REVIEW PAPER

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Glucocorticoids and regulation of brown adipose tissue in humans – physiological and pathophysiological considerations

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ABSTRACT

This review discusses the effects of glucocorticoids (GCs) on brown adipose tissue (BAT) in the context of obesity prevention and therapy. Due to the unique expression of the uncoupling protein 1 (UCP1), BAT is capable of non-shivering thermogenesis, also defined as a metabolic heat production, related to increased metabolic rate. All processes that contribute to an increase in activity and/or quantity of BAT are able to upturn metabolism, and thus enable the above therapeutic goals to be achieved. GCs may stimulate BAT differentiation and proliferation. In the case of differentiation, the opposite effect of GCs has been also described. Within white adipose tissue (WAT) GCs inhibit the formation of so called beige adipocytes that are functionally and morphologically similar to the adipocytes from BAT. The activity of GCs with concomitant inhibition of WAT browning is mediated by the induction of microRNA-27b (MIR27B) expression. GCs are responsible for the decline in BAT activity as the body ages. Depriving the body of an enzyme responsible for local reduction of cortisone into an active GC-cortisol in BAT (11β-hydroxysteroid dehydrogenase type 1; 11β-HSD1) prevents the reduction of BAT activity. The effects of high doses of GCs on BAT generally depend on the exposure time. Prolonged elevation in GCs level decreases BAT activity. During adrenergic stimulation the effect of GCs on BAT is ambiguous, because both decrease and increase in activity has been described. A full understanding of the GCs impact on brown remodeling in WAT may reveal a discovery of a novel preventive and therapeutic strategies for obesity and possibly other metabolic disorders.

Keywords: brown adipose tissue, glucocorticoids, obesity therapy, obesity, browning.

Introduction

In human body, there are two types of adipose tissue with different locations, structures, colors, and pathologic characteristics. WAT's content is far greater and its main function is the accumulation of triglycerides (TG) and endocrine activity. While WAT builds up energy in the form of TG, BAT being more metabolically active, works for energy expenditure and heat dissipation. A high amount of BAT was primarily found in newborn humans and hibernating mammals. In recent years, using functional imaging techniques, studies have demonstrated presence and physiological significance of BAT in adults [1]. Mature BAT contains higher number of mitochondria than WAT and possess unique ability of non-shivering thermogenesis, possibly due to the presence of mitochondrial uncoupling protein 1 (UCP1) [2]. Through the mechanisms of non-shivering/metabolic thermogenesis BAT accelerates weight loss increasing the basal metabolic rate (BMR) and reduces risk for obesity. Processes associated with BAT activity may be of particular importance for a new therapeutic strategies to treat obesity and obesity-related disorders. Additionally, endo- and exogenous factors (eg. GCs)

that impact beneficial effects related with BAT-stimulated energy expenditure require detailed investigation.

The aim of this review was to present the current state of knowledge about the influence of GCs on brown fat cells and ways through which GCs affect functioning of BAT.

Effect of GCs on BAT's development and proliferation

Differentiation

GCs significantly influence BAT differentiation process. Most of the reports confirm their stimulating effect, however, the mechanisms still remain not fully explained. GCs stimulate gene expression of proteins that are crucial for non-shivering thermogenesis in humans [3]. GCs deficiency inhibits the expression of genes responsible for storage of triglycerides (TG) in the mice's differentiated brown adipocytes [4]. They also affect factors inhibiting thermogenesis and differentiation, e.g. PREF-1 [5]. Armengol et al. [6] have demonstrated that mice treated with dexamethasone (DEXA) exhibit suppression of PREF-1 down-regulation observed during differentiation of brown preadipocytes, and increase in transcription factor C/EBPδ (CCAAT-enhancer binding protein delta). They suggested that induction of C/EBPδ by GCs may provide an indirect mechanism for stimulation of PREF-1 gene by GCs in brown preadipocytes. Complete understanding of the GC's influence on BAT differentiation may play role in the future procedures that therapeutically target this process. However, given that the current results are still incomplete and often conflicting, more studies are required.

Browning of WAT

In the WAT, GCs affect formation of so called beige adipocytes (browning of WAT), which are functionally and anatomically related to brown fat cells by the ability to induce thermogenesis due to their high mitochondrial UCP1 content [7]. It has been demonstrated that corticosterone inhibits formation of beige adipocytes in the mice's inguinal WAT [8]. Studies investigating the effect of dexamethasone on the WAT browning have revealed the role of MIR27B in this process [9]. DEXA induced MIR27B expression, which in turn, by affecting the three major untranslated regions of PRDM16 mRNA, led to inhibited transformation of WAT into BAT [10]. GCs stimulated expression of MIR27B gene through GC-receptor dependent mechanism at post-transcriptional level. Similar results were observed when MIR27B function was antagonized and mice treated with DEXA *in vivo* exhibited an efficient induction of WAT browning [9]. Therefore, it has been suggested that antagonizing MIR27B may serve as a new target for the obesity prevention and/or treatment. Additionally and perhaps more importantly, this process can obstruct GC's unfavorable influence on the WAT in the context of the development of central obesity [11]. Thus, patients with chronically elevated levels of GCs (eg. with Cushing syndrome, or being treated with high doses of GCs) may benefit from these new discoveries.

Proliferation

An in vitro study by Barclay et al. [3] has shown that DEXA markedly stimulates the proliferation and differentiation of brown preadipocytes, while lowering the proliferation of white preadipocytes. On the other hand, DEXA inhibited adrenergic stimulation of the cultured brown adipocytes indicating a complexity of GC action within fat cells.

BAT ageing

Animal model studies have shown that as the body ages, expression and activity of an enzyme capable of converting inactive cortisone into active cortisol (11β-HSD1) increase [12]. Cortisol is likely to impair BAT's thermogenic activity. It has been observed that aged 11β-HSD1 deficient mice exhibit a higher level of UCP1, and hence the desirable for non-shivering thermogenesis characteristic of brown adipose tissue, as well as greater number of mitochondria in the brown fat cells [12]. Further research on the 11β-HSD1 may provide a background for the genotherapy of obesity, because reducing local cortisol level within BAT can ensure significant thermogenesis and increase BMR.

Comparison of the effects of high concentrations of GCs on metabolic effect in BAT according to exposure time

Chronic effect

GCs in high concentrations cause various effects depending on BAT exposure time to their elevated level. Several authors have shown that in response to the chronic GCs' influence, thermogenesis rate is decreased [12, 13] and oxygen consumption in brown adipocytes is reduced [9]. It has been postulated that these processes may also occur in the human body [12]. In another study, ablation of LSD1 (lysine-specific demethylase 1 responsible for the repression of 11β-HSD1), in mice showed enhanced 11β-HSD1 activity accompanied by

elevated GCs level and disturbances in BAT metabolism [14]. Chronic exposure to GCs accompanies, among others, abdominal obesity and hepatic steatosis [13], and DEXA in a long term interaction with BAT may work as one of the major causative factors for "buffalo hump" in Cushing's syndrome [3]. It was also discovered that cold-induced increase in adrenergic activity partially reverses hypertriglyceridemia triggered by GCs via stimulation of BAT metabolism [8]. Given the negative effect of chronically elevated GCs on BAT thermogenic activity, it is clinically important to understand and evaluate all the processes and factors that may participate in inhibition of GCs' influence on BAT.

Short-term effect

Nonshivering thermogenesis as a defense against cold and obesity/obesity related disorders occurs in response to cold-induced β-adrenergic stimulation. As shown by authors, intracellular conversion of thyroxine (T4) to triiodothyronine (T3) is essential for the optimal thermogenic function of BAT [15, 16]. T3 is required for and potentiates the adrenergic stimulation of deiodinase 2 (DIO2) activity in BAT, which participates in the formation of T3. Depending on the time of exposure and concentration of GCs, DEXA and hydrocortisone regulate adrenergic stimulation and DIO2 activity in different ways. In a short time high doses of hydrocortisone (1–10 μM) inhibit DIO2, whereas low doses (1–100 nM) of hydrocortisone and longer time of exposure to DEXA results in an increase of DIO2 activity [17]. This observation allows researchers to consider GCs as a potential factors stabilizing activity of DIO2 and mRNA of DIO2.

Although a large number of studies confirm negative acute effect of high dose GCs on metabolic thermogenesis in BAT [3, 18], Ramage et al., in their recent work, reported that prednisolone significantly increases the uptake of 18-fluorodeoxyglucose by brown adipose tissue in lean healthy men during exposure to mild cold (16–17°C). This was followed by an increase in energy expenditure, likely by increasing BAT activity. The same study provided significant observation regarding different effects of isoprenaline on intracellular respiration and UCP1 stimulation in human versus mice BAT. In human primary brown fat cells GCs increased stimulated by isoprenaline intracellular respiration and UCP1 but significantly reduced both parameters in primary murine beige and BAT adipocytes [19]. Taken together, the existence of non-consistent findings about how GCs influence BAT metabolism in humans suggests that any interpretation should be made with caution and further replicate experiments are required. In this connection, it should be borne in mind that there are anatomical and functional differences regarding brown adipocytes in mice as compared with humans [7]. In mice BAT is more important for the survival in a dynamic temperature environment generating heat and to maintaining constant body temperature in response to cold acclimation (up to 60% of entire animal's energy expenditure [20]), whereas human BAT plays similar role only in neonates. In adult humans brown fat cells are more significant for the metabolic processes and their depots significantly decline with ageing [21].

Full understanding of the short-term effects of GC on BAT under adrenergic stimulation is clinically relevant. For example, short-term BAT exposure to GCs administered by local injections might increase BMR and, therefore, could possibly serve as a helpful additional procedure controlling body weight for patients who cannot be physically active for medical reasons.

Summary

GCs may influence beneficial effects related to BAT-stimulated energy expenditure. Based on the previous studies, one may conclude that the effect of GCs on brown adipocyte metabolism is rather complex. Recently, particular attention has been paid to the interaction between GCs and PRDM16, 11β-HSD1 proteins/microRNA (MIR27B), which are all recognized as key regulators in the BAT energy management. Understanding the impact of GCs on human BAT can be an attractive medical background for medical purposes in order to develop a novel strategies to combat obesity. Thus, the main targets of future therapeutic procedures may include induction of the brown fat formation, browning of WAT, as well as stimulation and maintaining of brown and beige fat cells activity.

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