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The gut hormone secretin triggers a gut–brown fat–brain axis in the control of food intake

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Abstract

Brown fat research concentrates on the energy expenditure function of this heating organ, whereas previous evidence for a role of brown fat in regulating energy intake has been mostly neglected. Ingestion of a single mixed meal activates human brown fat thermogenesis to the same degree as cold. In mice, activation of brown fat thermogenesis with a β_3-adrenergic receptor agonist inhibits food intake. Pharmacological β-blockade, however, inhibits neither meal-associated thermogenesis nor food intake. We recently identified the gut hormone secretin as a non-adrenergic activator of brown fat. *In vivo*, secretin treatment acutely increases energy expenditure and inhibits food intake in wild-type, but not in uncoupling protein 1 (UCP1)-knockout (KO) mice, which lack thermogenic brown fat function. Concurrently, secretin alters gene expression of melanocortinergic peptides of hypothalamic neurons in wild-type mice, but not UCP1-KO. Blocking endogenous secretin with a neutralizing antibody attenuates brown fat thermogenesis during refeeding, increases food intake of mice, and alters *ad libitum* feeding behaviour. Taken together, these findings demonstrate that secretin triggers an endocrine gut–brown adipose tissue–brain axis in the control of satiation. We hypothesize that meal-associated activation of brown adipose tissue thermogenesis induced by secretin results in a rise in brain temperature and increased melanocortinergic signalling. Taken together, brown fat is not a mere heating organ dissipating excess calories but also involved in gut–brain communication in the control of food intake.

KEYWORDS
brown adipose tissue, food intake, mitochondria, thermogenesis

1 | BROWN ADIPOSE TISSUE BEYOND COLD-INDUCED THERMOGENESIS

We are experiencing a global epidemic of obesity, a major risk factor for the development of non-communicable diseases such as diabetes mellitus, dyslipidaemias, hepatic steatosis, hypertension and arteriosclerosis. Despite enormous effort, there is no efficient treatment for people with obesity, other than bariatric surgery. Neither the various lifestyle interventions nor the limited number of pharmacological remedies induce sustained weight reduction with long-term health benefits and well-being of people with obesity. Based on the rationale that obesity is caused by a chronic imbalance of energy intake and expenditure, there is a widespread misconception that a change in lifestyle should fix the problem. The standard recommendation for patients with obesity is to ingest less calories, eat more healthy food and exercise more. In other words, decrease energy intake and increase energy expenditure.

In this context, brown adipose tissue is of prime interest. In contrast to white adipose tissue, which stores fat as the major backup for times of limited food supply, brown fat generates heat in response to cold exposure (Rosen & Spiegelman, 2006) and thereby dissipates chemical energy of nutrients by uncoupling oxygen consumption from ATP synthesis (Klingenspor, 2003). This mechanism depends on uncoupling protein 1 (UCP1), which is exclusively found in the

inner mitochondrial membrane of brown adipocytes. In 2009, seminal reports on metabolically active brown fat in adult humans largely stimulated the interest in this thermogenic tissue (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). It was found that acute cold exposure activates human brown fat. Cold-induced activation of brown fat is elicited by the binding of noradrenaline to β-adrenergic receptors, which triggers the canonical cAMP–protein kinase A (PKA)–lipolysis pathway. Therefore, sympathomimetic drugs were evaluated early on for pharmacological activation of human brown fat. Unfortunately, neither non-specific sympathomimetics nor selective agonists for the relatively fat-specific β_3-adrenergic receptor (AR) can stimulate human brown fat without marked effects on the cardiovascular system (Carey et al., 2013; Cypess et al., 2015; Vosselman et al., 2012). Thus, druggable non-adrenergic receptors in brown fat that activate this heating organ are in demand to attenuate body fat accumulation by increasing resting energy expenditure in humans.

Other than cold-induced thermogenesis, resting metabolic rate is also increased in association with a meal, known as the specific dynamic action or thermal effect of food. Although this effect is partially due to the obligatory costs of digestion and resorption, a facultative component mediated by brown fat has been discussed for a long time (Glick, Teague, & Bray, 1981; Rothwell & Stock, 1979). A recent study demonstrated that a single mixed meal activates human brown fat to the same degree as cold exposure (U Din et al., 2018). While obligatory costs for food digestion and resorption are inevitable and comprehensible, the existence of a facultative component is still debated, including the source of thermogenesis (brown fat-dependent or not), the functional significance, and the potential mediators (Cannon & Nedergaard, 2004; Kozak, 2010). In this context, the hypothesis of thermoregulatory feeding proposed that during a meal brown fat thermogenesis may serve as a feedback signal to the brain to control meal initiation and termination (Brobeck, 1948; Himms-Hagen, 1995). Thus, aside from the mere capacity to burn excess calories, brown fat would play a role in the control of energy intake (Glick, 1982; Himms-Hagen, 1995). In rats, brown fat temperature increases about 15 min prior to meal initiation, and drops upon meal termination (Blessing, Mohammed, & Ootsuka, 2013). An increased periprandial tone of the sympathetic nervous system was suggested to activate thermogenesis by the release of noradrenaline from the sympathetic nerves in brown fat, which may lead to meal termination. Accordingly, acute pharmacological activation of brown fat in fasted mice using a β_3-AR agonist reduced cumulative food intake during a refeeding trial (Grujic et al., 1997; Susulic et al., 1995).

All macronutrients elicit meal-associated thermogenesis, but pertaining to nutritional neurophysiology, only carbohydrates activate the sympathetic nervous system (SNS; Glick, 1982; Himms-Hagen, 1995; Welle, Lilavivat, & Campbell, 1981). Furthermore, blockage of β-ARs with propranolol does not attenuate the early meal-associated rise in whole body heat production caused by a carbohydrate meal or carbohydrate-rich meal (Astrup, Simonsen, Bulow, Madsen, & Christensen, 1989; Thorne & Wahren, 1989; Zwillich et al., 1981).

New Findings

- **What is the topic of this review?**
  Brown fat's role in meal-associated thermogenesis and the related consequences for energy balance regulation with a focus on the gut hormone secretin, which has been identified as the endocrine molecular mediator of meal-associated brown fat thermogenesis.

- **What advances does it highlight?**
  The finding of the secretin-induced gut–brown fat–brain axis creates new opportunities to manipulate brown fat and thereby energy balance in a natural way while living in a thermoneutral environment. The role of brown fat as a mere catabolic heater organ needs to be revised and more attention should be directed towards the regulatory role of brown fat beyond energy expenditure.

Therefore, so far unknown triggers other than the SNS are likely to contribute.

As the release of gastrointestinal peptides is one of the first physiological responses to eating, periprandially secreted gut hormones are potential evokers of meal-associated brown fat thermogenesis. All along the gastrointestinal tract, specialized endocrine cells produce peptide hormones, making the gut one of the largest endocrine organ in the body (Coate, Kliewer, & Mangelsdorf, 2014). During a meal, secretion of gut hormones initiates complex neuroendocrine responses encoding information on the nutritional status (Cummings & Overduin, 2007). Gut hormones not only act locally to orchestrate gastrointestinal motility, secretion, digestion and nutrient absorption, but also promote the central perception of satiation via central neuronal circuits in the brain controlling food intake and limiting meal size (Chaudhri, Small, & Bloom, 2006). Most prominently, glucagon-like peptide (GLP-1), cholecystokinin (CCK), oxyntomodulin, peptide YY (PYY) and secretin inhibit food intake as demonstrated in various animal experiments, whereas ghrelin promotes hunger (Batterham et al., 2002; Chaudhri et al., 2006; Cheng, Chu, & Chow, 2011; Dakin et al., 2004; Gibbs, Young, & Smith, 1973; Turton et al., 1996; Weller, Smith, & Gibbs, 1990). Indeed, some of these gut hormones activate brown fat through their effects on the efferent SNS tone, such as CCK and GLP-1 (Beiroa et al., 2014; Blouet & Schwartz, 2012). Some gut hormones also modulate fat metabolism in white adipocytes, which is of particular interest as the mobilization of free fatty acids is an essential prerequisite for the activation of UCP1. For example, PYY inhibits lipolysis via Y2-receptor (Y2R) coupling to signalling by G_i (Valet et al., 1990), which is a specific isoform of the G-protein α-subunit initiating a signalling cascade that inhibits adenylyl cyclase and thereby decreases intracellular cAMP levels. Secretin, on the other hand, stimulates lipolysis through the secretin receptor (SCTR) coupling to G_S signalling in white adipocytes by activation of adenylyl cyclase and rising cAMP levels (Butcher & Carlson, 1970; Miegueu, Cianflone, Richard, & St-Pierre, 2013; Rudman & Del Rio, 1969; Sekar

& Chow, 2014). None of these gut hormones had been demonstrated to directly activate brown fat thermogenesis during a meal.

2 | SECRETIN – THE ENDOCRINE MOLECULAR MEDIATOR OF MEAL-ASSOCIATED BROWN FAT THERMOGENESIS

We recently revealed a novel endocrine gut–brown fat–brain axis triggered by secretin release from the intestine during a meal (Li et al., 2018). Our transcriptome analysis of murine brown fat demonstrated that SCTR is abundantly expressed, while receptors for other gastrointestinal peptides are absent. Therefore, the gut hormone secretin, which is classically known as a stimulant of pancreatic water and bicarbonate secretion upon food intake, represented the top candidate in our search for novel endocrine mediators of meal-associated brown fat thermogenesis. Indeed, in primary brown adipocytes, secretin increased UCP1-dependent respiration. Further detailed *in vitro* analysis established that secretin initiates the canonical SCTR–cAMP–PKA–lipolysis–UCP1 pathway in brown adipocytes. *In vivo*, the thermogenic effect of secretin was consolidated by indirect calorimetry and multispectral optoacoustic tomography in three different mouse models. The thermogenic effect was (i) UCP1-dependent, (ii) comparable to noradrenaline, (iii) significantly present at room temperature and thermoneutrality, and (iv) accompanied by a rise in the temperature of interscapular brown fat (T_{iBAT}), the largest brown fat depot in mice (Cinti, 2005). In addition, plasma secretin levels were decreased by fasting and increased significantly within 1 h after refeeding, which was congruent with changes in T_{iBAT}. Furthermore, a single secretin injection prior to refeeding of fasted mice reduced food intake in a UCP1-dependent manner, which was reflected by the regulation of anorexigenic and orexigenic hypothalamic peptides in wild-type, but not UCP1-knockout (KO) mice. This effect on food intake was induced by a direct activation of brown fat, independent of the SNS, as assessed by pretreatment with propranolol, which blocks the sympathetic neuronal input to brown adipose tissue. We reasoned that any signal working through the brain from activation of secretin receptors either in vagal afferents or hypothalamic nuclei will be blocked. As pretreatment with propranolol did not alter secretin's effect on brown fat activity and food intake, but completely abolished the effect of the β_3-adrenergic receptor agonist CL-316,243, we exclude a gut–brain–SNS–brown fat route. Our findings are in contrast to a previous study reporting that the anorexigenic action of secretin depends on the activation of secretin receptors in vagal sensory nerves and melanocortin signalling in the brain (Cheng et al., 2011).

In further experiments we substantiated the importance of meal-induced endogenous secretin release for the function of the endocrine gut–brown fat–brain axis by antibody-based neutralization of secretin activity. In mice refed after an overnight fasting, neutralization caused attenuation of the meal-associated rise in T_{iBAT} as well as an increase in cumulative food intake. The link between secretin-induced brown fat thermogenesis and satiation was underlined by a negative correlation of food intake and meal-associated rise in T_{iBAT}. Meal-pattern analyses revealed that the interplay of secretin and brown fat regulates food intake in mice. Although total food intake was not altered in the absence of either secretin or intact brown fat, the number of meals per night and inter-meal bout lengths were decreased, while meal size and meal duration were increased.

In humans, postprandial secretin correlated with oxygen consumption and fatty acid uptake rates in brown fat. Direct evidence for the metabolic action of secretin in brown fat was obtained by fluorodeoxyglucose (FDG)–positron emission tomography (PET)–computed tomography (CT) scans demonstrating that two secretin infusions significantly increased glucose uptake into human brown fat. Additionally, we demonstrated the presence of the secretin receptor on transcript and protein level in human brown fat (manuscript in preparation).

Taken together, our findings demonstrate that secretin mediates a gut–brown fat–brain axis in the control of satiation. Conclusively, targeting this endocrine axis might hold promise for developing novel obesity therapies as it promotes negative energy balance through both increasing energy expenditure and decreasing energy intake (Figure 1). In addition to elucidating a novel mechanism of satiation, these findings have a number of interesting implications. First, they may explain the presence of functional brown fat in humans and many even larger mammalian species, for which allometric modelling of thermogenic brown fat capacity (Heldmaier, 1971) and comparative genomics of *Ucp1* (Gaudry, Campbell, & Jastroch, 2019) exclude non-shivering thermogenesis in brown fat. Thus, in humans, heat dissipated by brown fat may serve a regulatory role, rather than a homeostatic role in thermoregulation. Second, these findings qualify brown fat as an even more attractive therapeutic target that not only increases energy expenditure but also reduces food intake at the same time. Based on these findings one may hypothesize that any brown fat activating stimulus could potentially induce satiation. By manipulating both sides of the energy balance at the same time, one of the most challenging difficulties during weight loss interventions, i.e. compensation (Hall et al., 2012), could be overcome.

3 | THE MISERY OF WEIGHT LOSS

In the course of evolution, humans and their hominin ancestors developed sophisticated physiological mechanisms to expand and defend their body fat stores to survive periods of famine. In our modern times with many people significantly exceeding a healthy expansion of body fat, these physiological mechanisms rather prove to be a health risk than an evolutionary advantage. Lowering energy intake, whether voluntarily by lifestyle changes or assisted by pharmacological interventions, is inevitably counteracted by a reduction in metabolic rate to defend the current body mass through energy homeostatic systems (Mole, 1990). Conversely, unconscious overeating will antagonize body mass loss as a result of an increased energy expenditure due to regular workouts (Blundell, Stubbs, Hughes, Whybrow, & King, 2003; King et al., 2007). Thus, a safe drug that increases energy expenditure and at
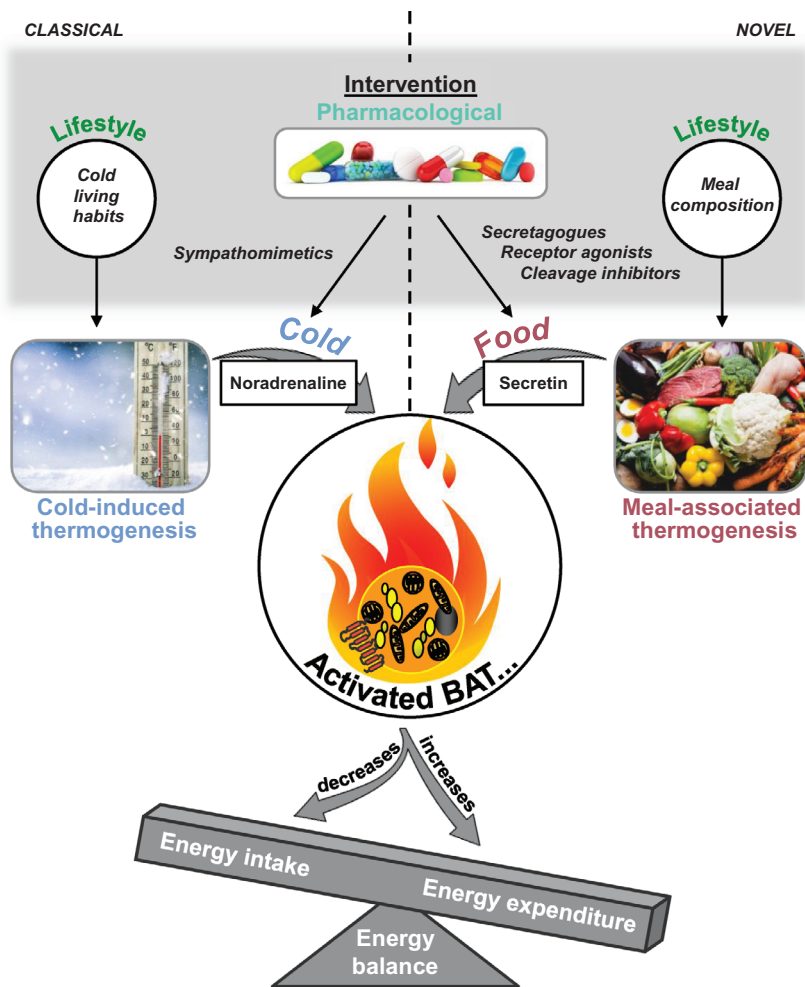
FIGURE 1 Targeting brown fat for energy balance regulation. Classically, brown fat is activated in response to cold exposure by noradrenaline from the sympathetic nervous system. Additionally, brown fat is activated in association with a meal by the gut hormone secretin. Upon activation, brown fat increases energy expenditure and decreases energy intake. Thus, it has an overall negative impact on energy balance. The augmentation of prandial released secretin, e.g. by secretagogues or cleavage inhibitors, represents besides sympathomimetics an alternative to pharmacologically activating brown adipose tissue

the same time counteracts hyperphagia would be the first-line therapy for the treatment of metabolic diseases. The adipocyte-derived protein hormone leptin, a key factor in energy balance regulation (Allison & Myers, 2014; Gautron & Elmquist, 2011), may be regarded as a showcase for such a factor. Leptin promotes satiety and prevents the lowering of energy expenditure in response to caloric restriction (Bolze et al., 2016; Doring, Schwarzer, Nuesslein-Hildesheim, & Schmidt, 1998). Despite these promising endocrine actions, leptin treatment of people with obesity was not successful, most likely due to leptin resistance (Rosenbaum & Leibel, 2014). In this respect, we regard secretin, perhaps in combination with other gastrointestinal hormones and leptin, as a promising candidate.

4 | ACHIEVING BROWN FAT ACTIVATION WHILE LIVING IN A COMFORTABLE THERMONEUTRAL ENVIRONMENT

Several novel molecular mediators for the recruitment of brown fat and/or the browning of white adipose tissue have been identified (Bartelt & Heeren, 2014). The mere augmentation of thermogenic capacity, however, is only one step in targeting brown fat for therapeutic purposes in obesity prevention and treatment because

UCP1 is constitutively inactive in brown adipocytes (Li, Fromme, Schweizer, Schottl, & Klingenspor, 2014). Classically, increased sympathetic tone in response to cold exposure will trigger intracellular signalling events that mobilize fatty acids and activate uncoupled respiration. However, humans spend most of their time in thermoneutral environments equipped with heating systems and put on warm clothing which normally precludes cold-induced brown fat thermogenesis. Even though cold acclimation can recruit cold-inducible heating capacity in human brown fat, this capacity will not be utilized while remaining in thermoneutrality. Cold mimetics or other pharmacological molecules to stimulate brown fat would be desirable, but so far, only a few activators of UCP1-mediated thermogenesis have been identified (Braun, Oeckl, Westermeier, Li, & Klingenspor, 2018). Thus, gut-derived secretin as a novel direct brown fat activator is of prime interest. With three to four meals ingested in a regular day, it is likely that periprandial secretion of secretin triggers repeated activation of brown fat thermogenesis according to daily meal patterns. This implies more frequent bouts of brown fat activation in a thermoneutral environment than previously anticipated. Moreover, it has been recently shown that brown adipose tissue volume and activity, measured by ^{18}F-FDG, are not associated with energy intake and meal-induced appetite-related sensations in young, healthy adults (Sanchez-Delgado et al., 2020). We hypothesize,

that meal-associated thermogenesis determines energy intake and appetite, rather than cold-induced activation. From an evolutionary perspective, this would prevent a limitation of energy intake during cold exposure when brown adipose tissue is activated to survive in the cold. The intensity of meal-associated brown fat activity may depend on caloric intake and meal type. Future studies will need to address the effect size and duration of thermogenic action of endogenous secretin release on brown fat.

5 | MANIPULATING MEAL-ASSOCIATED BROWN FAT THERMOGENESIS TO ACHIEVE WEIGHT LOSS

A recently developed novel optoacoustic imaging tool for the non-invasive assessment of metabolic processes without using contrast agents could be applied to determine meal-associated brown fat thermogenesis in humans. This technique employs haemoglobin as an intrinsic tissue biosensor and resolved oxygen utilization (rate of tissue oxygen saturation) as a metabolic indicator, enabling the label-free measurement of brown fat activation in mice and human subjects (Reber et al., 2018). Characterizing the physiological underpinnings of meal-associated brown fat thermogenesis in humans could pave the way for the development of new strategies to increase brown fat activity independent of the SNS. When considering secretin-induced activation of brown fat for obesity therapy, secretin's short half-life of 2.5 min as well as its actions on pancreatic and gastric functions must be taken into account. Comparative assessment of dose–response relationships for secretin's stimulatory effect on brown fat thermo-genesis and gastrointestinal actions, respectively, would provide insight into whether chronic administration of secretin is feasible without potential adverse effects, like desensitization of the G-protein-coupled secretin receptor or pancreatic inflammation. Nevertheless, it is unlikely that chronic administration of secretin would promote negative energy balance. Chronic treatment with a secretin receptor agonist only transiently increased energy expenditure in diet-induced obese mice, and systemic blockade of secretin signalling by antibody treatment in lean mice had no effect on daily energy intake, despite alterations in the number of meals, meal duration and meal size.

Alternatively, the prandial surge of endogenous secretin could be boosted in a timely manner to promote satiation. Secretagogues or cleavage-inhibitors of secretin may efficiently accelerate meal termination and thereby reduce caloric intake by increasing the yield of prandial secretin (Klingenspor, 2019). Since duodenal acidification is the primary stimulus for secretin release from S-cells in the epithelium of the duodenum into the circulation, meal composition could also be a crucial determinant for secretin release and sub-sequent brown fat activation. Therefore, nutritional interventions with meals tailored to boost prandial secretin release would be the most natural and least invasive approach to promote satiation (Figure 1). Conversely, one would assume that a reduction of duodenal acidification results in lower secretin levels and thus attenuated meal-associated activation of brown fat. Proton pump inhibitors (PPI)

and histamine H2 receptor antagonists are groups of medications whose main action is a pronounced and long-lasting reduction of gastric acid secretion. Interestingly, PPI use has been reported to be associated with a significant weight gain in men, while energy intake, physical activity and sedentary behaviour were unchanged (Czwornog & Austin, 2015; Yoshikawa, Nagato, Yamasaki, Kume, & Otsuki, 2009). Furthermore, it has been demonstrated that children prescribed with PPIs and H2 receptor antagonists were slightly more likely to develop obesity, with increasing manifestation depending on medication duration (Stark, Susi, Emerick, & Nylund, 2019). Although most of these effects are attributed to changes in gut microbiota, the impact on secretin levels, meal-associated brown fat thermogenesis and food intake needs to be further investigated.

For bariatric surgery – the only successful treatment of people with obesity – the molecular mediators of the beneficial metabolic effects remain elusive. Since intestinal expression of secretin has been reported to be markedly upregulated in a rat model of Roux-en-Y gastric bypass (van Witteloostuijn et al., 2017), the gut hormone might be a potential endocrine contributor. This further underlines secretin's role in metabolic regulation.

6 | DIMENSIONS OF BROWN FAT'S CONTRIBUTION TO ENERGY EXPENDITURE AND WEIGHT LOSS IN THE LONG RUN

When targeting brown fat for obesity treatment it has to be taken into account that the incidence of active brown fat is altered by age, sex, body mass index, plasma glucose, season, outdoor temperature and medication (Carey & Kingwell, 2013; Hanssen et al., 2015; Lee, Greenfield, Ho, & Fulham, 2010; Nedergaard & Cannon, 2010; Ouellet et al., 2011; Persichetti et al., 2013; Skillen, Currie, & Wheat, 2012). Although there is some evidence, that the prevalence of brown fat is not affected by body mass index, there seems to be no doubt that active brown fat declines with age (Gerngross, Schretter, Klingenspor, Schwaiger, & Fromme, 2017). Thus, not only must the thermogenic process be activated, but the total mass and oxidative capacity of brown fat in the human body must be increased. To date it is unclear whether sufficient brown fat capacity for energy expenditure can be recruited in people with obesity to reduce their body fat mass effectively (Marlatt & Ravussin, 2017). Several studies have estimated the impact of brown fat on energy expenditure based on various investigations and calculations. In order to illustrate the heterogeneity of these estimates, we have compiled a list of studies in which explicit calculations of the daily surplus have been performed (Table 1). But apart from that it is obvious that brown fat has more potential than previously anticipated, as it targets both sides of the energy balance equation. Therefore, simple calculations based on the estimated mass specific heating capacity are insufficient to predict the impact of brown fat on energy balance. For sure, targeting brown fat as sole treatment of metabolic imbalance might not be satisfactory. Nevertheless, it may at least facilitate weight loss and prevent the positive weight trajectory observed with ageing, which approximates 0.5–1 kg per year (Dutton

TABLE 1 How much energy can be dissipated by human brown fat?

Rank	Daily surplus (kJ)	Method of estimation	Reference	Comment
1	+2000	Estimation based on brown fat thermogenesis in rodents	Rothwell & Stock (1983)	Estimation based on the assumption that BAT (40–50 g) is maximally activated
2	+483–2176	Refined PET/CT analyses	Leitner et al. (2017)	Estimation based on fully activated brown fat and browning of white fat
3	+850	Indirect calorimetry and glucose uptake (^{18}FDG-PET/CT)	Cypess et al. (2015)	β_3-Adrenergic receptor agonist
4	+192–883	Estimation based on radiological 3D mapping of BAT (volume) and oxygen consumption ($^{15}O_2$-PET/CT)	Carpentier et al. (2018)	Oxygen consumption (U Din et al., 2016); BAT mass (Leitner et al., 2017); 20 kJ (l $O_2)^{-1}$ (Leonard, 2010); AT density 0.925 g.ml^{-1} (Martin et al., 1994)
5	+523	Glucose uptake (^{18}FDG-PET/CT)	Weir et al. (2018)	Mild cold
6	+125	Glucose uptake (^{18}FDG-PET/CT)	Virtanen et al. (2009)	Mild cold plus ice-water immersions of feet
7	+63–105	Indirect calorimetry, oxygen consumption ($^{15}O_2$-PET/CT) and near-Infrared spectroscopy	Muzik et al. (2013)	Mild cold; subjects with relatively large BAT depots
8	+54	Indirect calorimetry and oxygen consumption ($^{15}O_2$-PET/CT)	U Din et al. (2018)	Postprandial state
9	+29–42	Oxygen consumption ($^{15}O_2$-PET/CT)	U Din et al. (2016)	Room temperature compared to acute cold

BAT, brown adipose tissue.

et al., 2016; Norman et al., 2003). However, there is no question that much more attention should be directed to the regulatory role of brown fat beyond energy expenditure.

In conclusion, the identification of the secretin-driven gut–brown fat–brain axis gives an impetus to rethink the role of brown fat as a mere catabolic heating organ and qualifies it as an even more attractive target for the treatment of obesity. Any stimulus of brown fat may potentially induce satiation, but may also increase resting energy expenditure without causing unwanted side effects. Further studies on the function and sensitivity of the endocrine gut–brown fat–brain-axis in people with obesity are urgently needed to exploit the potential of brown fat to impact the complex and redundant system of energy balance controlling hunger and satiety, energy partitioning and energy expenditure and promote metabolic health.

COMPETING INTERESTS

The Technical University of Munich has applied for a patent (PCT/EP2017/062420).

AUTHOR CONTRIBUTIONS

K.S. drafted the M.S. and created the figure. M.K. and Y.L. edited the manuscript. All authors contributed to the revision. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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