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Review

Acetylation-mediated epigenetic regulation of glucocorticoid receptor activity: Circadian rhythm-associated alterations of glucocorticoid actions in target tissues

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ABSTRACT

Glucocorticoids influence organ functions through the glucocorticoid receptor, a protein acetylated and deacetylated by several histone acetyltransferases and deacetylases. We reported that the circadian rhythm-related transcription factor "Clock", a key component of the biological CLOCK with inherent histone acetyltransferase activity, acetylates glucocorticoid receptor lysines within its hinge region—a "lysine cluster" containing a KXKK motif—and represses its transcriptional activity. This Clock-induced repression of the glucocorticoid receptor activity is inversely phased to the diurnally circulating glucocorticoids and may act as a local counter regulatory mechanism to the actions of these hormones. Importantly, uncoupling of the central CLOCK-regulated hypothalamic–pituitary–adrenal axis and peripheral CLOCK-mediated alterations of glucocorticoid action, such as chronic stress and frequent trans-time zone travel or night-shift work, may cause functional hypercortisolism and contribute to various pathologies. Thus, acetylation-mediated epigenetic regulation of the glucocorticoid receptor may be essential for the maintenance of proper time-integrated glucocorticoid action, significantly influencing human well-being and longevity.

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Abbreviations: ACTH, adrenocorticotropic hormone; Dbp, albumin gene D site-binding protein; AMPK, AMP-activated protein kinase; AR, androgen receptor; AVP, arginine vasopressin; bHLH, basic helix-loop-helix; Bmal1, brain-muscle-arnt-like protein 1; CNS, central nervous system; Clock, circadian locomotor output cycle kaput; CRH, corticotropin-releasing hormone; Cry, cryptochrome; CTE, C-terminal extension; DBD, DNA-binding domain; ER, estrogen receptor; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HSP, heat shock protein; HAT, histone acetyltransferase; HDAC, histone deacetylase; HPA axis, hypothalamic–pituitary–adrenal axis; INHAT, inhibitor of histone acetyltransferases; LBD, ligand-binding domain; MR, mineralocorticoid receptor; MAPK, mitogen-activated protein kinase; NTD, N-terminal or immunogenic domain; NF-κB, nuclear factor of κB; NL, nuclear localization signal; NRID, nuclear receptor-interacting domain; NR3C1, nuclear receptor superfamily 3, group C, member 1; p/CAF, p300/CBP-associated factor; CBP, p300/CREB-binding protein; PVN, paraventricular nucleus; PAS, PER-ARNT-SIM; Per, period; PR, progesterone receptor; RORα, retinoic acid receptor-related orphan receptor α; SCN, suprachiasmatic nucleus; Tip60, Tat-interacting protein 60; TAF-Iβ, temperature-activating factor-Iβ; TSA, tricostatin-A; DRIP/TRAP, vitamin D receptor-interacting protein/thyroid hormone receptor-associated protein.

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1. Introduction

Mammalian organisms are influenced by unforeseen changes in the environment called "stressors", and thus, have developed a highly sophisticated and conserved system, the Stress System, to help deal with them. This system is composed of the hypothalamic–pituitary–adrenal (HPA) axis and the locus caeruleus/norepinephrine-autonomic nervous systems (Chrousos, 1995; Miller and O'Callaghan, 2002; Sheridan, 2003; Chrousos, 2009; Chrousos, 2010). The HPA axis consists of the parvicellular corticotropin-releasing hormone (CRH)- and arginine vasopressin (AVP)-secreting neurons located in the hypothalamic paraventricular nucleus (PVN), the corticotrophs of the pituitary gland, and the adrenal gland cortices (Elenkov et al., 2000; Chrousos, 2009; Kudielka and Wust, 2010). The PVN neurons release CRH and AVP into the hypophyseal portal system located under the median eminence of the hypothalamus in response to signals from higher brain regulatory centers. Secreted CRH and AVP reach the pituitary gland and synergistically stimulate the secretion of adrenocorticotropic hormone (ACTH) (Bao et al., 2008; Chrousos, 2009; Aguilera, 2010). ACTH released into the systemic circulation finally stimulates production and secretion of glucocorticoids from the cortex of the adrenal glands (Chrousos, 1995). Secreted glucocorticoids in turn suppress higher regulatory centers, the PVN and the pituitary gland, forming a closed negative feedback loop that aims to reset the activated HPA axis and restore its homeostasis (Chrousos, 1995; Arafah, 2006; Chrousos, 2009; Aguilera, 2010).

The stress-responsive HPA axis is essential for survival in mammals and has strong and diverse actions on every aspect of their physiology (Kino and Chrousos, 2005; Aguilera, 2010; Chrousos, 2010). Indeed, its end-effector molecules, the glucocorticoids, are necessary for proper functioning of virtually all organs and tissues, including the central nervous system (CNS), and the respiratory, cardiovascular, immune and musculoskeletal systems (Eskandari and Sternberg, 2002; Kino and Chrousos, 2005). Upon exposure to stress, glucocorticoids secreted into the systemic circulation in large amounts dramatically alter physiology, influencing behavior, and shifting intermediary metabolism towards catabolism and modulating immune function (Chrousos, 1995; Chrousos, 2001; Kino and Chrousos, 2005; Kyrou and Tsigos, 2009).

The activity of the Stress System is diurnally linked to the rotation of the planet and appropriately connected with the daily activity/rest of the organism and circulating glucocorticoid levels, i.e. cortisol in humans and corticosterone in rodents, are under the strong circadian influence of the suprachiasmatic nucleus (SCN) of the hypothalamus (Chrousos, 1995; Nader et al., 2010a,b). In humans, the cortisol diurnal zenith is reached in the early morning and the nadir at midnight, with the purpose of helping adjust the body's activities to the regular periodicity of day/night changes. The time-integrated daily secretion of glucocorticoids is tightly regulated; indeed, the circadian, negative feedback and stress-related activities of the HPA axis are integrated "rheostatically" by higher brain centers (Chrousos, 1995; Nader et al., 2010a,b).

The overall sensitivity of tissues to glucocorticoids, on the other hand, is also regulated by various physiologic and pathologic processes (Kino et al., 2003; Chrousos and Kino, 2005). For example, glucocorticoid action in cells is specifically adjusted during the different phases of the cell cycle (Cidlowski and Michaels, 1977; Abel et al., 2002), while adrenomedullary cells exposed to very high concentrations of glucocorticoids directly diffusing from the adjacent adrenal cortex, are resistant to these hormones in a gene-specific fashion (Wurtman, 2002; Ehrhart-Bornstein and Bornstein, 2008). In addition, several autoimmune/allergic/inflammatory disorders, the metabolic syndrome, septic conditions and even infection with the human immunodeficiency virus type-1, have been associated with alterations in the responsiveness of specific organs and tissues to glucocorticoids (Kino et al., 2003; Webster et al., 2004; Chrousos and Kino, 2005; Chrousos and Kino, 2007). Underlying mechanisms(s) for the alterations of local glucocorticoid actions, however, have not been fully elucidated as yet.

2. Glucocorticoid receptor (GR) and regulation of its activities

The diverse actions of glucocorticoids at their target tissues are mediated by a single intracellular protein molecule the glucocorticoid receptor (Chrousos, 1995; Nicolaides et al., 2010) (Fig. 1). This receptor, also known as the "nuclear receptor superfamily 3, group C, member 1 (NR3C1)", is expressed virtually in all organs and tissues of the human body, and belongs to the steroid/sterol/thyroid/retinoid/orphan nuclear receptor superfamily, which consists of 48 members in humans (O'Malley, 1990; Kino et al., 2003; Chrousos and Kino, 2005). The human GR gene, located in the short arm of chromosome 5 (5q31.3), is composed of 9 exons, and encodes two protein molecules GRα and GRβ through alternative use of specific exons 9α and 9β (Kino et al., 2009; van der Vaart and Schaaf, 2009) (Fig. 1). GRα is the ubiquitously expressed classic receptor that binds to and mediates most of the known actions of glucocorticoids, while GRβ, although also expressed widely, does not bind glucocorticoids and its physiologic actions have not been fully elucidated as yet (Kino et al., 2009). It recently became evident that the GRα variant mRNA is translated from at least 8 initiation sites into multiple amino terminal GRα isoforms, termed A through D (A, B, C1-C3 and D1-D3), with distinct specific transcriptional activities on glucocorticoid-responsive genes (Lu and Cidlowski, 2005).

The human GRα consists of 777 amino acids and has 3 major distinct functional domains, the N-terminal or immunogenic (NTD), the DNA-binding (DBD) and the ligand-binding (LBD) domains (Hollenberg et al., 1985; Kino and Chrousos, 2004) (Fig. 1). GRα has also a hinge region (HD), located between the DBD and LBD and spanning amino acids 481 to 520 (Nader et al., 2009). GRα is located primarily in the cytoplasm in the absence of glucocorticoid ligand, as part of hetero-oligomeric complexes containing heat shock proteins (HSPs) 90, 70, 50, 20 and, possibly, other proteins as well (Pratt, 1993; Hager, 2002; Revollo and Cidlowski, 2009). After binding to its agonist ligand, GRα undergoes conformational changes, dissociates from the heat shock proteins, homo- or heterodimerizes, and translocates as a dimer and/or monomer into the nucleus through the nuclear pore, via an active ATP-dependent process mediated by its nuclear localization signals (NL)-1 and -2 (Savory et al., 1999). NL-1 is located in the junction of DBD and the hinge region, while NL-2 spans the entire LBD (Savory et al., 1999) (Fig. 1).

Inside the nucleus, the ligand-activated GRα directly interacts as a homo- or hetero-dimer with specific DNA sequences, the glucocorticoid response elements (GREs), in the promoter regions of target genes, (Beato et al., 1989; Kino et al., 2003; Chrousos and Kino, 2005; So et al., 2007). GR contains two transactivation domains, activation function (AF)-1 and -2, located at its NTD and LBD, respectively (Fig. 1), through which it interacts with many proteins and protein complexes, such as the nuclear receptor coactivator [p160, p300/CREB-binding protein (CBP) and p300/CBP-associated factor (p/CAF)] complexes and the SWI/SNF and vitamin D receptor-interacting protein/thyroid hormone receptor-associated protein (DRIP/TRAP) chromatin-remodeling complexes, eventually influencing the activity of the RNA polymerase II and its ancillary factors, modulating the transcription rates of glucocorticoid-responsive genes (McKenna and O'Malley, 2002; Kino and Chrousos, 2004; Chrousos and Kino, 2005; Rosenfeld et al., 2006).