Molecular and Cellular Endocrinology 380 (2013) 79–88

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

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

Metabolic functions of glucocorticoid receptor in skeletal muscle

Taiyi Kuo [a,b], Charles A. Harris [c,d,1], Jen-Chywan Wang [a,b,*]

[a] Department of Nutritional Science & Toxicology, University of California at Berkeley, Berkeley, CA 94720, United States
[b] Graduate Program of Endocrinology, University of California at Berkeley, Berkeley, CA 94720, United States
[c] Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, United States
[d] Department of Medicine, University of California at San Francisco, San Francisco, CA 94143, United States

ARTICLE INFO

Article history:
Available online 21 March 2013

Keywords:
Glucocorticoids
Glucocorticoid receptor
Insulin
Skeletal muscle
Glucose metabolism
Protein metabolism

ABSTRACT

Glucocorticoids (GCs) exert key metabolic influences on skeletal muscle. GCs increase protein degradation and decrease protein synthesis. The released amino acids are mobilized from skeletal muscle to liver, where they serve as substrates for hepatic gluconeogenesis. This metabolic response is critical for mammals' survival under stressful conditions, such as fasting and starvation. GCs suppress insulin-stimulated glucose uptake and utilization and glycogen synthesis, and play a permissive role for catecholamine-induced glycogenolysis, thus preserving the level of circulating glucose, the major energy source for the brain. However, chronic or excess exposure of GCs can induce muscle atrophy and insulin resistance. GCs convey their signal mainly through the intracellular glucocorticoid receptor (GR). While GR can act through different mechanisms, one of its major actions is to regulate the transcription of its primary target genes through genomic glucocorticoid response elements (GREs) by directly binding to DNA or tethering onto other DNA-binding transcription factors. These GR primary targets trigger physiological and pathological responses of GCs. Much progress has been made to understand how GCs regulate protein and glucose metabolism. In this review, we will discuss how GR primary target genes confer metabolic functions of GCs, and the mechanisms governing the transcriptional regulation of these targets. Comprehending these processes not only contributes to the fundamental understanding of mammalian physiology, but also will provide invaluable insight for improved GC therapeutics.

1. Introduction

Glucocorticoids (GCs) are steroid hormones secreted from the adrenal cortex to regulate whole-body metabolic homeostasis. The three major endogenous GC hormones are cortisol (hydrocortisone), corticosterone, and cortisone. In humans, the principal endogenous GC is cortisol, while in rodents it is corticosterone. Cortisone is inactive until converted to cortisol or corticosterone by 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1) (Seckl and Walker, 2001; Tomlinson et al., 2004). On the other hand, 11β-HSD type 2 (11β-HSD2) converts active cortisol to inactive cortisone (Krozowski et al., 1999). GCs convey their signals mainly through an intracellular glucocorticoid receptor (GR). Cortisol has equal binding affinity for the mineralocorticoid receptor (MR) and GR; therefore, aldosterone-selective tissues, such as kidney, express 11β-HSD2 to inactivate cortisol. Thus, the levels of 11β-HSD1 and 11β-HSD2 in tissues help determine the tissue concentrations of active GCs, thereby modulating these effects. Notably, in some tissues, such as hippocampus and macrophages, GCs act via both GR and MR under normal physiological conditions, in which MR significantly influences cellular responses to GCs.

GCs exert specific metabolic influence on different tissues. Skeletal muscle accounts for approximately 40% of body mass and is a major GC target tissue. Based on myosin heavy-chain isoform expression profile, skeletal muscle fibers are classified into type I, type IIa, type IIx and type IIb. Type I myofibers are also known as slow-twitch fibers, and type II, fast-twitch fibers. Slow-twitch myofibers are slow to fatigue, are rich in mitochondria, and have long contraction times. Fast-twitch myofibers fatigue rapidly and display quick contractions. Type I muscles appear red in color due to the presence of oxygen-binding protein, myoglobin, while type II appear pale. On the basis of the degree of oxidative phosphorylation, type I and IIa fibers exert oxidative metabolism, while type IIx and IIb mainly use glycolytic metabolism to generate ATP. Interestingly, GCs appear to impact type II muscle fibers much more than type I (Dekhuijzen et al., 1995; Falduto et al., 1990; Fournier et al., 2003), though the mechanism of such fiber-specific GC response is unclear.

* Corresponding author. Address: Department of Nutritional Science and Toxicology, 315 Morgan Hall, University of California at Berkeley, Berkeley, CA 94720-3104, United States. Tel.: +1 510 643 1039.
E-mail address: walwang@berkeley.edu (J.-C. Wang).
[1] Present address: Division of Endocrinology, Washington University School of Medicine, St. Louis, MO 63110, United States.

0303-7207/$ - see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.mce.2013.03.003

In skeletal muscle, GCs mainly regulate protein and glucose metabolism (Fig. 1). Under stressful conditions, such as fasting and starvation, circulating GC levels are increased, which in turn decreases the rate of protein synthesis and increases proteolysis to generate amino acids to serve as precursors for hepatic gluconeogenesis. The resulting glucose can then be used by the brain as fuel. Under pathophysiological conditions, having excess endogenous (Cushing's Syndrome) or exogenous (prolonged medical treatment) sustained GC-mediated protein degradation can lead to skeletal muscle atrophy and muscle weakness. Moreover, GCs preserve plasma glucose through inhibiting glucose uptake and utilization in skeletal muscle, and play a permissive role in epinephrine-induced glycogenolysis. This adaptive course maintains adequate circulating glucose to fuel the brain during stress. However, this course becomes maladaptive upon chronic or excess exposure to GCs. Notably, reducing the level of available bioactive GCs has been shown to improve insulin sensitivity in animal models. The approach of inhibiting 11β-HSD1, thus reducing the level of available bioactive GCs in tissues, is currently under clinical trials for treating type 2 diabetes (Hollis and Huber, 2011; Rosenstock et al., 2010).

Upon binding to GCs, cytosolic GR enters the nucleus and associates with specific genomic sequences called glucocorticoid response elements (GREs). Direct binding of GR to GRE, or negative GRE (nGRE) (Surjit et al., 2011), leads to the recruitment of transcription cofactors to activate, or repress, the transcriptional rate of nearby genes, respectively. Other modes of GR action include tethering (GR binding to other transcription regulators) and squelching (GR binding to and taking away transcription regulator from DNA), which often lead to transcription repression. These genes, defined as GR primary target genes, in turn trigger biological responses of GCs. The goal of this review is to discuss the current understanding of mechanisms governing GC-regulated glucose and protein metabolism, with a main focus on potential GR primary target genes identified in skeletal muscle and mediating the metabolic functions of GCs.

2. The regulation of glucose metabolism by glucocorticoids

Skeletal muscle is one the major tissues accountable for glucose homeostasis in mammals. Approximately 80% of glucose utilization occurs in skeletal muscle (DeFronzo and Tripathy, 2009; Ferrannini et al., 1988). Skeletal muscle also serves as a reservoir for glycogen storage. GCs inhibit glucose uptake and utilization and glycogen synthesis, and play a permissive role for catecholamine-stimulated glycogen breakdown in skeletal muscle (Fig. 1). These actions counteract those of insulin, which promotes glucose utilization and glycogen synthesis. Mice treated with GCs have reduced insulin-stimulated glucose uptake, caused by attenuated insulin-induced GLUT4 translocation to the cell membrane in myotubes (Dimitriadis et al., 1997; Morgan et al., 2009; Weinstein et al., 1998). Furthermore, insulin signaling and glycogen synthase activity are suppressed by GCs (Coderre et al., 1991, 1992; Morgan et al., 2009). These metabolic effects are due to, at least in part, the direct effect of GCs on myotubes, as GC treatment of cultured myotubes inhibits insulin-stimulated glucose utilization (Gathercole et al., 2007; Morgan et al., 2009).

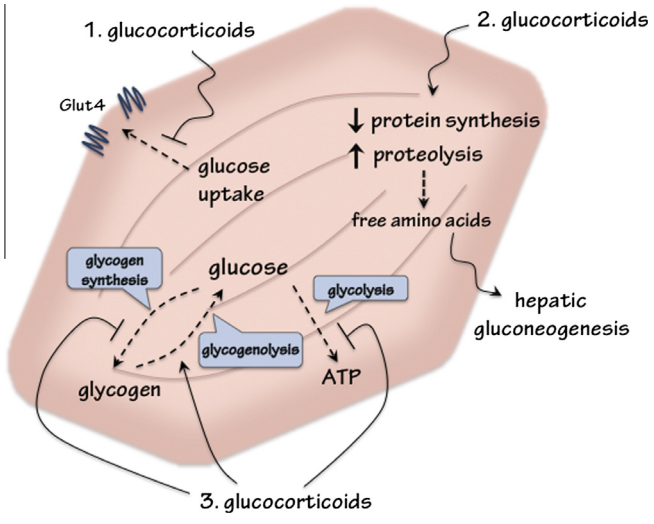

Fig. 1. Metabolic influences of glucocorticoids (GCs) in skeletal muscle to regulate glucose homeostasis. (1) GCs inhibit insulin-stimulated glucose uptake. (2) GCs decrease protein synthesis and increase proteolysis to release amino acids for hepatic gluconeogensis. (3) GCs downregulate glucose utilization by inhibiting glycolysis. GCs also suppress glycogen synthesis, and act with catecholamine to upregulate glycogenolysis.

One major mechanism by which GCs regulate glucose metabolism is to inhibit insulin signaling (Morgan et al., 2009; Pivonello et al., 2010; Schakman et al., 2008). Insulin binds to the cell-surface insulin receptor (IR), a tyrosine kinase that autophosphorylates and phosphorylates the insulin receptor substrate (IRS) (Lee and White, 2004). Tyrosine-phosphorylated IRS associates with IR and activates downstream signaling pathways (Lee and White, 2004). Mice treated with GCs have reduced levels of tyrosine-phosphorylated IR and total IRS-1 proteins in skeletal muscle (Morgan et al., 2009). The activities of phosphoinositide-3-kinase (PI3K) and Akt, two key signaling molecules downstream of IR and IRS-1, are also decreased (Giorgino et al., 1993; Morgan et al., 2009; Saad et al., 1993). Moreover, the phosphorylation of serine 307 of IRS-1 (pSer307-IRS-1) is increased upon GC treatment (Morgan et al., 2009). This phosphorylation disrupts the association between IR and IRS-1, thus reducing the insulin response (Draznin, 2006; Gual et al., 2005). However, recent studies showed that mice harboring IRS-1 serine 307 mutated to alanine had reduced insulin sensitivity (Copps et al., 2010; Copps and White, 2012). It suggested that serine 307 phosphorylation positively regulates insulin sensitivity in vivo. Downstream of Akt, glycogen synthase kinase-3 (Gsk3) phosphorylates and inhibits glycogen synthase (Cohen and Goedert, 2004; Rayasam et al., 2009), an enzyme involved in converting glucose to glycogen. While Akt phosphorylates and reduces the activity of Gsk3, GCs, on the other hand, decrease the phosphorylation status of Gsk3 (Buren et al., 2008; Ruzzin et al., 2005).

In parallel with the PI3K/Akt signaling, another mechanism by which insulin promotes glucose uptake is to initiate the TC10 pathway (Leto and Saltiel, 2012). Insulin treatment triggers the phosphorylation of APS (adapter protein with Pleckstrin homology (PH) and Src homology 2 (SH2) domains), which then facilitates the phosphorylation of Cbl (Hu et al., 2003). Cbl-associated protein (CAP, also known as Sorbs1), as its name suggests, associates with Cbl (Baumann et al., 2000). This phosphorylated Cbl-CAP protein complex translocates to the lipid-raft microdomain at the plasma membrane, leading to the recruitment of Rho GTP-binding protein TC10 and the assembly of the exocyst complex, and finally the translocation of Glut4 to cell surface. Whether GCs can modulate this alternative insulin-initiated pathway is unknown. In contrast to insulin resistance induced by excess GCs, reducing GC level improves insulin sensitivity. Circulating GC levels are higher in obese *ob/ob*, *db/db* and lipotrophic *A-ZIP/F-1* mice than normal mice, and adrenalectomy improved insulin-stimulated muscle glucose disposal in these mice (Haluzik et al., 2002; Ohshima et al., 1989). *A-ZIP/F-1* mice expressed a dominant-negative protein, A-ZIP/F, under the control of the adipose-specific aP2 promoter, and had no WAT and markedly reduced brown adipose tissue (Moitra et al., 1998). This A-ZIP/F protein prevents DNA binding of basic leucine zipper (B-ZIP) transcription factor families, such as C/EBP and Jun. Kuo Kondo (KK) mice, derived from selective inbreeding