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Review

Phosphodiesterase 5 as target for adipose tissue disorders

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ABSTRACT

Introduction: Adipose tissue as an endocrine organ is responsible for the release of multiple cytokines, which have the most diverse metabolic functions. Therefore, it is extremely important to preserve its physiological health in order to avoid local and systemic disorders. Experiments available in literature show the importance of the nitric oxide (NO)/guanosine 3′5′ cyclic monophosphate (cGMP)/protein kinase G (PKG) pathway in adipocyte biology. Phosphodiesterase 5 (PDE5) is an enzyme responsible for cGMP inactivation, and the use of its inhibitors can be an alternative in the search of a more balanced adipose tissue.
Objective: This review aims to describe the PDE5 role and the possibility of using PDE5 inhibitors in adipocyte physiology derangements and their consequences.
Design and methods: Studies published in the last 10 years that related PDE5 and its inhibitors to adipose tissue were raised in major databases.
Results: PDE5 is present in adipocyte, and PDE5 inhibitors can promote adipogenesis, interfere with adipokines secretion, decrease inflammatory markers expression, and increase the thermogenic potential of white adipose tissue.
Conclusions: PDE5 plays an important role in adipocyte physiology and the use of its inhibitors may prove a useful tool to combat adipose tissue disorders and its highest expression, metabolic syndrome.

Contents

Introduction

While hunger was a constant presence during human evolution, nowadays 65% of the world's population live in countries where overweight and obesity kill more people than underweight [1,2].

Over the last years adipose tissue rose from a simple energy deposit to an endocrine organ, producing hormones known as adipokines, and also cytokines related to the onset and perpetuation of inflammation [3–5]. On account of its role in metabolic control, adipose tissue expansion leads to alteration of its normal

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physiology, generating autocrine, paracrine, and finally systemic imbalances [6,7]. The dysfunction of these adipokines and cytokines is responsible for decreased systemic cellular sensitivity to insulin, and consequently the onset of metabolic syndrome [6,7].

Nitric oxide (NO), a small gaseous molecule, is composed of one nitrogen atom and one oxygen atom, and has a half-life of several seconds [8]. NO is produced by a family of NO synthases (NOS) and is released from many cell types in the body, where it acts either as a neurotransmitter or as a paracrine agent [8]. NO binds to soluble guanylyl cyclase (sGC), and causes a 100- to 200-fold activation of the enzyme [8]. Activation of sGC increases conversion of guanosine-5′-triphosphate (GTP) to guanosine 3′5′ cyclic monophosphate (cGMP), resulting in the elevation of cGMP, which initiates the cGMP-signaling pathway and subsequent physiological changes [8]. These changes are largely mediated through the activation of cGMP dependent protein kinase (PKG) [8]. Some studies available in the literature suggest the involvement of the NO/cGMP/PKG pathway in various aspects of adipose tissue physiology, and consequently a link with metabolic syndrome [9–15]. In fact, endothelial nitric oxide synthase (eNOS) deficient mice develop symptoms of human metabolic syndrome, with insulin resistance, hyperlipidemia and hypertension [16,17]. Another way to increase the levels of cGMP is through the atrial natriuretic peptide (ANP) action. This occurs in a dose-dependent manner, and is mediated by the natriuretic receptor-A (NPR-A). Thus, adipose tissue can be considered a target for the natriuretic peptide, where adipocyte differentiation takes place via NPR-A/cGMP/PKG [18–20].

Cyclic nucleotide phosphodiesterase 5 (PDE5) is the enzyme responsible for cGMP hydrolysis to generate the product 5′-GMP, which is inactive in the cyclic nucleotide (cN) pathway [21,22]. Sildenafil, a PDE5 inhibitor, initially designated as UK-92,480, was first synthesized by Pfizer in United Kingdom to treat hypertension and angina pectoris, but interestingly, exhibited a different pharmacological effect, a marked penile erection, and became the first-line treatment option to erectile dysfunction (ED) [23–25]. A population favored by the appearance of these drugs are diabetics, who frequently have dysfunction of the physiological mechanism of penile erection [24]. Initially cautious, physicians from various specialties gradually felt more comfortable prescribing this class of drugs to their diabetic patients, even with multiple comorbidities [26,27]. Paradoxically, some researchers are evaluating the effect of these drugs in disorders related to the genesis of metabolic syndrome, such as adipose tissue inflammation, insulin resistance, atherosclerosis, and finally cardiovascular mortality [9–11].

This review aims to describe and analyze studies related to the role of PDE5 and the use of PDE5 inhibitors in adipose tissue disorders, and its consequences.

Cyclic nucleotide phosphodiesterases

- Phosphodiesterase (PDE) definition and function

The PDEs are enzymes that selectively catalyze the hydrolysis of 3′ cyclic phosphate bonds of adenosine (cAMP) and/or guanosine 3′5′ cyclic monophosphate (cGMP) [21,22]. Cellular levels of cAMP and cGMP are regulated by the relative activities of adenylyl and guanylyl cyclases (AC and GC), which synthesize these cyclic nucleotides, and by PDEs, which hydrolyze them [21]. Besides the PDE action, which constitutes the main form for lowering active cyclic nucleotide (cN) levels in cells, other processes can do the same. Such examples are the extrusion of cN into the extracellular milieu, and/or transit of cN from one cell type to another [21].

- PDE family

Eleven families of mammalian PDEs are derived from 21 genes and classified based on amino acid sequences, regulatory properties, and catalytic characteristics [21]. PDEs share a conserved catalytic domain (C domain), but amino acid sequence outside this region differs markedly [21]. Based on their sequence relatedness, kinetics, modes of regulation, and pharmacological properties is that the class I PDEs (protozoa/metazoan) is divided into 11 families (PDE1-PDE11) [28]. Certain PDEs are highly specific for hydrolysis of cAMP (PDEs 4, 7, and 8) or cGMP (PDEs 5, 6, and 9), and others hydrolyze both (PDEs 1, 2, 3, 10, and 11) [21].

- PDE localization

One single cell type can express several different PDEs, and the nature and localization of these PDEs are likely to be a major regulators of the local concentration of cAMP or cGMP in the cell [22]. PDEs 1, 2, 3, and 4 are expressed in many tissues, whereas others are more restricted [21]. In most cells, PDE 3 and 4 provide the major portion of cAMP-hydrolyzing activity [21]. PDE5 is abundant in vascular and airway smooth muscle and platelets, but also is present in cerebellar Purkinje cells, gastrointestinal epithelial cells, and endothelial cells [21]. The PDE6 family is found primarily in retina, but also in pineal and certain melanoma cells, while PDEs 7, 8, 9, 10, and 11 are not widely expressed [21].

Phosphodiesterase 5 (PDE5)

PDE 5 was originally identified, isolated, and characterized from platelets in 1978, and received little notoriety, until it was discovered to be a regulator of vascular smooth muscle contraction and target for the drug sildenafil [22,29]. Only one PDE 5 gene has been discovered, PDE5A, although several variants under the control of differentially regulated promoters have been identified [22]. PDE5 is composed of an amino-terminal regulatory domain (GAF A and B) and a carboxy-terminal metal-binding catalytic domain [30]. The structural basis for the high-affinity cGMP binding to PDE5 takes place because of the presence of these two highly homologous GAF domains [21,22,31]. In PDE5 high-affinity cGMP binding occurs only to the GAF-A domain [22]. GAF-B is autoinhibitory for cGMP binding to GAF-A, and consequently for activation of the catalytic site [21]. Under many physiological conditions, it is thought that GAF-A domain is likely to be occupied by cGMP and therefore fully active [22]. To compensate for that, there are short-term regulatory mechanisms in PDE5 catalytic site function, like allosteric cGMP binding at GAF-A and phosphorylation at Ser-102, which increase V_{max} and affinity for cGMP substrate or inhibitors [21]. Phosphorylation that occurs in intact cells is mediated by PKG, and facilitated by allosteric cGMP binding or ligand occupation of the catalytic site [21]. Therefore the product of GC and substrate for PDE5, cGMP, acts as a feed-forward activator of the enzyme [22]. Another form of PDE 5 regulation is the control of its expression in tissues in response to a variety of stimuli, and interestingly overexpression is a likely culprit in many vascular maladies, including hypertension, angina, diabetic angiopathy, and ED [21].

Phosphodiesterase inhibitors

PDE inhibitors are drugs able to block phosphodiester hydrolysis caused by PDEs, resulting in higher levels of cyclic nucleotides [32]. For inhibitor binding to PDEs there is a common conserved scheme that is important for selectivity toward individual PDE family members [32]. The first conserved feature is that the planar ring portion of the inhibitor is held tightly by a P clamp, formed by highly conserved hydrophobic residues, and the second is that the inhibitor always forms one or two hydrogen bonds with the purine-selective glutamine [32].