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Mini-review

Several agents and pathways regulate lipolysis in adipocytes

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ABSTRACT

Adipose tissue is the only tissue capable of hydrolyzing its stores of triacylglycerol (TAG) and of mobilizing fatty acids and glycerol in the bloodstream so that they can be used by other tissues. The full hydrolysis of TAG depends on the activity of three enzymes, adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL) and monoacylglycerol lipase, each of which possesses a distinct regulatory mechanism. Although more is known about HSL than about the other two enzymes, it has recently been shown that HLS and ATGL can be activated simultaneously, such that the mechanism that enables HSL to access the surface of lipid droplets also permits the stimulation of ATGL. The classical pathway of lipolysis activation in adipocytes is cAMP-dependent. The production of cAMP is modulated by G-protein-coupled receptors of the Gs/Gi family and cAMP degradation is regulated by phosphodiesterase. However, other pathways that activate TAG hydrolysis are currently under investigation. Lipolysis can also be started by G-protein-coupled receptors of the Gq family, through molecular mechanisms that involve phospholipase C, calmodulin and protein kinase C. There is also evidence that increased lipolytic activity in adipocytes occurs after stimulation of the mitogen-activated protein kinase pathway or after cGMP accumulation and activation of protein kinase G. Several agents contribute to the control of lipolysis in adipocytes by modulating the activity of HSL and ATGL. In this review, we have summarized the signalling pathways activated by several agents involved in the regulation of TAG hydrolysis in adipocytes.

1. Introduction

The first described function of white adipose tissue (WAT) was the capacity to store triacylglycerol (TAG) and to mobilize fatty acids (FAs) and glycerol, according to energetic demands. Approximately 90% of the adipocyte volume is TAG located in a only lipid droplet that dislocates the nucleus to the periphery, resulting in limited cytosolic space [1,2]. Lipid droplets are composed of a neutral lipid core surrounded by a phospholipid monolayer, within which PAT[2] proteins reside [3,4]. PAT is derived

Abbreviations: ACTH, adrenocorticotrophin hormone; AdPLA, adipose-specific phospholipase A2; Ang II, angiotensin II; ANP, atrial natriuretic peptide; AT1R, Ang II type 1 receptor; ATGL, adipose triglyceride lipase; cAMP, cyclic adenosine monophosphate; CGI-58, comparative gene identification-58; cGMP, cyclic guanosine monophosphate; EC50, median effective concentration; EP, prostaglandin receptor subtypes (EP1, EP2, EP3 and EP4); ERK, extracellular signal-regulated kinase; ETAR, endothelin receptor-A; ETBR, endothelin receptor-B; FAs, fatty acids; FFAs, free fatty acids; FoxO1, forkhead box class O 1; GH, growth hormone; HSL, hormone-sensitive lipase; IRS-1 and IRS-2, insulin receptor substrate 1 or 2; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MC, melanocortin; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PAT, derives from names of three proteins, perilipin 1 (perilipin A), perilipin 2 (ADRP, adipocyte differentiation-related protein) and perilipin 3 (TIP47, tail-interacting protein of 47 kDa); PDE3B, phosphodiesterase 3B; PDK, phosphoinositide-dependent kinase; PI3K, phosphatidylinositol-3-kinase; PIP3, phosphatidylinositol-3,4,5-triphosphate; PGE_2, prostaglandin E_2; PKA, cAMP-dependent protein kinase; PKB, protein kinase B; PKC, protein kinase C; PKG, cGMP-dependent protein kinase; PLC, phospholipase C; PMA, phorbol 12-myristate 13-acetate; PRL, prolactin; PRLR, prolactin receptor; PYY, peptide YY; PUMA-G, protein up-regulated in macrophages by interferon-gamma; SH2, Src homology 2; STAT, signal transducers and activators of transcription; TAG, triacylglycerol; TNF-α, tumour necrosis factor alpha; TSH, thyroid-stimulating hormone; TSHr, thyroid-stimulating hormone receptor; WAT, white adipose tissue.

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[2] PAT, derives from names of three proteins, perilipin 1 (perilipin A), perilipin 2 (ADRP, adipocyte differentiation-related protein) and perilipin 3 (TIP47, tail-interacting protein of 47 kDa), with each having highly related N-terminal sequences and common affinity for intracellular neutral lipid storage droplets.

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from the names of three proteins, perilipin 1 (perilipin A), perilipin 2 (ADRP, adipocyte differentiation-related protein) and perilipin 3 (TIP47, tail-interacting protein of 47 kDa), with each having highly related N-terminal sequences and a common affinity for intracellular neutral lipid storage droplets [5,6]. Perilipin 1 is the most abundant protein associated with lipid droplets of adipocytes and controls both basal and stimulated lipolysis. Under basal or fed conditions, perilipin 1 shields stored TAG from cytosolic lipases, thus promoting TAG storage [7]. The mobilization of FAs, which are incorporated into TAG by WAT, depends on the activity of two major lipases: hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL). These lipases are responsible for approximately 95% of TAG hydrolase activity in adipocytes [8]. ATGL is predominantly responsible for the hydrolysis of TAG [8,9], whereas the hydrolysis activity of HSL on diacylglycerol is 10 times higher than that of TAG [10]. In the basal state, HSL is dispersed in the cytoplasm, whereas perilipin coats lipid droplets and binds to CGI-58 (comparative gene identification-58), a key coactivator of ATGL [11]. In the stimulated state, phosphorylation of perilipin 1 is required to facilitate the access of phosphorylated HSL to lipid substrates [7]. Perilipin phosphorylation also promotes CGI-58 release, which then activates ATGL [11]. It has recently been shown that ATGL activity can also be inhibited by its interaction with a cell cycle protein [12]. The activity of ATGL, HSL and monoacylglycerol lipase is necessary for full hydrolysis of TAG and for the release of free fatty acids (FFAs) and glycerol. In recent years, adipose tissue lipolysis has been extensively revised. Special emphasis has been given to the lipolytic enzymes, mainly the ATGL [13,14], its regulation by autocrine/paracrine factors [14,15] and its interfacial behaviour [16]. There is strong evidence to suggest that lipase activity is a function of interfacial composition and changes concurrently with lipolytic conversion [16]. Trafficking of FAs into and out of adipocytes and the biochemical basis of this procedure was also revised [1]. Recently, lipolysis has been interpreted in the physiological context of energetic metabolism, and it has been suggested that age, sex, anatomical site, genotype and species differences are important variables that must be analyzed [14,17]. Despite considerable advances in understanding the regulation of adipose tissue lipolysis, few works emphasize the intracellular signalling cascade involved in this metabolic process. The main pathway leading to lipolysis is the cAMP-dependent protein kinase (PKA) pathway, through which the stimulation of Gs-coupled receptors induces the activation of adenylyl cyclase, and the subsequent increase in intracellular cAMP levels leads to the activation of PKA and the phosphorylation and translocation of HSL to fat droplets [18]. In addition, protein kinase C (PKC) activation induces adenylyl cyclase activity in rat adipocytes [19]. These findings led us to agree that PKC activation may promote lipolysis via adenylyl cyclase activation and subsequent elevation of cAMP levels. There is also evidence that increased lipolytic activity in adipocytes occurs after stimulation of the mitogen-activated protein kinase (MAPK) pathway [20–22]. However, guanylyl cyclase and cyclic guanosine monophosphate (cGMP) have also been implicated in increased FFA and glycerol release from fat cells [23,24]. In this work, we have summarized the signalling pathways recruited by some regulators of TAG hydrolysis in adipocytes (Fig. 1), such as adenosine, atrial natriuretic peptide, β-hydroxybutyrate, catecholamines, endothelin-1, insulin, glucocorticoids, growth hormone, lactate, leptin, melanocortins, neuropeptide Y, peptide YY, prostaglandin E_2, thyroid-stimulating hormone and tumour necrosis factor alpha. In the following sections, each lipolytic or antilipolytic agent will be classified according to the major intracellular signalling pathways involved in the induction of its actions. However, some agents stimulate more than one intracellular transduction pathway.

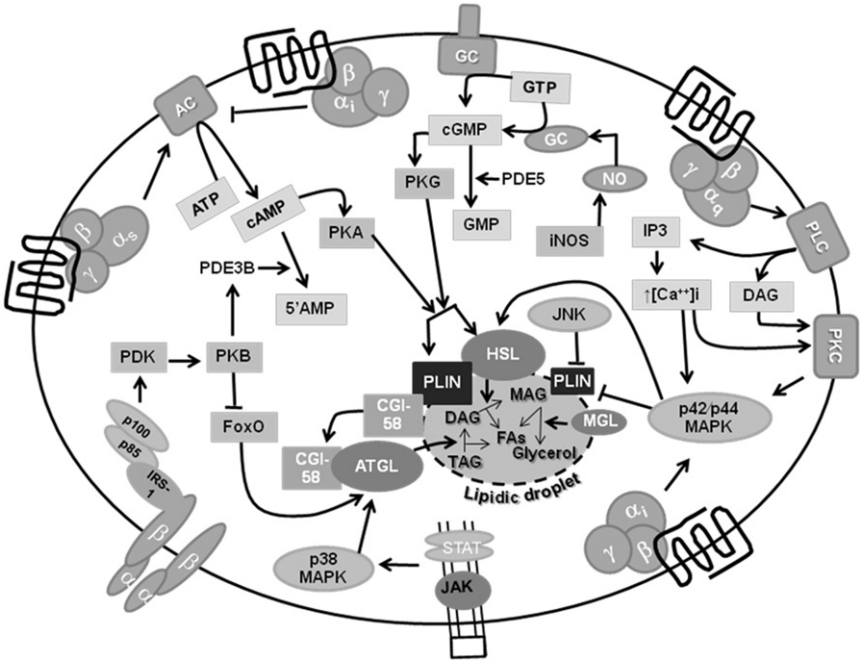

Fig. 1. Summary of possible intracellular signalling pathways involved in the regulation of lipolysis in adipocytes. AC, adenylyl cyclase; ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CGI-58, comparative gene identification-58; cGMP, cyclic guanosine monophosphate; DAG, diacylglycerol; FAs, fatty acids; FoxO1, forkhead box class O 1; GC, guanylyl cyclase; GTP, guanosine triphosphate; HSL, hormone-sensitive lipase; iNOS, inducible nitric oxide; IP3, inositol triphosphate; IRS-1, insulin receptor substrate 1; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MAG, monoacylglycerol; MGL, monoacylglycerol lipase; NO, nitric oxide; PDE, phosphodiesterase; PDK, phosphoinositide-dependent kinase; PKA, cAMP-dependent protein kinase; PKB, protein kinase B; PKC, protein kinase C; PKG, cGMP-dependent protein kinase; PLC, phospholipase C; PLIN, perilipin; STAT, signal transducers and activators of transcription; TAG, triacylglycerol.