Brief Communication

MOLECULAR METABOLISM

β_3-Adrenergically induced glucose uptake in brown adipose tissue is independent of UCP1 presence or activity: Mediation through the mTOR pathway

Jessica M. Olsen [1,5], Robert I. Csikasz [1,5], Nodi Dehvari [1], Li Lu [2,3], Anna Sandström [1], Anette I. Öberg [1], Jan Nedergaard [1], Sharon Stone-Elander [3,4], Tore Bengtsson [1,*]

ABSTRACT

Objective: Today, the presence and activity of brown adipose tissue (BAT) in adult humans is generally equated with the induced accumulation of [2-^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) in adipose tissues, as investigated by positron emission tomography (PET) scanning. In reality, PET-FDG is currently the only method available for *in vivo* quantification of BAT activity in adult humans. The underlying assumption is that the glucose uptake reflects the thermogenic activity of the tissue.

Methods: To examine this basic assumption, we here followed [^{18}F]FDG uptake by PET and by tissue [^{3}H]-2-deoxy-D-glucose uptake in wildtype and UCP1(−/−) mice, i.e. in mice that do or do not possess the unique thermogenic and calorie-consuming ability of BAT.

Results: Unexpectedly, we found that β_3-adrenergically induced (by CL-316,243) glucose uptake was UCP1-independent. Thus, whereas PET-FDG scans adequately reflect glucose uptake, this acute glucose uptake is not secondary to thermogenesis but is governed by an independent cellular signalling, here demonstrated to be mediated via the previously described KU-0063794-sensitive mTOR pathway.

Conclusions: Thus, PET-FDG scans do not exclusively reveal active BAT deposits but rather any tissue possessing an adrenergically-mediated glucose uptake pathway. In contrast, we found that the marked glucose uptake-ameliorating effect of prolonged β_3-adrenergic treatment was UCP1 dependent. Thus, therapeutically, UCP1 activity is required for any anti-diabetic effect of BAT activation.

Keywords Brown adipose tissue; Uncoupling protein 1; Glucose uptake; Adrenergic signaling; Positron emission tomography

1. INTRODUCTION

Brown adipose tissue (BAT) can combust (surplus) energy through uncoupled respiration mediated by uncoupling protein 1 (UCP1). The possibility to use this ability to ameliorate obesity and diabetes has long been discussed [1—3]. However, as BAT was thought not to be present in adult humans, this strategy was largely disregarded. The realization that [2-^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission scanning tomography (PET-FDG) data, from a series of clinical investigations indicated the presence of active BAT in adult humans [4], and the subsequent confirmations of this new paradigm [5—9] have suggested new avenues for ameliorating obesity and diabetes, through BAT activity.

The PET-FDG technique has been applied clinically to detect cancer, based on the tenet that many cancer cells display a high metabolism, mainly fueled by glucose. Thus, the metabolism of the cells functions to clear glucose from the blood, and the accumulation of [^{18}F]FDG in the cells is interpreted to indicate a high rate of metabolism. Accordingly, the uptake of [^{18}F]FDG in BAT has generally been equated with thermogenic activity [4], as this activity would result in uptake of glucose, driven by the catabolic thermogenesis. In practice, no other methods for examining BAT activity, location, and amount in humans are currently routinely in use. However, the assumption that glucose uptake directly mirrors thermogenic activity [10] may not be correct.

BAT thermogenesis is activated by adrenergic stimulation [2]. Apparently, a large increase in BAT glucose uptake (as monitored by PET-FDG scans) is observed after treatment of humans with sympathomimetics [11] and in pheochromocytoma patients [12—14]. Particularly, a strong pattern of BAT glucose uptake is seen in PET scans after activation of β_3-adrenergic receptors [15]. The aim of the present

[1]Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, SE-106 91, Stockholm, Sweden [2]Karolinska Experimental Research and Imaging Center, Karolinska University Hospital, Solna, SE-171 76, Stockholm, Sweden [3]Department of Clinical Neurosciences, Karolinska Institutet, SE-171 77, Stockholm, Sweden [4]Department of Neuroradiology, Karolinska University Hospital Solna, SE-171 76, Stockholm, Sweden

[5] Jessica M. Olsen and Robert I. Csikasz contributed equally to this work.

*Corresponding author. E-mail: tore.bengtsson@su.se (T. Bengtsson).

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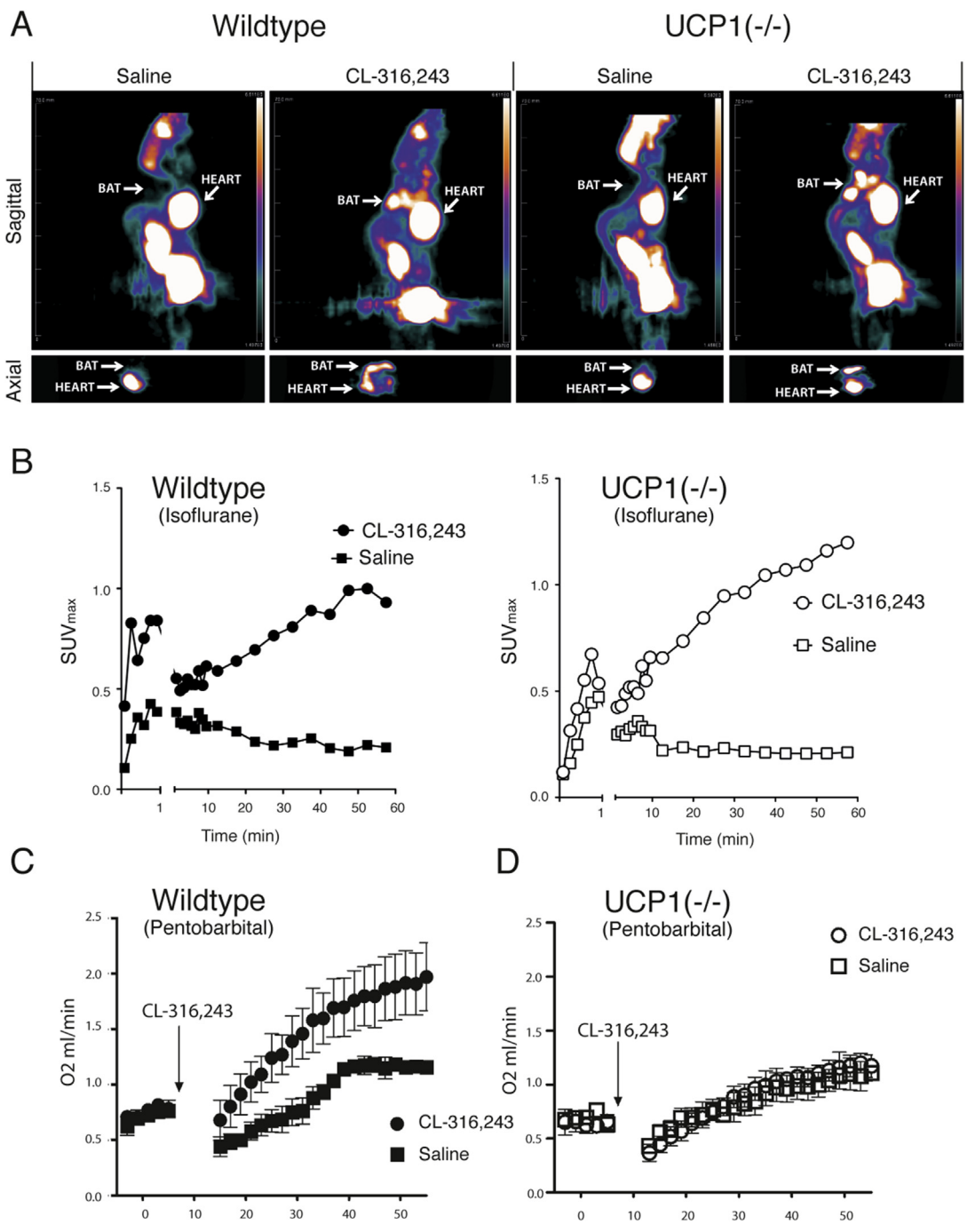

Figure 1: Adrenergically induced glucose uptake in BAT is independent of thermogenic competence. (A–B) Representative figures of wildtype and UCP1(−/−) adult lean mice that were anesthetized with isoflurane and in which the uptake of [^{18}F]FDG was followed for 60 min in a MicroPET scanner. (A) Sagittal and axial PET images of the [^{18}F]FDG uptake in two representative mice treated with saline (control) and CL-316,243 (1 mg/kg) on separate days. The images are sums of the last 25 min of the measurements. (B) Time activity curves of the [^{18}F]FDG uptake in BAT in the mouse in A (SUVmax = maximum Standardized Uptake Values) over the entire 60 min scan. (C–D) CL-316,243-stimulated (1 mg/kg per body weight) oxygen consumption in (C) wildtype (n = 3–4) and (D) UCP1(−/−) (n = 3–4) mice housed at thermoneutrality (30 °C) for 3 weeks. The mice were anesthetized with pentobarbital (55 mg/kg i.p.). The arrow indicates i.p. injection of saline or of CL-316,243 at a dose of 1 mg per kg body weight.

study was to investigate whether such adrenergically induced glucose uptake adequately reflects thermogenesis. We found, unexpectedly, that acute β_3-adrenergic stimulation induces glucose uptake in BAT *independently* of the presence and activation of UCP1 and thus *independently* of thermogenesis. Our results thus demonstrate that acute glucose uptake is a mechanism separate from thermogenesis.

2. RESULTS

2.1. UCP1 is not essential for the glucose uptake into BAT as visualized by PET-FDG

To verify the relationship between thermogenesis and β_3-adrenergically induced glucose uptake, we used mice possessing UCP1 (wildtype), that

