 7A expression. PDE8B shows increased expression at both the transcriptomic and protein levels. AKAP2 and AKAP13 expression is increased at the level of protein expression. There is increased expression of AKAP8 and PI3K-γ proteins and upregulation at the level of mRNA transcription. Changes in the expression of AKAP12 have been investigated, but conflicting results have been found. The expression of AKAP12 is increased at the proteomic level but not at the transcriptomic level. This may be because of differences in the transcription and translation of AKAP12 but may also reflect differences between RA and LA samples or patient populations. It is unclear whether there are changes in the expression of PDE2A. PDE2A transcription is either not changed or is decreased, which again may be a result of differences in the population of the patients from which the samples are collected or differences in the location of where atrial tissue samples are collected.

proarrhythmic pathways. Interestingly, 5-HT-induced arrhythmias (but not the positive inotropic effects) become insensitive to PDE3 and PDE4 inhibition in atrial strips from patients with persistent AF (22), while proarrhythmic adenosine A_{2A} receptor stimulates a larger cytosolic cAMP signal in cAF cells (268). This implies that as AF progresses, the efficacy of PDE3 and PDE4 activators as antiarrhythmics may decrease, necessitating treatments to restore their expression and localization.

Reduced cytosolic PDE3 activity combined with reduced PDE3A expression could increase SR Ca^{2+} content or uptake in AMs from patients with cAF versus sinus rhythm (309). This would be via decreased PDE3A-mediated negative regulation of SERCA2a through PDE3A-AKAP18delta's regulation of the phosphorylation of phospholamban as found in human VMs (244). However, basal SR Ca^{2+} content in patients with cAF is not increased and neither is the increase in SR load in response to β-adrenergic stimulation greater (309), despite the reported increased PKA-mediated phosphorylation of phospholamban in cAF (310). This suggests that reduced cytosolic PDE3A in the cytosol does increase the susceptibility of patients with cAF to basal or β-adrenergic-stimulated SR Ca^{2+} overload and spontaneous Ca^{2+} release events and arrhythmias.

Reduced cytosolic PDE3 and or PDE4 activity could increase proarrhythmic EPAC1-mediated signaling in the atria that has been shown to cause AF in a mouse model (311). EPAC1 can stimulate CaMKIIδ signaling, and this would explain the CaMKII-dependent increased hyperphosphorylation of the RyR2 and increased Ca^{2+} spark frequency in AMs from patients with cAF versus sinus rhythm (309). These findings support the idea that a loss of cytosolic PDE3 and PDE4 could promote EPAC1 and CaMKII activation around RyR2s and the higher-frequency spontaneous Ca^{2+} release events seen in AF. Notably, PDE4 inhibition does increase spontaneous Ca^{2+} release events (71), although diastolic Ca^{2+} is also increased in AMs from patients with cAF (312) and this may instead explain the increased CaMKII phosphorylation of RyR2s versus reduced PDE3 and 4 expression and activity. Moreover, the basal higher frequency of transient inward currents seen in AMs of patients with cAF is PKA, not CaMKII dependent (309), suggesting that this CaMKII-dependent regulation of spontaneous Ca^{2+} release events may not be directly related to arrhythmias in human AMs from patients with cAF.

Changes in Subsarcolemmal Phosphodiesterase 3 Localization and Activity in Chronic Atrial Fibrillation is Potentially Antiarrhythmic

Subsarcolemmal PDE3 activity negatively regulates β-adrenergic receptor cAMP signaling (71). In patients with cAF, there is increased expression of the phosphoinositide 3-kinase-γ (PI3Kγ) (21, 225) (see Table 4) and thus likely increased tethering and maintenance of the negative regulation of β-2-adrenergic receptors by PDE3 and PDE4 (313). NO-mediated blunting of the β-2 adrenergic response is retained in AMs from patients with cAF (314), suggesting that the negative regulation of proarrhythmic β-2 adrenergic receptor signaling by NO/cGMP is retained. This is supported by the finding that β-adrenergic signaling is not more proarrhythmic in patients with chronic AF versus patients in sinus rhythm despite decreases in cytosolic PDE3 activity (309).

Potentiation of $I_{Ca,L}$ by cGMP appears to be lost in cAF as cGMP-induced cAMP signal and PKA-mediated phosphorylation and stimulation of $I_{Ca,L}$ is lost in AMs from patients with cAF (270), potentially reflecting the loss of PDE3 from the LTCC complex. There is a reduced importance of PDE3 in regulating the cAMP signal around LTCC in response to 5-HT in human AMs from patients with cAF (268) providing further evidence for reduced PDE3 regulation of the LTCC. This loss of cGMP-PDE3-mediated stimulation of the LTCC via reduced PDE3A expression may be protective against cellular Ca^{2+} overload induced by natriuretic peptides, NO, or NO-producing agents such as α-adrenergic agonists. Supporting this, olprinone, a

PDE3 inhibitor inhibits postoperative AF in patients with elevated BNP levels and lung cancer (288). Similarly, in dogs (where NO production or natriuretic peptide release may have been stimulated via rapid atrial pacing induced a rise in intracellular Ca^{2+}), PDE3 inhibition with cilostazol suppressed rapid atrial pacing-induced AF in vivo (315). Moreover, β-2 adrenergic receptor-induced ectopic beats in human atrial strips were abolished by PDE3 inhibition (71). Crucially, as these experiments were performed on whole organisms or tissues, it is unclear whether the antiarrhythmic effects of PDE3 inhibition in these experiments were via effects in AMs or other cell types. However, the functional loss of PDE3 from the LTCC domain may represent an antiarrhythmic mechanism that helps protect AMs from Ca^{2+} overload caused by natriuretic peptides or NO-producing agents.

Subsarcolemmal PDE3 may protect against atrial arrhythmias. This is because PDE3 negatively regulates HCN2/4 channels, at least in the mouse SAN (316) and patients with cAF have increased expression of HCN2/4 (317–319). Moreover, HCN 2/4 channels mediate hyperpolarization-induced depolarizing Na^+ and Ca^{2+} currents and crucially are positively regulated by cAMP-PKA-mediated activity in mouse SAN cells (316). cAMP-PKA stimulation of HCN2/4 is crucial for sustained automaticity in the rabbit SAN (227) and thus potentially ectopic AMs. HCN2/4 may therefore represent the major source of the PKA-dependent transient inward currents observed in AMs from patients with cAF (309). Basal PKA-mediated stimulation of HCN channels in the mouse SAN is specifically under the control of PDE3 but not PDE4 (316). Meaning that there may be an increased antiarrhythmic importance of PDE3's negative regulation of HCN2/4 channels in patients with cAF AMs.

Changes in Subsarcolemmal Phosphodiesterase 4 Localization and Its Sustained Activity is Likely Antiarrhythmic in Chronic Atrial Fibrillation

Subsarcolemmal PDE4 in human AMs negatively regulate LTCC and subsarcolemmal RyR2s (71). Thus, subsarcolemmal PDE4 activity likely protects against excess Ca^{2+} entry and crucially subsarcolemmal Ca^{2+} sparks and waves, through subsequent triggered depolarizations via activation of depolarizing NCX or altering the properties of other ion currents in the membrane (e.g., $I_{Ca,L}$ or K^+ currents) through CaM or CaMKII activity (312).

In cAF AMs, cAMP's regulation of KCNQ1 channels and subsequently the I_{Ks} it conducts is likely lost or reduced. This is due to decreased expression of AKAP9/Yotiao (21), which tethers PDE4D and PKA to KCNQ1 channels in mouse VMs (260, 261, 279). In mouse VMs, PDE4D negatively regulates β-adrenergic stimulation of this K^+ current (260, 261, 279). Therefore, loss of AKAP9 likely leads to a loss of the PDE4D-mediated negative regulation of subsarcolemmal cAMP domains around these K^+ channels. In addition, loss of AKAP9 likely prevents PKA-mediated stimulation of the basal I_{Ks} current and β-adrenergic-stimulated I_{Ks} current. This would lead to a prolonged QT interval that would be insensitive to β-adrenergic stimulation-induced QT shortening. This loss of repolarizing K^+ current stimulation would likely increase the susceptibility to early-after depolarizations (EADs) and DADs. However, the longer QT interval with sympathetic nervous stimulation may protect against the creation of a greater number of self-sustaining re-entry circuits by sustaining longer refractory period in AMs and allowing a longer time for Ca^{2+} removal and myofilament relaxation. Furthermore, β-adrenergic stimulation of I_{Ks} current is required to increase the frequency of spontaneous electrical activity in the guinea pig pulmonary vein myocardium (280). Therefore, the loss or decrease of AKAP9 could protect against β-adrenergic-stimulated ectopic activity in the pulmonary vein and the subsequently triggered AF.

Despite potentially proarrhythmic decreases in cytosolic PDE3 and 4 activities, β-adrenergic signaling is no more proarrhythmic in patients with cAF than those in sinus rhythm (268). In addition, there is a reduced cytosolic cAMP response to isoprenaline (268). What causes this decreased β-adrenergic receptor signaling in cAF? As mentioned in the paragraph above, loss of AKAP9 in patients with cAF may or may not protect against atrial arrhythmias. However, in cAF, there is also a prominent increase in phosphoinositide 3-kinase gamma expression (21, 225). Interestingly, PI3Kγ facilitates PDE3A, PDE4A, and PDE4B's activation via PKA (313). This leads to increased cAMP hydrolysis and subsequently reduced PKA-mediated phosphorylation and reduced stimulation of the LTCC following β-2-adrenergic receptor signaling in mice VMs (313). PI3Kγ is also required for the protection of phospholamban from PKA-mediated phosphorylation by PDE4 in mice VMs (320). PI3Kγ thus inhibits β-2-adrenergic receptor stimulation of SERCA (313) and a subsequent increase in SR Ca^{2+} load at least in mice VMs (313). Ultimately, these effects of Ca^{2+} handling mean PI3Kγ inhibits β-2-adrenergic receptors proarrhythmic signaling (313). Therefore, AMs of patients with cAF may have decreased proarrhythmic β-2 adrenergic receptor signaling through PI3Kγ-mediated increases in PDE3 and PDE4 activity following β-2 adrenergic receptor signaling.

Phosphodiesterase 8B2 Isoform is Potentially a Target for the Treatment of Chronic Atrial Fibrillation

AMs from patients with cAF have decreased $I_{Ca,L}$, LTCC hypophosphorylation, and show the subsequent shortening of the APD and depolarization of the plateau potential. These changes in $I_{Ca,L}$ and LTCC phosphorylation are associated with each other and are both caused by increased expression of atrial-specific PDE8B2 (24). This is because in cAF, PDE8B2 associates with the LTCC and negatively regulates LTCC basal phosphorylation and therefore $I_{Ca,L}$ (24). Moreover, PDE8 inhibition increases the APD and hyperpolarizes the action potential plateau in AMs from patients with cAF (24). In contrast, PDE8A expression is not increased in cAF and PDE8A localization to the cytosol of AMs in patients with sinus rhythm is not altered (24). This suggests that overexpression of PDE8B2 plays an important role in the electrical remodeling that occurs in cAF leading to an increased susceptibility to re-entry currents. Therefore, PDE8B2-specific inhibitors have been suggested as potential atrial specific antiarrhythmics that would increase the APD and thus protect against re-entry arrhythmias (24). In cAF, structural remodeling (321) and fibrosis (322) are thought to contribute substantially to the creation of multiple re-entry

circuits. Therefore, an increase in APD alone may be of limited efficacy in these patients. However, a recent result conflicts with the idea that all patients with cAF have increased atrial fibrosis (323).

The increase in PDE8 in cAF may provide a protective role. This is because in tissues from patients with persistent AF, 5-HT causes a reduced cytosolic cAMP signal and reduced positive inotropic and proarrhythmic response that cannot be reversed by concurrent PDE3 and 4 inhibitions (22). This suggests that increased PDE8 activity may be responsible for the protection from 5-HT-induced arrhythmias. Regulation of subsarcolemmal cAMP levels by PDE8 is increased in cAF (23, 24). Therefore, PDE8 may regulate subsarcolemmal antiarrhythmic targets other than the LTCC. For example, PDE8 may protect against further increases in already elevated RyR2 hyperphosphorylation, which causes spontaneous diastolic Ca^{2+} leak and increases diastolic cytosolic [Ca^{2+}] in cAF (312, 324). The PDE8B2 mediated decrease in the $I_{Ca,L}$ (24) explains the reduced Ca^{2+} influx (324) and the decreased strength of atrial contraction (325). This possibly protects AMs against Ca^{2+} overload and the metabolic stress caused by the constant fast rate of electrical depolarization caused by cAF. Therefore, PDE8B2 inhibition in patients with cAF may not be a good target in AF unless it is proven that PDE8B2 inhibition has no long-term negative effects on rapidly paced AMs from patients with cAF.

Summary of the Role of Phosphodiesterases in Persistent and Chronic Atrial Fibrillation and Their Potential as Drug Targets

Overall, it is unclear how the changes in PDE3,4 and PDE8 expression in chronic AF (or persistent AF; see Fig. 5) contribute to its pathology. The changes in PDE3,4 and 8 expression and activity may be protective and enable AMs to survive under the stress caused by cAF but this requires further research. Therefore, the therapeutic value of reversing the changes in PDE expression in chronic and persistent AF patients remains unknown.

THE NEED FOR HIGH-SPECIFICITY ATRIAL-TARGETED PHOSPHODIESTERASE THERAPIES IN ATRIAL FIBRILLATION

The optimal healthcare strategy for AF is to detect and treat AF early before considerable, irreversible, atrial remodeling occurs (326–328) as seen in cAF. However, as previously mentioned, current AF treatments are not always efficacious. For example, an average of 34% of patients with AF do not respond to flecainide (329). The lack of efficacy is clearly highlighted by the finding that despite conventional treatment, 77% of patients with paroxysmal AF develop a chronic form of AF within 14 years of diagnosis (330). Moreover, current treatments for AF can have serious adverse effects. For example, patients with AF who undergo pulmonary vein catheter ablation have been reported to have a 1 in 200 chance of developing a life-threatening cardiac tamponade (331), a complication 1 in 100 are reported to develop following radiofrequency pulmonary vein ablation (332). One in 200 patients with AF die within 30 days of catheter ablation for AF, with patients that develop complications during the procedure being four times more likely to die (333). These findings highlight the inherent risks of catheter ablation. Pharmacological treatments are no better with many associated with causing life-threatening ventricular arrhythmias or heart failure through impaired ventricular contraction (334–336). For example, 8% of patients treated with flecainide develop ventricular arrhythmias (337). The current antiarrhythmic treatments are contraindicated for 33–57% of patients with new-onset paroxysmal AF due to comorbidities or concomitant treatments (338). Overall, this means patients with new-onset paroxysmal AF can have a limited choice of treatment options with a substantial risk of significant adverse effects caused by treatments. Therefore, there is a clear medical need for novel treatments for AF. The development of improved rhythm control therapies has greater potential as early rhythm control is associated with better outcomes for patients with AF over rate control (339, 340). As highlighted above, PDEs in atrial or pulmonary vein cardiomyocytes may be key players in the triggering of paroxysmal and persistent AF before AF becomes permanent. Thus, PDEs may be an ideal target for the prevention of paroxysmal or persistent AF.

The targeting of PDEs for the prevention of paroxysmal or persistent AF relies on developing a PDE-targeting treatment that will benefit patients who often have an absence of, or only mild symptoms of AF (341–344) and who may already have other, though not ideal, treatment options. Therefore, any novel treatments need to be efficacious with a low risk of side effects. The current rhythm and rate control treatments for both cAF and paroxysmal AF are mostly nonpatented and thus cheaper treatments (345). Of the common rate and rhythm control medications used for AF (bisoprolol, atenolol, carvedilol, pindolol, bebivolol, diltiazem, digoxin, flecainide, sotalol, amiodarone, dronedarone, and dofetilide), only dronedarone is not available as a generic drug costing an average retail price of $800/mo in 2019 compared with generic antiarrhythmic drugs average retail price of $100/mo (345) in a single zip code in Los Angeles. Therefore, any novel treatments need to be much more efficacious in treating patients and better tolerated than current treatments or treat currently untreatable patients. This highlights the importance of developing safe, well-tolerated, and efficacious PDE-targeting therapies.

Unfortunately, currently available PDE-targeted therapies used for other conditions show low efficacy and tolerability due to their poor specificity. Current treatments can only target PDE families (e.g., PDE1 or PDE4) or some PDE4 subtypes, however, these are still often broadly expressed throughout the body and heart. For example, PDE1 is present in the kidney, smooth muscle cells, the endocrine system, the immune system, neurons, and the sino-atrial node. Therefore, low-specificity PDE-targeted therapies have a higher risk of causing either antagonistic effects leading to low-efficacy treatments and failure of phase II clinical trials or serious adverse side effects that already cause them to fail at phase I clinical trials. A good example of PDE-targeted therapies causing adverse side effects is that of PDE4 inhibitors like roflumilast that are poorly tolerated as they cause nausea, emesis, diarrhea, and headaches within the therapeutically efficient dose range (346, 347). Therefore, only low efficacy doses can be

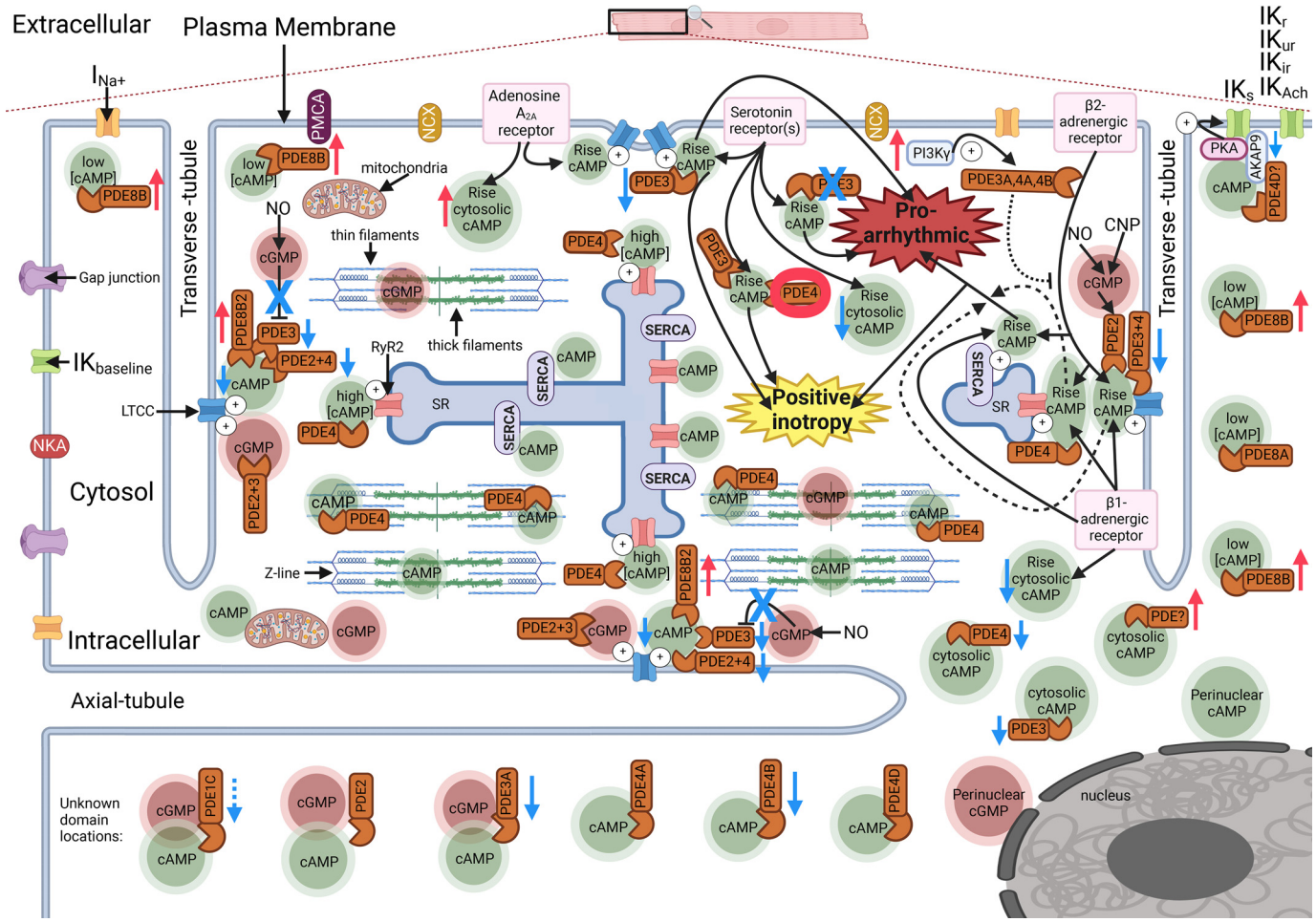

Figure 5. Representation of the changes in PDE expression, localization, and roles in human atrial myocytes from patients with chronic atrial fibrillation. In AMs from patients with chronic AF, there is decreased expression of PDE4B, PDE3A, and probably PDE2, whereas PDE8 expression and importance is increased. The domain regulating the LTCC shows reduced [cAMP]. This is caused by an increase in PDE8B2 activity in this domain, while PDE2,3,4 activity is decreased. This leads to a reduction in the $I_{Ca,L}$ and likely helps to sustain atrial fibrillation. The ability of NO/cGMP to cause a rise in cAMP in the LTCC cAMP domain is lost due to loss of PDE3A. The cAMP response to β-adrenergic stimulation around RyR2s and LTCCs is unchanged despite reduced PDE3 and 4 expressions around LTCC. The rise in cAMP around the LTCC caused by serotonin or adenosine-2A receptors is not altered, although the importance of PDE3 in regulating the cAMP signal around LTCC is reduced. Cytosolic cAMP domains show a reduced rise in cAMP in response to serotonin or β-adrenergic receptor stimulation but an increased rise in cytosolic cAMP domains in response to adenosine A_{2A} receptor stimulation. PDE3 and PDE4 are less important in regulating cytosolic cAMP levels, although the net cytosolic cAMP levels remain constant, suggesting increased expression of another yet identified cAMP hydrolyzing PDE in the cytosol. The proarrhythmic cAMP signal from serotonin receptors is no longer regulated by PDE3 or 4, but the positive inotropic cAMP signal remains regulated by PDE3 and additionally PDE4. The increased expression of PI3Kγ may indicate that there is increased negative regulation of β-2 adrenergic receptor signaling in AMs from patients with chronic AF. Decreased AKAP9 expression could imply that regulation of IKs by cAMP, PDE4, and PKA is impaired or lost. Blue arrow next to PDE - decreased activity and/or expression of PDE. Blue arrow next to cAMP or cGMP nanodomains - decreased [cAMP] or [cGMP]. Red arrow next to PDE - increased activity and/or expression of PDE. Red arrow next to cAMP or cGMP nanodomains - increased [cAMP] or [cGMP]. Blue cross - this function no longer occurs in AMs from patients with chronic AF. Red O - this is a new function of PDEs compared with healthy AMs. AKAP, A Kinase Anchoring Protein; APD, action potential duration; EC, extracellular; GPCR, G-protein-coupled receptor; IC, intracellular; IK_{Ach}, acetylcholine-activated K^+ current; $IK_{baseline}$, baseline K^+ current; INa^+, sodium current; IK_r, delayed rectifier K^+ current; IK_s, slowly activating delayed rectifier K^+ current; IK_{ur}, ultrarapid delayed rectifier K^+ current; NCX, Na^+- Ca^{2+} exchanger; NKA, sodium potassium ATPase; NO, nitric oxide; PM, plasma membrane; PMCA, plasma membrane Ca^{2+} ATPase; RyR2, ryanodine type 2 receptor; SERCA, sarcoplasmic endoplasmic reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum. Created in BioRender. Burton, R. (2024) https://BioRender.com/f22n840.

used, which narrows the therapeutic index. Another example is that inhibition of PDE1A leads to a severe reduction in blood pressure (20, 348). PDE1A inhibition therefore may promote increased sympathetic tone through the baroreceptor reflex, which may promote AF (349) or heart failure (350) or ventricular arrhythmias (88). Similarly, it has been hypothesized that the reported cases of AF following PDE5 inhibition (351–353) may be due to increased sympathetic tone following PDE5-induced vasodilation and hypotension (352) [a common side effect of PDE5 inhibitors (354–360)]. However, no placebo-controlled studies have found that PDE5 inhibition causes AF (361, 362), even in patients who are at an increased risk of developing AF (363). These potential and known adverse effects of PDE inhibitors highlight that a strategy to specifically target such treatments to AMs and arrhythmic signaling pathways would be desired to minimize the risks of adverse side effects.

To achieve PDE-targeted AF therapies with higher efficacy and minimal side effects, research needs to identify the PDE isoforms promoting AF, their subcellular location, the cell type they are present in, and their expression in different types of AF. Studies such as Grammatika Pavlidou et al. (24), which identify the exact PDE8 isoform (PDE8B2), the signalosome (LTCC), the cell type (AMs), and the AF type (cAF) provide rationale for future studies investigating the role of PDEs in AF. This will help to facilitate the development of highly specific PDE-targeted therapies with potential utility in patients with either paroxysmal, persistent, or cAF.

The targeting of specific PDE isoforms with either small molecules or genetic technologies is beyond the scope of this review, but as a start, information can be found elsewhere, e.g., in study by Baillie et al. (2). Overall, in the short-term, the development of PDE-specific small molecules, together with improved selective drug delivery systems may represent the most viable option for translation of PDE research from bench to bedside. However, in the future, with growing scientific knowledge and technological improvements, PDE-targeted gene therapies may have greater potential to achieve high-precision medicine with ultimately improved efficacy, safety, and tolerability for patients with AF.

CONCLUSIONS

The presence and role of PDEs in the atria is starting to be understood but much remains unknown including the difference in expression between the atria and ventricles for most PDEs. Overall specific PDE isoforms are potential targets to achieve high precision treatment of AF. Research should aim to identify the presence, localization, and function of more specific PDE isoforms in healthy and diseased human atria and the specific cell types within the atria. The technologies to perform these experiments already exist, for example, by creating cell type-specific-inducible PDE isoform knockout/down/up in animal models, human iPSC-derived AMs, and cultured adult human AMs. Moreover, future validation, testing, and development strategies to improve the specificity of PDE targeting in the system of interest (atria, AM, atrial fibroblasts, pulmonary vein cardiac myocytes) are required for the translation of this work into viable treatment options for patients.

SUPPLEMENTAL MATERIAL

Supplemental Table S1: https://doi.org/10.6084/m9.figshare.28350698.v2.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.J.R. prepared figures; M.J.R., S.J.B., and R.A.B.B. drafted manuscript; M.J.R., A.K., S.J.B., and R.A.B.B. edited and revised manuscript; A.K. and R.A.B.B. approved final version of manuscript.

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