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Review article

Phosphodiesterase4D (PDE4D) — A risk factor for atrial fibrillation and stroke?

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ABSTRACT

Mutations in the gene encoding phosphodiesterase 4D (PDE4D) enzyme are associated with ischemic stroke; however the functional implications of such mutations are not well understood. PDE4D is part of a complex protein family modulating intracellular signalling by cyclic nucleotides. The PDE4 family includes subtypes A–D, all of which show unique intracellular, cellular and tissue distribution. PDE4D is the major subtype expressed in human atrial myocytes and involved in the pathophysiology of arrhythmias, such as atrial fibrillation. The PDE4D enzyme hydrolyses cyclic adenosine monophosphate (cAMP). Though diverging results are reported, several population based studies describe association of various PDE4D single nucleotide polymorphisms (SNP) with cardio-embolic stroke in particular. Functionally, a down regulation of PDE4D variants has been reported in stroke patients.

The anti-inflammatory and vasodilator properties of PDE4 inhibitors make them suitable for treatment of stroke and cardiovascular disease. PDE4D has recently been suggested as factor in atrial fibrillation. This review summarizes the possible function of PDE4D in the brain, heart, and vasculature. Further, association of the described SNPs, in particular, with cardioembolic stroke, is reviewed. Current findings on the PDE4D mutations suggest functionality involves an increased cardiac risk factor as well as augmented risk of atrial fibrillation.

Contents

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1. Introduction

Ischemic stroke is a major cause of death and disability worldwide. Prevalence is high in high-income countries with incidence increasing in low- to middle-income countries resulting in large socio-economic consequences to both demographics [1–3]. In general, stroke is considered to be a multi-factorial and heterogeneous disorder. Ischemic stroke is categorized as cardio-embolic (CE), large artery atherosclerosis (LAA), small-vessel lacunar (LAC) stroke, or stroke of other determined (SOD) or undetermined (UN) aetiology [4]. The latter may in part contribute to cardio-embolic stroke [5].

Both genetic and life-style related factors may increase risk of stroke; genetic factors involving single nucleotide polymorphisms (SNPs) can indicate a predisposition to certain subtypes of stroke [6,7]. Several mutations in microsatellite markers and SNPs of the STRK1 locus, chromosome 5q12, encoding phosphodiesterase (PDE) type 4D (PDE4D), were identified as independent risk factors for ischemic stroke, in particular, large artery (carotid) and cardiogenic stroke subtypes [7]. However, the physiological consequences and importance of the PDE4D mutation in stroke pathophysiology remains an open question. Several reviews have debated the inconsistency of the genetic findings [8]. Referencing both basic and in vivo experiments, this review explores the possible pathophysiological involvement of PDE4D in atherosclerosis and atrial fibrillation relating to the reported association of PDE4D with large artery and cardiogenic stroke, as well as the potential use of PDE4 modulators in stroke treatment.

2. The PDE superfamily

2.1. Structure of PDE

PDEs are intracellular enzymes which degrade the cyclic nucleotides adenosine and/or guanosine monophosphate (cAMP and/or cGMP) thereby modulating cellular signalling via the cAMP/cGMP pathways (Fig. 1). 21 genes encoding PDEs, distributed into 11 different PDE families, have been described [9]. All PDE genes have a high degree of conservation. The PDE enzymes exhibit highly conserved catalytic domains localized proximal to the C-terminal of the PDE gene; whereas different regulatory domains and motifs are located to the N-terminal part. Another common feature of the PDEs is a complex gene structure which generates multiple splice variants through multiple promotors; alternative start sites, and splicing. Approximately 100 different isoforms may exist in mammals, though far less are currently known [9]. PDEs are pharmacological targets of interest due to their unique tissue, cellular, and intracellular localisation [10]. The PDE4D gene is located at chromosome 5q12 [11]. The locus is at least 150 kb wide, composed of at least 22 or more exons, some of which overlap with adjacent gene PART1 [7,12] (OMIM; 600129). Eleven different splice variants or isoforms of PDE4D are recognized (PDE4D1-11), though PDE4D10-PDE4D11 are only recognized as mice isoforms [11,13–15].

Such include long isoforms (PDE4D3, 4, 5, 7, 8, 9, 11), short isoforms (PDE4D1, 2), and super-short isoform (PDE4D6, 10) [11,14,15] (Fig. 2). The enzyme activity of the PDE4D isoforms depends on the presence of the N-terminal related upstream conserved regions 1 and 2 (UCR-1 and UCR-2), which modulate the PDE4D enzyme activity [13]. N-terminals are unique to the specific splice variant and denote differences in protein-protein interactions or membrane associations. N-terminals locate the splice variants to specific cellular or sub-cellular compartments to exert their functions.

2.2. PDE4 function and expression

All members of the PDE4 family selectively degrade cAMP. Four genes encode the PDE4 family; PDE4A, −B, −C and –D. More than 20 different PDE4 subtypes are generated under the control of variant-specific promotors and first exons, and less so by co-transcriptional

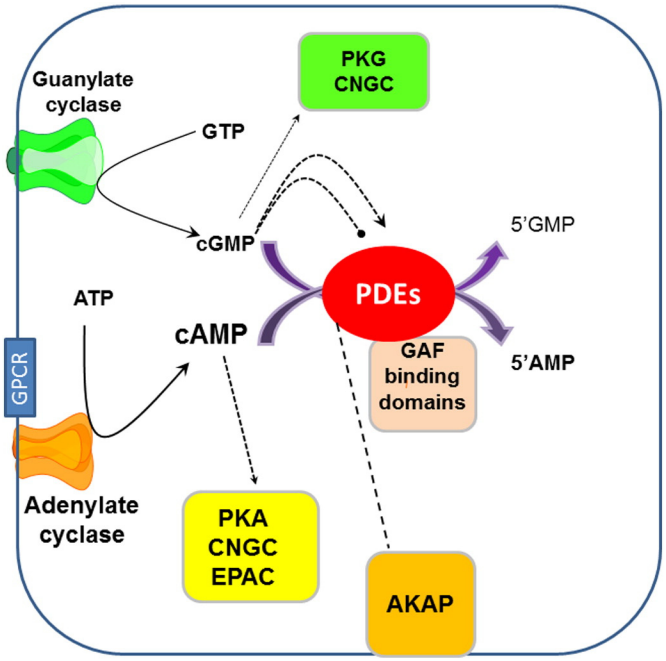

Fig. 1. Cellular signalling pathways associated with PDEs. Within the brain, both cAMP and cGMP degrading PDEs co-exist in cells though the cellular distribution of the PDE subtypes varies. The illustration reflects the interplay of PDEs in cell signalling where cAMP and cGMP signalling may run in parallel. In most cells, the PDE families display a closely connected regulation of cyclic nucleotide signalling, i.e. cGMP inhibits PDE3-associated but activates PDE2-associated cAMP degradation. The regulatory GAF domains are found in both cAMP and cGMP degrading PDEs. AKAP: A-kinase anchoring protein, PKA: protein kinase A, PKG: protein kinase G, EPAC: exchange protein activated by cAMP, GAF domain: cGMP-activated PDE, adenylyl cyclase- and Fh1A-binding domain, CNGC: cyclic nucleotide gated channel, CPCR: G-protein-coupled receptors.

modification of precursor mRNA [16,17]. PDE4 subtypes are selectively expressed in various tissues. They are expressed in specific areas of the brain, in organs such as the spleen, lung, heart, liver, kidney, testis, and in vascular tissue in general [13,18,19]. In the brain, PDE4D is expressed in the hippocampus, cerebral cortex [20], and thalamus [21] which may be associated with memory and depression [22]. PDE4D is also found in the area postrema, nucleus tractus solitarius, and locus coeruleus all of which associate with the emetic effects induced by PDE4 inhibition [23].

2.3. PDE4 in disease pathophysiology

PDE4 is associated with both normal physiological functions, and disorders pertaining to cAMP signalling where PDE4 modulate cAMP response to stimuli. The role of the PDE4 enzyme family relates to specific isoforms, though all are specific with regard to cAMP hydrolysis. PDE4A is linked to depression, PDE4B to schizophrenia [24], PDE4D to ischemic stroke, and in particular, carotid and cardiogenic stroke [7]. As the role of PDE4D in humans is not fully understood, assumptions of various PDE4D functions are mainly derived from animal studies.

In the regulation of artery diameter, PDE4 contributes to the cAMP homeostasis in endothelial and smooth muscle cells though the PDE4 isoform remains elusive. Inhibition of PDE4 causes dilatation of cerebral arteries [25,26]. More specifically, PDE4 is detected in both vascular smooth muscle (human, bovine, and rat aorta) [27] and in endothelial cells [28]. Further, PDE4 inhibition causes endothelial-dependent vasodilatation [29]. In ischemic stroke, inhibition of PDE4 promotes protection of blood brain barrier [30] and reduces both inflammation and thrombosis [31] (see Fig. 3). Inflammation, endothelial cell integrity, and smooth muscle cell function are significant in the development of atherosclerosis [32] as well as in cardiogenic and carotid stroke [33,34]. The interplay between PDE3 and PDE4 is a key element in the