Cell Metabolism

Volume 2, Issue 5, November 2005, Pages 278–281

Preview

Enlightening the adrenal gland

Ueli Schibler[1], Steven A. Brown[1, 2]

[1] Department of Molecular Biology and NCCR Frontiers of Genetics, Sciences III, University of Geneva, 30, Quai Ernest Ansermet, CH-1211, Geneva-4, Switzerland

[2] Present address: Institute for Medical Immunology, Charité Hospital, Humboldt University, Hessische Strasse 3-4, D-10115 Berlin, Germany

Available online 8 November 2005.

http://dx.doi.org/10.1016/j.cmet.2005.10.001, How to Cite or Link Using DOI
Permissions & Reprints

The secretion of glucocorticoid hormones is tightly regulated by the circadian clock and by negative humoral feedback loops, both acting on the hypothalamic-pituitary gland-adrenal axis. However, a new study (Ishida et al., 2005 [this issue of *Cell Metabolism*]) shows that light can influence the adrenal's glucocorticoid output by a more direct pathway.

Main Text

It has been known for a long time that plasma glucocorticoid hormone levels follow robust daily oscillations, which are driven by the master circadian clock in the suprachiasmatic nucleus (SCN) via the hypothalamic-pituitary gland-adrenal axis. As a consequence, the transcription of many glucocorticoid-responsive genes in peripheral organs may fluctuate during the day. However, glucocorticoids may also act on the circadian expression of genes that are not directly glucocorticoid sensitive, namely by acting as timing cues for cell-autonomous clocks in peripheral tissues. The paper by Ishida et al. (2005) suggests that this synchronization could be accomplished by a novel pathway in which light directly stimulates adrenal glucocorticoid synthesis and secretion via the SCN and the splanchic nerve.

Glucocorticoids—cortisone in humans and corticosterone in rodents—participate in a dazzling array of physiological functions. During starvation, they increase glucose supply for the brain and other tissues by promoting hepatic gluconeogenesis and by stimulating the breakdown of lipids and proteins to metabolites that can serve as substrates for gluconeogenesis. They act as immunosupressors by stimulating T-lymphocyte apoptosis, and as anti-inflammatory agents by interfering with proinflammatory cytokine secretion. Furthermore, they play important roles in lung surfactant production, bone homeostasis, mammary gland development, and memory consolidation (Miller and Tyrell, 1995). More recently, glucocorticoid signaling has also been shown to participate in the timing of circadian rhythms in peripheral cell types and organs (Le Minh et al., 2001). Mice homozygous for a glucocorticoid null allele die shortly after birth due to respiratory failure (Cole et al., 1995).

Glucocorticoids are produced from cholesterol in the adrenal cortex. Due to their lipophilic nature, they can directly diffuse into cells, where they activate the glucocorticoid receptor by releasing it from inactive, cytosolic complexes with chaperones and immunophilins. The ligand bound receptor migrates to the nucleus, binds to glucocorticoid-responsive elements (GREs) within promoter or enhancer regions, and, depending on the protein-protein interactions it establishes with other transcription factors such as cJun, cFos, NFkB, STATs, and SMADs, can enhance or repress transcription of target genes (Schoneveld et al., 2004).

Given the critical functions glucocorticoids have in many physiological processes, the plasma levels of these hormones are tightly regulated. Classically, this control was believed to be exerted exclusively by the central nervous system on the hypothalamic-pituitary-adrenal (HPA) axis and by negative humoral feedback loops within this axis. Thus, inputs from various brain regions, including the suprachiasmatic nucleus harboring the central circadian timekeeper, elicit secretion of corticotropin-releasing factor (CRF) from specialized neurons in the hypothalamus. CRF then stimulates the secretion of adrenocorticotropic hormone (ACTH) from corticotroph cells in the pituitary gland, which in turn triggers the synthesis and secretion of glucocorticoid hormones in the adrenal cortex. Due to the influence of the circadian clock on CRF secretion, glucocorticoid levels oscillate with robust daily rhythms in the plasma of most mammals, reaching peak levels just before the onset of the activity period. In addition, glucocorticoids repress their own synthesis through two negative feedback loops, by inhibiting the synthesis of CRF in hypothalamic neurons and ACTH in pituitary gland corticotrophs (Tronche et al., 1998).

Recent evidence, however, has suggested that in response to dehydration, the sympathetic nervous system can stimulate glucocorticoid secretion in the adrenal gland of rats directly via splanchnic nerve innervation. Such regulation might be of wide physiological significance since glucocorticoid synthesis has been documented in the absence of elevated ACTH levels in a wide variety of cases—anorexia, depression, Alzheimer's disease, ischemic injury, and abdominal or brain injury (Ulrich-Lai and Engeland, 2002, and references therein).

abdominal organs. When examining anesthetized *mPer1-luc* mice exposed to light, the authors found that *mPer1* expression was strongly induced in the adrenal gland shortly after the light treatment. Subsequent microarray analysis showed that this surge of *mPer1* expression was accompanied by the expression of other immediate early genes, such as CREM (cAMP responsive element modulator) and members of the Nr4a and Nr5a nuclear receptor subfamilies. More importantly, light potently induced the production of corticosterone in the adrenal cortex and elicited a rise of corticosterone concentrations in both the blood plasma and the cerebrospinal fluid. Lesion experiments indicated that both the SCN and the adrenal nerve are required for light-induced corticosterone secretion. However, as light had no influence on ACTH plasma levels, the stimulation of adrenal cortex activity by light does not appear to involve the HPA axis.

The physiological significance of this new pathway, which is schematically outlined alongside the more classical one in Figure 1, is still open to speculations. Conceivably, the light-induced increase in corticosterone secretion could participate in the phase resetting of circadian oscillators throughout the body. Consistent with this hypothesis, the glucocorticoid receptor is present in all peripheral tissues and in most brain regions. Interestingly, however, it is absent from the suprachiasmatic nucleus itself, perhaps preventing the master clock from being influenced by its own commands (Balsalobre et al., 2000). In peripheral organs and fibroblasts grown in tissue culture, *mPer1* expression and subsequent phase shifts in circadian gene expression are induced by a large variety of chemical signals, including the glucocorticoid receptor agonist dexamethasone (Balsalobre et al., 2000). Moreover, Cushing's syndrome patients, who experience a wide range of physiological problems due to constitutively elevated cortisone levels, also suffer from sleep-related circadian abnormalities (Friess et al., 1995).

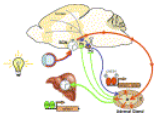

Figure 1. Model of humoral and light-induced regulation of glucocorticoid secretionIn the classical pathway (indicated by blue arrows), hypothalamic neurons producing corticotropin-releasing factor (CRF) receive input from afferent neurons in the cortex (dotted blue lines) and other brain regions reacting to physical and psychic stress (abbreviation of brain structures: SCN, suprachiasmatic nucleus; Hy, Hypothalamus; T, Thalamus, Cb cerebellum; PG, pituitary gland). These neurons also receive input from the SCN, which controls the circadian secretion of CRF. The phase of the SCN master clock is reset every day by light inputs from the retina via the retino-hypothalamic tract (blue arrow from eye to SCN). CRF triggers the production and release of ACTH from the pituitary gland, which in turn elicits the production and release of glucocorticoid hormones from the adrenal cortex (C). In the new pathway discovered by Ishida et al. (2005) (red arrows), light can induce the synthesis and secretion of glucocorticoids more directly through connections of the SCN with the sympathetic nervous system innervating the adrenal medulla (M). Epinephrine, secreted by the medulla, triggers the expression of *mPer1* and other immediate early genes (*IEGs*) in the cortex, perhaps via the activation of CREB (cyclic AMP response element binding protein) through MAP kinase-mediated phosphorylation (P). Some of the IEG products affect the accumulation and/or activity of steroidogenic enzymes, leading to an enhanced secretion of glucocorticoid hormones into the bloodstream (green arrow) and the activation of glucocorticoid receptor (GR) in many peripheral organs (e.g., liver, as shown here). *mPer1*, a direct target gene of GR, is induced, and the surge of mPER1 accumulation resets the clock in peripheral organs. High levels of glucocorticoids inhibit the synthesis of CRF and ACTH in the hypothalamus and the pituitary gland, respectively (green repression bars).

If a light-induced pathway were also operative in humans, a question that could readily be examined by recording plasma cortisone levels after light exposure, it would be tempting to speculate that cortisone-mediated synchronization of peripheral circadian clocks would be one of the beneficial effects light therapy has on patients affected by seasonal affective disorder (SAD). It might also explain why bright light therapy can aid patients with other depressive disorders not typically associated with the circadian clock (e.g., major depressive disorder and bipolar disorder) (Kripke, 1998). In short, from the perspectives of both chronobiologists and clinicians, sympathetic signaling to the adrenal gland could prove to be of great physiological interest.

Selected reading

Balsalobre et al., 2000 A. Balsalobre, S.A. Brown, L. Marcacci, F. Tronche, C. Kellendonk, H.M. Reichardt, G. Schutz, U. Schibler
Science, 289 (2000), pp. 2344–2347

View Record in Scopus| Full Text via CrossRef | Cited By in Scopus (557)

Cole et al., 1995 T.J. Cole, J.A. Blendy, A.P. Monaghan, K. Krieglstein, W. Schmid, A. Aguzzi, G. Fantuzzi, E. Hummler, K. Unsicker, G. Schutz
Genes Dev., 9 (1995), pp. 1608–1621

View Record in Scopus| Full Text via CrossRef | Cited By in Scopus (496)

Friess et al., 1995 E. Friess, K. Wiedemann, A. Steiger, F. Holsboer
Adv. Neuroimmunol., 5 (1995), pp. 111–125

Article | PDF (1151 K) | View Record in Scopus | Cited By in Scopus (74)

Ishida et al., 2005 A. Ishida, T. Mutoh, T. Ueyama, H. Bando, S. Masubuchi, D. Nakahara, G. Tsujimoto, H. Okamura
this issue Cell Metab., 2 (2005), pp. 297–307

Article | PDF (852 K) | View Record in Scopus | Cited By in Scopus (119)

Kripke, 1998 D.F. Kripke
J. Affect. Disord., 49 (1998), pp. 109–117

Article | PDF (291 K) | View Record in Scopus | Cited By in Scopus (111)

Le Minh et al., 2001 N. Le Minh, F. Damiola, F. Tronche, G. Schutz, U. Schibler
EMBO J., 20 (2001), pp. 7128–7136

View Record in Scopus| Full Text via CrossRef | Cited By in Scopus (71)

Miller and Tyrell, 1995 W.L. Miller, J.B. Tyrell
P. Felig, J. Baxter, L. Frohman (Eds.), Endocrinology and Metabolism, McGraw-Hill, New York (1995), pp. 555–711

Schoneveld et al., 2004 O.J. Schoneveld, I.C. Gaemers, W.H. Lamers
Biochim. Biophys. Acta, 1680 (2004), pp. 114–128

Article | PDF (791 K) | View Record in Scopus | Cited By in Scopus (129)

Tronche et al., 1998 F. Tronche, C. Kellendonk, H.M. Reichardt, G. Schutz
Curr. Opin. Genet. Dev., 8 (1998), pp. 532–538

Article | PDF (836 K) | View Record in Scopus | Cited By in Scopus (107)

Ulrich-Lai and Engeland, 2002 Y.M. Ulrich-Lai, W.C. Engeland
Neuroendocrinology, 76 (2002), pp. 79–92

View Record in Scopus| Full Text via CrossRef | Cited By in Scopus (38)

Ph: +41 22 379 61 75; F: ++41 22 379 68 68