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FIELD OF VISION

Circadian rhythms of hormone secretion and obesity

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Abstract

The adipose tissue homeostasis is profoundly affected by circadian rhythms of corticosteroid secretion and chronic loss of hormonal oscillations is associated with obesity. How adipose tissue differentially responds to pulsatile *vs* continuous presence of glucocorticoids is poorly defined. To address this question, Bahrami-Nejad *et al* studied differentiation of pre-adipocytes, containing endogenously tagged CCAAT/enhancer binding protein and peroxisome proliferator-activated receptor (PPAR) γ (key regulators of adipocyte differentiation), in response to corticosteroids that were delivered either in an oscillatory fashion or continuously. The authors show that the bi-stable state of differentiation of pre-adipocytes and adipocytes was regulated by a combination of fast and slow positive feedback networks, that determined unique threshold of PPARγ in these cells. Evidently, pre-adipocytes used the fast feedback loop to reject differentiation cues of oscillating pulses of glucocorticoids and failed to differentiate into fat cells. In contrast, when glucocorticoids were delivered continuously, precursor cells exploited the slow feedback loop to embark on a path of maximal differentiation. This differential differentiation response of pre-adipocytes to pulsatile *vs* continuous exposure to glucocorticoids was corroborated *in vivo*. Thus, mice receiving non-oscillating doses of exogenous glucocorticoids, for 21 d, elicited excessive accumulation of visceral and subcutaneous fat. These data shed new light on the mechanisms of obesity caused by putative misalignment of circadian secretion of glucocorticoids or their persistently high levels due to chronic stress or Cushing's disease.

Key words: Circadian rhythms; Glucocorticoids; Adipose tissue; Pre-adipocytes; Stem cells; Terminal differentiation

Core tip: Bahrami-Nejad *et al* examined pre-adipocytes for their ability to differentiate into fat cells in response to hormonal stimuli that were presented either in a pulsatile manner, mimicking circadian rhythms, or delivered continuously. These experiments revealed that

adipocyte differentiation program, made up of slow and fast feedback circuits, was able to distinguish between the oscillating and continuous hormonal signals. The authors showed that pre-adipocytes apparently used the fast, positive feedback network to reject the oscillating hormonal cues. In contrast, if delivered continuously, similar strength glucocorticoids impinged on the slow positive feedback circuit to trigger maximal differentiation of pre-adipocytes into bone fide fat cells. The pulsatile *vs* continuous hormone stimuli were similarly discriminated *in vivo* since mice receiving glucocorticoids in a non-oscillating manner for 21 d elicited increased accumulation of subcutaneous and visceral fat. These data elucidate a potential mechanism underling the development of obesity associated with chronic stress or Cushing's disease.

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COMMENTARY ON HOT TOPICS

Disturbance of diurnal rhythms of day and night, as experienced by night-shift workers, has been linked to obesity and type 2 diabetes mellitus. However, the mechanistic connection between circadian misalignment and obesity are poorly defined. Persistent interruption of diurnal rhythms leads to dysfunctional patterns of secretion of hormones, including corticosteroids, which adversely affect many tissues that include the adipose tissue.

Circadian secretion of glucocorticoids is pivotally involved in the mechanisms of adipose tissue homeostasis[1]. Adipocyte stem cells, pre-adipocytes, embedded in the subcutaneous and visceral adipose tissues comprise about 20% of the cell population[2]. Although pre-adipocytes are exposed to diurnal pulses of glucocorticoids, their terminal differentiation occurs at a very slow rate. For instance, in healthy humans, on a given day, approximately 1% pre-adipocytes embark on the process of differentiation which is completed in about 12 d[3]. This behavior of pre-adipocytes is even more puzzling since these cells mount a robust, dose-dependent differentiation response to glucocorticoids *in vitro*. Sustained non-pulsatile exposure to glucocorticoids, as occurs during chronic stress or in patients with Cushing's disease, leads to the development of visceral obesity[4-6]. This raises an important mechanistic question: How does the machinery of adipocyte differentiation distinguish between the physiological (diurnal glucocorticoid oscillations) and pathological (persistently high glucocorticoid levels) presence of glucocorticoids? This question was recently addressed by Bahrami-Nejad *et al*[7] *via* a series of elegant *in vitro* and *in vivo* experiments. To further supplant brief methodological and conceptual description contained in my FOV commentary, motivated readers should consult the original publication and its' Graphical Abstract.

The cellular and molecular underpinnings of how pre-adipocytes differentiate into bona fide fat cells have been studied in model cell lines and in stem cells isolated from adipose[3]. These studies, facilitated by methods of molecular biology, quantitative mass spectrometry and single cell imaging, combined with computer modeling, indicate that differentiation of pre-adipocytes into adipocytes involves key cell-intrinsic elements and their interactions with hormones such as glucocorticoids, insulin, ghrelin, and others. It is also evident from these studies that unique gene expression signatures distinguish pre-adipocytes from bone fide fat cells; apparently, these bi-stable phenotypes are maintained by unique thresholds of CCAAT/enhancer binding protein α (CEBPA) and peroxisome proliferator-activated receptor γ (PPARG). A positive feedback loop between CEBPA and PPARG is thought to interact with additional feedback networks to induce adipocyte differentiation in response to different hormonal inputs[8]. Hierarchical interactions among putative gene regulatory networks and their temporal regulation during *de novo* adipogenesis are poorly defined.

Since unique thresholds of PPARG and CEBPA proteins are thought to distinguish pre-adipocytes from bona fide fat cells[8,9], Bahrami-Nejad *et al*[7], created a clone of murine pre-adipocytes (OP9 cells) that harbored fluorescently tagged *CEBPA* and *PPARG* genes. These model pre-adipocytes enabled the authors to simultaneously monitor the expression of *CEBPA* and *PPARG* and their relationship with a progressive emergence of canonical markers of adipocyte differentiation[10] in live cells, over a period of several days. When cultured in medium (DMI) containing a cocktail of differentiation inducing factors (1 μmol/L of dexamethasone, 250 μmol/L of IBMX and 1.75 nmol/L of insulin) OP9 cells (and stromal vascular fraction-associated primary pre-adipocytes) vigorously differentiated into mature fat cells. Progressively longer exposure to either dexamethasone (a synthetic glucocorticoid) or corticosterone (a physiological corticosteroid), for 12, 24, 36 and 48 h, induced a correspondingly larger fraction of pre-adipocytes to differentiate. However, when glucocorticoid-containing DMI was presented in oscillating pulses, only a small fraction of pre-adipocytes elicited terminal differentiation. Thus, the differentiation program seemed to reject the circadian rhythms of glucocorticoid treatment, but responded robustly to sustained presence of glucocorticoids in the DMI. In contrast, rosiglitazone (a direct activator of PPARG) induced adipocyte differentiation in a dose-dependent manner, regardless of the mode of temporal delivery. These data were interpreted to mean that filtering of temporal glucocorticoid signals occurred either prior to or simultaneously with the induction of PPARG gene expression.

To further explore the regulatory behavior of the putative bi-stable switch separating pre-adipocytes from adipocytes, Bahrami-Nejad *et al*[7], tracked the expression

of fluorescently tagged PPARG in OP9 cells continuously over a 4-d period. Interestingly, the abundance of nuclear PPARG in individual cells was positively correlated with their progressive phenotypic transformation into bona fide fat cells. When cells were exposed to glucocorticoids in repeated 12-h on/12-h off cycles, a small fraction of OP9 and primary pre-adipocytes (SVF cells) concomitantly traversed a high threshold of PPARG and underwent terminal differentiation. In contrast, if glucocorticoid stimuli of similar strength were applied in a sustained manner, a high proportion of pre-adipocytes differentiated into fat cells.

Since the of PPARG gene expression is known to be activated by the transcription factor CCAAT/enhancer binding protein β (CEBPB), the authors tracked expression of CEBPB in live cells while they were cultured in DMI. These experiments revealed that nuclear abundance of CEBPB was dynamically regulated, and even more importantly, temporal expression CEBPB closely mirrored the oscillations of glucocorticoids. Since CEBPB is known to have a rapid rate of turnover, the authors reasoned that CEBPB could potentially form a fast feedback loop with PPARG. In response to circadian glucocorticoid stimuli, such a fast responsive system will not allow nuclear levels of PPARG to reach the threshold needed to initiate differentiation. An additional feature of such regulation would be that the positive feedback loop will become independent of external differentiation stimuli once a certain threshold of PPARG was reached. Quantification of nuclear abundance of PPARG *via* continuous, live cell imaging of OP9 cells revealed that an irreversible PPARG threshold was indeed reached after 36-48 h exposure to DMI[7]. Although, an involvement of a fast feedback loop between CEBPB and PPARG was confirmed by experiments assessing differentiation of pre-adipocytes in response to diurnally oscillating glucocorticoids, such a fast feedback loop could not explain how a progressive build-up of PPARG occurred in response to continuous, days-long exposure to glucocorticoids.

The mode of differentiation of pre-adipocytes in response to prolonged, non-oscillating exposure to glucocorticoids predicted the existence of a slow positive feedback loop regulating nuclear abundance of PPARG. Such a slow positive feedback circuit would enable adipocyte precursors to discriminate between oscillating *vs* continuous signals and mount a differential differentiation response.

From a number of candidate genes that might be linked to PPARG in a slow positive feedback loop[8], the authors favored FABP4, a known regulator of PPARG with a long half-life[11]. It was noted that the rate of turnover of FABP4 was low, and even more importantly, accumulation of FABP4 in the cytoplasm and nuclear abundance of PPARG followed similar kinetics. Thus, authors posited that FABP4, *via* its ability to transport fatty acid ligands that activate PPARG, formed a slow positive feedback loop with PPARG; involvement of such a slow positive feedback regulatory loop would enable pre-adipocytes to mount a differential response to oscillatory *vs* continuous stimuli. Of course, these data did not rule out the existence of additional regulatory circuits that could further modulate the mechanisms of *de novo* adipogenesis.

Experimental findings derived from *in vitro* differentiation of pre-adipocyte cell lines were subjected to computer simulations. The authors used an ordinary differentiation equation model to test the predicted dynamics of nuclear abundance of PPAG, *via* actions of the combined fast and slow positive feedback circuits. Indeed, such simulations could explain the observed rejection of single and repetitive pulses of differentiation stimuli. However, this model failed to explain why a small fraction of cells still differentiated in response to oscillating signals and why prolonged pulses of < 12 h induced a larger fraction of cells to undergo differentiation. To reconcile these observations, the authors modified their theoretical model of combined fast and slow positive feedbacks by adding a factor of stochastic variation in PPARG levels in the population of pre-adipocytes. These analyses revealed that a regulatory system consisting of fast and slow positive feedback links, when combined with putative stochastic abundance of nuclear PPARG (a cell-intrinsic property), could not only explain the variable delay in cells reaching PPARG threshold but also why low differentiation rates were seen in response to daily oscillations of glucocorticoids.

To corroborate these *in vitro* findings *in vivo*, the authors implanted continuous release pellets of cortisone in 8-wk old C57BL/6J mice. Experimental flattening of circadian rhythms of cortisone secretion, for 21 d, led to enhanced accumulation of subcutaneous (inguinal) and epidydimal (visceral) fat in mice. Mice with cortisone implants had significantly larger adipocytes compared with animals containing sham implants. Moreover, the visceral adipose tissues of mice exposed to sustained high levels of cortisone had more numerous adipocytes. Thus, persistently high circulating levels of cortisone not only enhanced *de novo* adipogenesis but also led to increased volume of adipocytes

In summary, Bahrami-Nejad *et al*[7], have shown that adipocyte differentiation was underpinned by cell-autonomous factors and their differential interaction with cortisone, depending on whether it was delivered continuously or in a circadian manner. While low signal variability was a key stochastic determinant that prevented de-differentiation of bone fide adipocytes, a high cell-to-cell signal variability was needed to ensure that only a small fraction of pre-adipocytes underwent differentiation in response to circadian delivery of glucocorticoids. The results of Bahrami-Nejad *et al*[7], in addition to elucidating how circadian exposure to glucocorticoid affects adipocyte differentiation, have broader clinical implications. It was demonstrated in a recent study that misaligned circadian rhythms had adverse effects on insulin sensitivity and energy metabolism in the skeletal muscles of healthy young adults[12]. Since mechanisms of repair and regeneration,

via recruitment of stem cells and their differentiation *in situ,* are central to tissue homeostasis across the animal kingdom[13], a role of circadian secretion of growth and differentiation factors in these processes is warranted.

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