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REVIEW

Cyclic nucleotide phosphodiesterases in heart and vessels: A therapeutic perspective

Phosphodiestérases des nucléotides cycliques dans le cœur et les vaisseaux : une perspective thérapeutique

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Summary Cyclic nucleotide phosphodiesterases (PDEs) degrade the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), thereby regulating multiple aspects of cardiac and vascular muscle functions. This highly diverse class of enzymes encoded by 21 genes encompasses 11 families that are not only responsible for the

Abbreviations: AKAP, A-kinase anchoring protein; β-AR, β-adrenergic receptor; Ca^{2+}, calcium; CaMKII, Ca^{2+}/calmodulin-dependent kinase II; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; Epac, exchange protein directly activated by cAMP; ERK, extracellular signal-regulated kinase; GC, guanylate cyclase; Gs, heterotrimeric G-protein stimulating adenylyl cyclase; HF, heart failure; KO, knock out; LTCC, L-type Ca^{2+} channel; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PLB, phospholamban; PKA, cAMP-dependent protein kinase; PKG, cGMP-dependent protein kinase; RyR2, ryanodine receptor; SERCA, sarco-endoplasmic reticulum Ca^{2+}-adenosine triphosphatase; SMC, smooth muscle cell; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell.

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termination of cyclic nucleotide signalling, but are also involved in the generation of dynamic microdomains of cAMP and cGMP, controlling specific cell functions in response to various neurohormonal stimuli. In the myocardium and vascular smooth muscle, the PDE3 and PDE4 families predominate, degrading cAMP and thereby regulating cardiac excitation-contraction coupling and smooth muscle contractile tone. PDE3 inhibitors are positive inotropes and vasodilators in humans, but their use is limited to acute heart failure and intermittent claudication. PDE5 is particularly important for the degradation of cGMP in vascular smooth muscle, and PDE5 inhibitors are used to treat erectile dysfunction and pulmonary hypertension. There is experimental evidence that these PDEs, as well as other PDE families, including PDE1, PDE2 and PDE9, may play important roles in cardiac diseases, such as hypertrophy and heart failure, as well as several vascular diseases. After a brief presentation of the cyclic nucleotide pathways in cardiac and vascular cells, and the major characteristics of the PDE superfamily, this review will focus on the current use of PDE inhibitors in cardiovascular diseases, and the recent research developments that could lead to better exploitation of the therapeutic potential of these enzymes in the future.

MOTS CLÉS
AMPc ;
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Phosphodiestérase des nucléotides cycliques ;
Maladies cardiovasculaires

Résumé Les phosphodiestérases des nucléotides cycliques (PDE) dégradent les seconds messagers AMPc et GMPc, régulant ainsi de multiples aspects des fonctions cardiaque et vasculaire. Cette classe d'enzymes très diversifiée, codée par vingt et un gènes, englobe onze familles responsables de la terminaison des signaux transmis par les nucléotides cycliques, et sont impliqués dans la génération de microdomaines dynamiques d'AMPc et de GMPc contrôlant des fonctions spécifiques des cellules en réponse à divers stimuli neuro-hormonaux. Dans le myocarde et le muscle lisse vasculaire, les PDE3 et PDE4 sont prédominantes pour dégrader l'AMPc et régulent le couplage excitation-contraction cardiaque et le tonus contractile des muscles lisses. Les inhibiteurs de PDE3 sont inotropes positifs et vasodilatateurs chez l'homme, mais leur utilisation est limitée au traitement de l'insuffisance cardiaque aiguë et de la claudication intermittente. La PDE5 est importante pour dégrader le GMPc dans le muscle lisse vasculaire, et les inhibiteurs de PDE5 sont utilisés pour traiter la dysfonction érectile et l'hypertension pulmonaire. Des travaux expérimentaux suggèrent que ces PDE ainsi que d'autres familles de PDE, en particulier PDE1, PDE2 et PDE9 jouent également un rôle important dans l'hypertrophie et l'insuffisance cardiaque ainsi que dans plusieurs maladies vasculaires. Après avoir donné un bref aperçu des voies des nucléotides cycliques dans les cellules cardiaques et vasculaires et des principales caractéristiques des PDEs, cette revue présentera les utilisations actuelles des inhibiteurs de PDE dans les maladies cardiovasculaires et les progrès de recherche récents susceptibles de conduire à une meilleure exploitation du potentiel thérapeutique de ces enzymes dans le futur.

Background

The cyclic nucleotides cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) participate in the main pathways regulating cardiac and vascular functions; they act as second messengers for sympathetic and parasympathetic systems, nitric oxide (NO) and natriuretic peptides. Cyclic nucleotides may exert beneficial or deleterious effects on the heart and vessels, depending on the strength and duration of the stimulation. Acute elevation of cyclic nucleotides regulates cardiac excitation-contraction coupling and vascular contractile tone. However, chronic elevation of cAMP contributes to the development of cardiac hypertrophy and progression to heart failure (HF), while cGMP possesses antihypertrophic properties. In vessels, cAMP and cGMP exert antiproliferative and antimigratory properties, therefore limiting atherosclerosis and angiogenesis. These second messengers also regulate endothelial barrier function, the disruption of which is associated with several pathological conditions, such as oedema and sepsis. The amplitude, duration and localization of cyclic nucleotide responses are determined by the balance between synthesis of cAMP and cGMP by adenylyl and guanylyl cyclases, respectively, and degradation by cyclic nucleotide phosphodiesterases (PDEs).

PDEs represent the main route to the rapid lowering of cyclic nucleotide concentrations inside the cells, and constitute a highly diverse superfamily of enzymes. The