Frontiers in Neuroendocrinology 35 (2014) 72–75

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Review

Why do we need nongenomic glucocorticoid mechanisms?

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ARTICLE INFO

Article history:
Available online 5 October 2013

Keywords:
Glucocorticoids
Nongenomic
Stress
Inflammation
Permissive
Glycogenesis
Physiological significance

ABSTRACT

Glucocorticoids (GCs) are a class of steroid hormones that have been known to be involved in various physiological processes and to play a pivotal role in preserving basal and stress-related homeostasis. GCs are also widely used clinically as anti-inflammatory, immunosuppressive, anti-shock drugs. It is believed traditionally that GCs exert most of their effects genomically. In addition to the well-known classical genomic mechanisms, GCs also affect various functions via rapid, nongenomic mechanisms. The therapeutic benefits of nongenomic GC actions have been exploited in clinical medicine, especially with high-dose pulsed glucocorticoid administration. However, it is certainly not the case that the inherent nongenomic glucocorticoid mechanisms evolved only for their clinical utility. Here, we review the recent literature on nongenomic actions of GCs related to stress and the physiological significance of these actions, and we propose reasons why nongenomic mechanisms of GC actions are needed.

1. Introduction

Glucocorticoids (GCs) are a class of steroid hormones that have been known to be involved in various physiological processes, including growth, metabolic, developmental and immune functions, and to play a pivotal role in preserving basal and stress-related homeostasis. GCs are also widely used clinically as anti-inflammatory, immunosuppressive, and antishock drugs. It is believed traditionally that GCs exert most of their effects genomically. According to the classic genomic theory of action, GCs bind to specific glucocorticoid receptors (GRs) located in the cell cytoplasm and the GC–GR complex translocates into the nucleus, where it modulates the transcriptional activity of glucocorticoid-responsive genes in one of two ways: either by binding to specific sequences, glucocorticoid-response elements (GREs), in the promoter region of target genes, or through protein–protein interactions with other transcription factors, such as nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and several signal transducers and activators of transcription (STATs), and positive or negative modulation of their effects on the expression of target genes Beato et al., 1996.

In addition to the well-known classical genomic mechanisms of GC action, mounting evidence suggests that GCs also affect various functions via rapid, nongenomic mechanisms (Borski, 2000; Losel and Wehling, 2003; Stahn and Buttgereit, 2008). The nongenomic GC mechanisms have been exploited in clinical therapy, where it has become increasingly evident that nongenomic GC activity may be relatively more important in mediating the therapeutic effects of intermediate-to-high doses of GCs, especially in high-dose pulsed glucocorticoid administration (Buttgereit et al., 1998; Lipworth, 2000).

However, cortisone was first used successfully to treat rheumatoid arthritis in 1948 (Hench et al., 1949). So, it is impossible that the evolution of the important nongenomic mechanisms of GC action only waits for the clinical usage since then. Moreover, it is also impossible that the inherent nongenomic mechanisms only exist for someone's clinical application one day. Why do we need the nongenomic mechanisms of GCs? Until now, the physiological significance of the nongenomic effects of GCs has not been clear.

Through review of the various reports about the nongenomic actions of GCs, it is not difficult to find that most of the dosages used to elicit the nongenomic effects of GCs are high and outside the physiological range. GCs are secreted from the adrenal glands in hourly ultradian pulses, on top of which a surge is superimposed following stress. Under stress conditions, the GC concentration in the blood can rise to reach up to ten times its basal level. During the stress response, therefore, the GC concentration may reach levels required for nongenomic effects (Sarabdjitsingh et al., 2012; Ganong, 2001).

It is well established that the GC secretory response to ACTH and stress is fast, occurring within a few minutes. However, the GC effects on target tissues do not begin for at least 1 h after the onset of the stressor (Sapolsky et al., 2000). The effects of steroids that are mediated by the modulation of gene expression are known to occur with a delay of hours or even days. So, there is a time lag

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0091-3022/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yfrne.2013.09.005

between the rapid secretion of GC during acute stress and the classical GC actions. What happens during this period? And from an evolutionary perspective, why is there a time lag following fast secretion?

It is inferred, therefore, that the physiological significance of the nongenomic effects of GCs is related to stress. However, although there is some indirect evidence (Haller et al., 2008; Groeneweg et al., 2011), a strong experimental basis for a physiological role of nongenomic GC mechanisms in the stress response is still lacking.

2. Nongenomic effects of GCs on enhancing stress tolerance

The sympathetic-adrenal medullary (SAM) system is considered to be recruited into action at the very start of the stress response. The cardiovascular and neuroendocrine functions activated by catecholamines mobilize energy to the muscles, heart, and brain and, at the same time, reduce blood flow to the skin, internal organs and gastrointestinal system. This is an efficient means of attending to an acute stress. Nevertheless, studies on the relative importance to survival of the adrenal cortex and the adrenal medulla have revealed that, in contrast to the cortex, the medulla is not essential for life. Sympathectomized animals tolerate a variety of stresses with relative impunity. Yet, an elevated circulating GC level is essential for survival (Ganong, 2001).

One of the most important actions of GCs is to enhance the response to stress and to protect the organism from specific challenges to homeostasis. Almost any type of stress, whether physical or psychogenic, causes a rapid and marked increase in ACTH secretion by the anterior pituitary gland, followed within minutes by greatly increased adrenocortical secretion of cortisol. Even though it is well known that cortisol secretion increases significantly in stressful situations, and that this enhances tolerance to stress, it is believed traditionally that GCs exert these effects genomically.

Nongenomic effects of GCs are characterized as short latency and insensitive to inhibitors of DNA transcription and protein synthesis (e.g. actinomycin D and cycloheximide) compared with genomic effects, which require at least 30 min and up to several hours or days to take effect.

Thus, we can infer that the nongenomic effects of GCs play a vital role in the early phase of acute stress. However, a strong experimental basis for this is still lacking. We have used an acute weight-loaded forced swim (AWLFS) test to investigate the rapid effects of a stress dose of corticosterone (CORT) on exhaustion stress tolerance in adrenalectomized mice. The experiment was designed such that, if the stress intensity was too low, such as mice loaded with a light weight load, and GC prolonged the exhaustion time more than 30 min, a genomic mechanism could not be excluded. Conversely, if the stress intensity was too high, such as if the temperature of the water was too low, it was difficult to show the significant results. A stress dose of CORT prolonged significantly the exhaustion time in AWLFS mice in less than 20 min, and this effect was not blocked by the GC receptor antagonist RU486. There was less tearing and lysis in skeletal muscle fibers in the CORT-treated group than in the control group. Electron microscopic analysis showed mitochondrial pyknosis and an increased density, dilatation and vacuolization of sarcoplasmic reticulum vesicles and loss of the Z disc and M line in the control group compared with CORT-treated animals. Blood glucose and skeletal muscle tissue ATP were higher in the CORT-treated group compared to the control group, an effect that was not blocked by RU486 (unpublished data). These results suggest that there exist nongenomic mechanisms of GC actions that enhance stress tolerance during stress response.

Therefore, GCs may improve the tolerance to acute stress and maintain stress-related homeostasis via nongenomic mechanisms at the beginning of the stress response, prior to the start of the genomic GC actions. In other words, GCs may also play a vital role in the stress response during the lag time between the rapid GC secretion and the classical GC genomic effects, and physiological significance of nongenomic effects of GCs is related to stress.

3. Nongenomic mechanisms of rapid GC actions during stress processes

When an animal or human is exposed to any of a wide variety of noxious or potentially noxious stimuli, there is an increased secretion of ACTH and, consequently, a rise in circulating GCs. This rise in GC level is essential for resisting stress and for survival. Hypophysectomized animals, or adrenalectomized animals treated with basal levels of GCs, die when exposed to the same noxious stimuli. Although they are definitely harmful in the long run, the high "pharmacologic" levels of plasma GCs induced by stress are life-saving in the short run (Ganong, 2001).

The reason an elevated circulating level of GCs is essential for resisting stress remains, for the most part, unknown. Nevertheless, there are similar descriptions in most textbooks about the mechanisms of rapid GC secretion for resistance to stress, including: (1) to suppress the synthesis and decrease the release of inflammatory factors to inhibit the inflammatory response to tissue injury, (2) to maintain blood pressure by optimizing the vascular response to catecholamines via permissive actions, and (3) to elevate blood glucose concentration by increasing gluconeogenesis and FAA-mobilizing actions.

According to these mechanisms of rapid GC actions during stress, here we review the recent literature and findings from our laboratory, and we ask whether nongenomic mechanisms play a part in these GC actions.

3.1. Inhibiting inflammatory factors and the inflammatory response

Although nongenomic steroid effects have been widely recognized recently, relatively little has been reported on the nongenomic effect of GCs on anti-inflammation and immunosuppression. GCs exert rapid effects on immune cells (Buttgereit and Scheffold, 2002; Stellato, 2004; Zen et al., 2011). Thus, GCs rapidly inhibit the signal transmission pathway mediated by T-cell receptors (TCR) using a nongenomic mechanism that requires the binding of GCs to membrane receptors and not nuclear receptors (Löwenberg et al., 2006). GCs regulate thymocyte apoptosis through a nongenomic GC signaling pathway (Boldizsar et al., 2010). GCs can directly regulate cell adhesion and locomotion by a nongenomic mechanism that is independent of modulation of gene expression (Pitzalis et al., 2002).

We have studied the nongenomic mechanisms of GCs actions in neutrophils, macrophages, and mast cells. GCs can inhibit the immune and inflammatory activities of these cells via nongenomic mechanisms. Few cells play as prominent a role as the neutrophil in the inflammatory response and, therefore, the effect of glucocorticoids on neutrophils from human and other species has been an area of great interest (Dallegri and Ottonello, 1997; Boxer and Smolen, 1998; Zen et al., 2011). Human neutrophils contain three main lysosomal granules, azurophil granules, specific granules and gelatinase granules, and secretory vesicles. Specific proteolytic and digestive enzymes capable of destroying the extracellular matrix and bacterial debris are stored inside these granules, which, therefore, are involved in immune and inflammatory processes as well as in a variety of diseases and tissue injuries (Borregaard and Cowland, 1997; Dupont et al., 1999). Both 6a-methylprednisolone and hydrocortisone showed significant inhibitory effects on