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COMMENTARY

Are we waking up to the effects of NEFA?

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Abstract NEFA are mobilised from adipose tissues during fasting or stress. Under conditions of acute or chronic NEFA excess, skeletal muscle and hepatic insulin resistance may ensue. Hence, a wealth of literature has focused on the crosstalk between NEFA and glucose in the pathogenesis of insulin resistance. Sleep restriction has also been shown to acutely induce insulin resistance, and self-reported short sleep duration is associated with diabetes. In this issue of *Diabetologia* (DOI: 10.1007/s00125-015-3500-4), Broussard and colleagues examine the impact of acute sleep restriction on detailed 24 h metabolic profiles, including plasma NEFA. Here, we address the potential clinical relevance of these findings and pose questions for further research.

Keywords Diabetes · Fatty acids · NEFA · Sleep restriction

Sleep loss, often resulting from voluntary sleep restriction, has become a norm of modern society. Beyond obvious cognitive impairments caused by lack of sleep, other detrimental health consequences are becoming apparent. As average sleep duration has declined, the incidence of diabetes and obesity has risen, and this phenomenon may be more than coincidence [1]: short sleep duration has been identified as a risk factor for incident type 2 diabetes in prospective studies [2, 3]. There is also direct evidence that sleep is critical for glucose homeostasis. A landmark study performed at the University of Chicago in 1999 restricted the sleep of healthy men to 4 h per night for six nights, followed by six nights of recovery sleep. Sleep restriction significantly impaired glucose tolerance, reduced glucose effectiveness and reduced the acute insulin response to glucose. HOMA of the glucose and insulin profiles also suggested peripheral insulin resistance [4]. In addition, sleep restriction may promote obesity [5, 6] by stimulating appetite [7, 8] while providing increased eating opportunities [9]. It may therefore play an unrecognised role in the epidemic of obesity and type 2 diabetes. However, the mechanisms underlying this relationship are not known.

In 1963, Randle, Garland, Hales and Newsholme proposed the 'glucose–fatty acid cycle', observing that NEFA availability and utilisation in tissues inhibited glucose oxidation, and vice versa [10, 11]. This revolutionary concept illustrated how competition between glucose and NEFA influences fuel utilisation by muscle, independent of hormonal influences. Details of the cellular basis for the Randle cycle have evolved over time. It was originally proposed that NEFA inhibit glycolysis, but subsequent studies have revealed that glucose transport is primarily affected [12]. In the last two decades it has been elucidated that NEFA affect early steps in the insulin signalling pathway, inhibiting tyrosine phosphorylation of the insulin receptor [13], and downstream IRS-1-associated phosphoinositide 3-kinase activity [12]. Regardless of the molecular underpinnings of the Randle cycle, its existence has profound implications for insulin signalling and the development of diabetes. It has been postulated that chronically elevated NEFA explains the propensity for diabetes in the obese [14]. Counter-intuitively, however, adiposity does not consistently increase plasma NEFA [15, 16]. Therefore, perhaps other factors leading to chronic NEFA elevation mediate risks of diabetes.

In this issue of *Diabetologia*, Broussard and colleagues [17] present their findings on the impact of sleep restriction on 24 h metabolic profiles, including NEFA. Nineteen healthy men were allowed to sleep a full 8.5 h per night or were restricted to 4.5 h of sleep per night for four consecutive nights. These two sleep protocols were performed in random

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order, with an intervening period of >4 weeks. On the third day of each protocol, detailed metabolic profiles were obtained, including plasma cortisol, noradrenaline (norepinephrine), glucose, insulin and NEFA. On the fourth morning of each protocol, insulin sensitivity was tested using an IVGTT. The authors found an increase in NEFA of about 15–30% during sleep restriction compared with normal sleep, with most of the increase occurring between 04:00 hours and 09:00 hours. In addition, sleep restriction increased nocturnal growth hormone, noradrenaline and cortisol. Morning insulin sensitivity was impaired and correlated with the extent of NEFA elevation during the night, but did not correlate with other hormonal changes. These findings suggest that NEFA may mediate insulin resistance during acute sleep restriction.

About one-third of human existence is spent asleep, such that even minor metabolic shifts that transpire during this period may have major chronic health implications. The authors should be commended for completing a rigorous study of metabolic profiles during 24 h of sleep restriction. Using this methodology they have shown how NEFA might be a mechanism by which sleep restriction induces insulin resistance. However, as the authors themselves point out, associated increases in counter-regulatory signals from growth hormone, cortisol and noradrenaline may have induced insulin resistance, either independently or in combination. For example, cortisol may directly stimulate lipolysis [18] or sensitise adipocytes to lipolytic effects of catecholamines and growth hormone [19]. To definitively link NEFA to sleep restriction-induced insulin resistance, studies involving lipolysis inhibitors and/or muscle insulin signalling would be highly informative. Another limitation is whether voluntary sleep restriction or insomnia (unwanted sleep restriction) elicits the same metabolic changes under real-world conditions.

Is a 15–30% increase in plasma NEFA for 5 h clinically significant? With regard to the duration of NEFA elevation, the answer is yes. After 3 h of lipid infusions in healthy volunteers, rates of glucose disappearance decreased by 55% [20]. Conversely, acutely lowering plasma NEFA with acipimox improved insulin sensitivity within 12 h [21]. In terms of the 15–30% increase, the answer is ‘perhaps’. Belfort et al [22] clamped plasma NEFA for 4 h at 58%, 184% and 283% above baseline and showed that glucose disposal rates fell by 22%, 30% and 34%, respectively. Vastus lateralis muscle IRS-1 phosphorylation and PI3 activity were reduced even at the lowest NEFA target. Qualitatively similar findings occurred with lipid infusions lasting several days [23]. Taken together, these studies indicate that physiological variations in plasma NEFA levels can dynamically affect glucose disposal and insulin receptor signalling. In their study, Broussard et al [17] detected insulin resistance in the morning following the fourth night of sleep restriction using an IVGTT. In a parallel manner, 1 day earlier in their experiment, glucose and insulin responses to breakfast were altered with sleep restriction. Interestingly, the metabolic responses to subsequent meals normalised, suggesting that insulin resistance was limited to the morning hours. It is not clear whether chronic sleep restriction would continue to elicit this pattern of insulin resistance, nor if insulin resistance of this nature can lead to diabetes in susceptible individuals.

This study opens the door to several additional intriguing questions and hypotheses. First, why is there such heterogeneity in the NEFA response to sleep restriction (see Fig. 5b in [17]) and could this heterogeneity explain susceptibility to metabolic consequences? Second, what is the origin, metabolic fate and composition of the NEFA mobilised during sleep restriction? Fatty acid species are differentially mobilised during lipolysis according to their structure [24], and degrees of fatty acid saturation and chain length induce variable degrees of insulin resistance [25, 26]. Third, could dysregulation of NEFA metabolism represent a common pathway linking several sleep disorders to the metabolic syndrome? For example, nocturnal [27] and morning [28] NEFA are increased in individuals with obstructive sleep apnoea. Inconsistent sleep patterns due to shift work or circadian rhythm disorders might cause sporadic surges in lipolytic hormones [29, 30]. Both sleep loss and obstructive sleep apnoea are associated with an overlapping set of cardio-metabolic disorders [31], and NEFA elevations are implicated in these same pathologies [32–35].

As we seek the answers to these questions, we should not lose sight of the proverbial forest through the trees: the evidence is abundantly clear that sleep loss constitutes a common modifiable risk factor for diabetes. The greater mystery may be why clinicians do not routinely ask their patients about sleep.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement JCJ and VYP were both responsible for drafting the article and revising it critically for important intellectual content. Both authors approved the version to be published.

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