Molecular Aspects of Medicine 46 (2015) 34–45

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Role of glycogen phosphorylase in liver glycogen metabolism

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ARTICLE INFO

Article history:
Received 10 September 2015
Accepted 11 September 2015
Available online 28 October 2015

Keywords:
Phosphorylase
Liver
Glucose
Glucose 6-phosphate
Glycogen targeting proteins
PPP1R3B
PPP1R3C
Insulin

ABSTRACT

Liver glycogen is synthesized after a meal in response to an increase in blood glucose concentration in the portal vein and endocrine and neuroendocrine signals, and is degraded to glucose between meals to maintain blood glucose homeostasis. Glycogen degradation and synthesis during the diurnal cycle are mediated by changes in the activities of phosphorylase and glycogen synthase. Phosphorylase is regulated by phosphorylation of serine-14. Only the phosphorylated form of liver phosphorylase (GPa) is catalytically active. Interconversion between GPa and GPb (unphosphorylated) is dependent on the activities of phosphorylase kinase and of phosphorylase phosphatase. The latter comprises protein phosphatase-1 in conjunction with a glycogen-targeting protein (G-subunit) of the PPP1R3 family. At least two of six G-subunits (GL and PTG) expressed in liver are involved in GPa dephosphorylation. GPa to GPb interconversion is dependent on the conformational state of phosphorylase which can be relaxed (R) or tense (T) depending on the concentrations of allosteric effectors such as glucose, glucose 6-phosphate and adenine nucleotides and on the acetylation state of lysine residues. The G-subunit, GL, encoded by PPP1R3B gene is expressed at high levels in liver and can function as a phosphorylase phosphatase and a synthase phosphatase and has an allosteric binding site for GPa at the C-terminus which inhibits synthase phosphatase activity. GPa to GPb conversion is a major upstream event in the regulation of glycogen synthesis by glucose, its downstream metabolites and extracellular signals such as insulin and neurotransmitters.

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Abbreviations: DAB, 1,4-dideoxy-1,4-imino-D-arabinitiol; G-subunits, glycogen targeting proteins of the PPP1R3A-G family; G1P, glucose 1-phosphate; G6P, glucose 6-phosphate; GPa, phosphorylated form of glycogen phosphorylase; GPb, unphosphorylated form of glycogen phosphorylase; GPI, glycogen phosphorylase inhibitors; GL, glycogen targeting protein encoded by PPP1R3B; GS, glycogen synthase; GSD, glycogen storage disease; GSK3, glycogen synthase kinase-3; Phk, phosphorylase kinase; Pi, inorganic phosphate; PKB, protein kinase B, also known as Akt; PP1c, catalytic subunit of protein phosphatase-1; PTG, protein-targeting to glycogen, encoded by PPP1R3C.

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http://dx.doi.org/10.1016/j.mam.2015.09.002
0098-2997/

1. Introduction

Glycogen is a branched polymer of glucosyl residues present in most mammalian cells, where it functions as a store of carbohydrate that can be rapidly degraded by phosphorolysis to generate glucose 1-phosphate (G1P). The glucosyl residues in the branched polymer are linked by α-1-4 bonds along the straight chains and by α-1-6 bonds at the branch points (Roach et al., 2012). Synthesis of glycogen is catalyzed by the enzymes glycogen synthase (GS) and glycogen branching enzyme which catalyze the transfer of glucosyl residues from UDP-glucose to the glycogen molecule and the formation of α-1-4 and α-1-6 bonds. Glycogen degradation is catalyzed by the actions of phosphorylase (1,4-α-D-glucan: orthophosphate α-D-glucosyltransferase), which in the presence of inorganic phosphate (Pi) releases the terminal glucosyl residue of the α-1-4 chains as glucose 1-phosphate (G1P), and by the debranching enzyme (AGL, amylo-α-1,6-glucosidase, 4-α-gluconotransferase) which has two catalytic activities, a transferase which transfers a terminal triose unit from an α-1-6 branch to an α-1-4 chain for catalysis by phosphorylase and a glucosidase which removes the remaining α-1-6 residue as glucose. Control of glycogen degradation in tissues is determined by the activity of phosphorylase, which responds to a wide range of both extracellular and intracellular signals.

In most tissues, glycogen serves as a source of glucose 6-phosphate (G6P) for glycolysis. However, in the liver it serves as a source of glucose to maintain blood glucose homeostasis in the interval between meals. Liver glycogen is synthesized after a meal in response to an increase in glucose concentration in the portal vein, an increase in the insulin-to-glucagon ratio and neuroendocrine signals activated by the substrates in the portal vein (Cherrington, 1999; Moore et al., 2012). In the post-absorptive state, the G1P formed from glycogen degradation is converted to G6P by phosphoglucomutase and transported into the endoplasmic reticulum and hydrolysed to glucose by glucose 6-phosphatase which is expressed at high activity in the liver.

Changes in liver glycogen storage during the diurnal cycle are associated with changes in the activities of phosphorylase and GS which regulated in a reciprocal manner (Udoh et al., 2015). Reciprocal changes in activities of phosphorylase and GS are in part mediated by a glycogen targeted binding protein of protein phosphatase-1 (PP1c) that positively regulates the activity of GS and has an allosteric inhibitor site for the activated phosphorylase (Bollen et al., 1998). Accordingly, activation of phosphorylase determines not only the rate of degradation of glycogen but also inhibition of activation of GS. Regulation of phosphorylase is therefore a major upstream event in the control of glycogen turnover by both extracellular and intracellular signals.

2. Phosphorylase

2.1. Three isoforms PYGL, PYGM, PYGB

There are three isoforms of phosphorylase encoded by 3 genes PYGL, PYGM and PYGB, and designated Liver, Muscle and Brain after the tissues in which they are expressed. There is high sequence identity (~97%) between human and respective rodent isoforms, and 80% identity between the liver isoform and the muscle or brain isoforms. The latter share 83% identity (Hudson et al., 1993a, 1993b; Newgard et al., 1989). Phosphorylase is a dimer composed of monomers of 846 (PYGL), 841 (PYGM) or 862 (PYGB) residues with pyridoxal phosphate, an essential cofactor, in the centre of each monomer covalently linked to a lysine residue.

All 3 isoforms of phosphorylase are regulated allosterically by binding of several metabolite effectors and by reversible phosphorylation of serine-14 (Newgard et al., 1989). Phosphorylase was the first enzyme shown to be regulated by covalent phosphorylation (Krebs and Fischer, 1956). Its regulation by acetylation was discovered recently (Zhang et al., 2012). The phosphorylated and dephosphorylated forms are designated, respectively, GPa and GPb (Fletterick and Madsen, 1980; Johnson, 1992; Newgard et al., 1989).

Phosphorylase exists as an equilibrium of conformational states, represented by the active conformation (Relaxed or R-state) and an inactive conformation (Tense or T-state). The R-state has a high affinity for substrates and certain allosteric effectors such as AMP. The T-state has a low affinity for the substrates, glycogen and Pi (Johnson, 1992; Fig. 1). Phosphorylation of serine-14 and AMP binding to an “allosteric activator site” favour the R-state. This “allosteric AMP activator site” which is adjacent to the phosphorylation site can bind several phosphoryl ligands