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Fat-brain connections: Adipocyte glucocorticoid control of stress and metabolism

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Abstract

Glucocorticoids act via multiple mechanisms to mobilize energy for maintenance and restoration of homeostasis. In adipose tissue, glucocorticoids can promote lipolysis and facilitate adipocyte differentiation/growth, serving both energy-mobilizing and restorative processes during negative energy balance. Recent data suggest that adipose-dependent feedback may also be involved in regulation of stress responses. Adipocyte glucocorticoid receptor (GR) deletion causes increased HPA axis stress reactivity, due to a loss of negative feedback signals into the CNS. The fat-to-brain signal may be mediated by neuronal mechanisms, release of adipokines or increased lipolysis. The ability of adipose GRs to inhibit psychogenic as well as metabolic stress responses suggests that (1) feedback regulation of the HPA axis occurs across multiple bodily compartments, and (2) fat tissue integrates psychogenic stress signals. These studies support a link between stress biology and energy metabolism, a connection that has clear relevance for numerous disease states and their comorbidities.

Introduction

Organisms require the capacity to respond efficiently to internal or environmental adversity. Adaptation is accomplished by engagement of multiple interacting regulatory systems to mobilize energy, with the end goal of providing resources for emergent challenges ('stressors'), be they real or anticipated. Stress regulation is accomplished by a number of neural and hormonal systems, acting in concert to promote redistribution of resources.

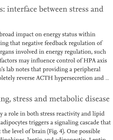
The importance of appropriate stress regulation is illustrated in the hypothetical schematic shown in Fig. 1 (Myers et al., 2014). As noted, if environmental or internal conditions require adaptive processes, additional energy needs to be added in the system in order to compensate. Ideally, the organism would be able to add sufficient energy to insure peak performance over a wide range of stressor intensity. The net adaptive capacity is limited by two factors: the total availability of resources and the catabolic processes that are initiated by the stress responses themselves. The latter may be considered as a 'cost of doing business', and the efficiency of the stress response may be a determining factor in overall adaptive capacity.

Figures

Stress and adaptation. The relationship between stress and energetics can be explained visually by examining the relationship between systems performance and environmental demand. Under conditions of ...

Impact of adipocyte-GR knockdown on gene expression within retroperitoneal white adipose tissue [rpWAT] of mice fed standard diet. (A) Schematic of adipocyte-GR knockdown generation as in de Kloet et ...

Glucocorticoid-lipolysis interactions during acute stress exposure. (A) Exposure to an acute 30 min restraint stress leads to a significant elevation in plasma glycerol levels. (B and C) Administratio...



Putative mechanisms of adipocyte glucocorticoid feedback. Adipocytes may interact directly or indirectly with HPA axis function via corticotropin-releasing hormone (CRH) in the paraventricular nucleu...

Section snippets

Glucocorticoids, HPA axis and stress energetics

Glucocorticoids comprise one of the key components of stress responses. Glucocorticoids act by genomic (and possibly non-genomic) mechanisms to promote gluconeogenesis in the liver, proteolysis and consequent amino acid mobilization in muscle, and lipolysis in fat (Exton, 1979, Cederre et al., 1991, Munck et al., 1984, Schweiger et al., 2006). All of these processes enhance glucose availability, thereby increasing circulating energy stores. Importantly, mechanisms of glucocorticoid production...

Physiology of glucocorticoid signaling mechanisms in fat

In the periphery, glucocorticoids play an integral role in the redistribution of energy stores in order to cope with stressors. Both GR and MR are densely-expressed in peripheral organs (John et al., 2016) and, during normal physiological responses to stress, the acute actions of glucocorticoids at the liver, muscle and adipose tissue are, as mentioned above, largely such that energy stores are mobilized. The result is an increased availability of substrates for mitochondrial oxidation (i.e...

Adipose glucocorticoid receptors: interface between stress and metabolism

As elevated glucocorticoids present such a broad impact on energy status within peripheral organs, it is perhaps not surprising that negative feedback regulation of this steroid hormone involves peripheral organs involved in energy regulation, such as fat. Prior studies suggest that metabolic factors may influence control of HPA axis reactivity. For example, work from Dallman's lab notes that providing a peripheral metabolic signal (sucrose) can almost completely reverse ACTH hypersecretion and ...

Adipocyte glucocorticoid signaling, stress and metabolic disease

Our studies suggest that adipocyte GRs play a role in both stress reactivity and lipid metabolism. It is likely that GR binding in adipocytes triggers a signaling cascade that culminates in inhibition of the HPA axis at the level of brain (Fig. 4). One possible candidate mechanism involves release of adipokines, leptin and adiponectin. Leptin is known to inhibit HPA axis responses to restraint stress and exercise via actions on PVN neurons (see Heiman et al., 1997, Stieg et al., 2015). In...

Conclusion

It is clear that stress and metabolism are closely linked, and that glucocorticoid signaling is an important component of this linkage. Glucocorticoid secretion and HPA axis activation are often thought of as stress-dependent processes. However, it is important to consider that energy redistribution (as discussed in the Introduction) is a principal responsibility of the HPA axis. Glucocorticoids signal to vital energy storage depots [liver, muscle] to mobilize glucose under conditions where...

Acknowledgements

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References (94)

M.E. Wilson et al.
Chronic subcutaneous leptin infusion diminishes the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis in female rhesus monkeys
Physiol. Behav. (2005)

M. Wieczorek et al.
Physiological and behavioral responses to interleukin-1beta and LPS in vagotomized mice
Physiol. Behav. (2005)

M. Wieczorek et al.
Effect of subdiaphragmatic vagotomy on the noradrenergic and HPA axis activation induced by intraperitoneal interleukin-1 administration in rats
Brain Res. (2006)

S. Suksmaran et al.
Glucocorticoid effects on adiponectin expression
Vitam. Horm. (2012)

M.R. Stieg et al.
Leptin: a hormone linking activation of neuroendocrine axes with neuropathology
Psychoneuroendocrinology (2015)

B.G. Slavin et al.
Hormonal regulation of hormone-sensitive lipase activity and mRNA levels in isolated rat adipocytes
J. Lipid Res. (1994)

M. Schweiger et al.
Adipose triglyceride lipase and hormone-sensitive lipase are the major enzymes in adipose tissue triacylglycerol catabolism
J. Biol. Chem. (2006)

G.J. Schwartz
Dirty dealing: hepatic vagal afferents reshuffle fat distribution
Cell Metab. (2006)

G. Rossi et al.
Aldosterone as a cardiovascular risk factor
Trends Endocrinol. Metab. (2005)

M. Rebuffe-Scrive et al.
Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism
Physiol. Behav. (1992)

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