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MINI-REVIEW

Renaissance of leptin for obesity therapy

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Abstract Diet-induced obesity and its metabolic comorbidities constitute an overwhelming health crisis and there is an urgent need for safe and effective pharmacological interventions. Being largely shelved for decades, scientists are now revisiting the anti-obesity virtues of leptin. Whereas it remains evident that leptin as a stand-alone therapy is not an effective approach, the potential for employing sensitising pharmacology to unleash the weight-lowering properties of leptin has injected new hope into the field. Fascinatingly, these leptin-sensitising agents seem to act via distinct metabolic pathways and may thus, in parallel with their clinical development, serve as important research tools to progress our understanding of the molecular, physiological and behavioural pathways underlying energy homeostasis and obesity pathophysiology. This review summarises a presentation given at the 'Is leptin coming back?' symposium at the 2015 annual meeting of the EASD. It is accompanied by two other reviews on topics from this symposium (by Thomas Meek and Gregory Morton, DOI: 10.1007/s00125-016-3898-3, and by Gerald Shulman and colleagues, DOI: 10.1007/s00125-016-3909-4) and an overview by the Session Chair, Ulf Smith (DOI: 10.1007/s00125-016-3894-7).

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Abbreviations

DIO	Diet-induced obese
ER	Endoplasmic reticulum
FGF21	Fibroblast growth factor 21
GLP-1	Glucagon-like peptide 1
HSF1	Heat shock transcription factor 1
IKKβ	IκB kinase β
MyD88	Myeloid differentiation primary response gene 88
PGC1α	Peroxisome proliferator-activated receptor-γ coactivator 1α
POMC	Pro-opiomelanocortin
PTP1B	Protein tyrosine phosphatase 1B
SOCS3	Suppressor of cytokine signalling 3
STAT3	Signal transducer and activator of transcription 3
TLR4	Toll-like receptor 4

Introduction

Although the misperception of obesity as a consequence of poor self-control and gluttony is still widespread, body weight has a strong genetic component orchestrating the neuroendocrine systems that govern food intake and energy expenditure [1]. When the adipocyte-derived hormone leptin and its profound impact on central circuits controlling energy and glucose metabolism were discovered [2], hopes were raised that obesity might be able to be reversed with single-hormone therapy. Discouragingly, most obese individuals are hyperleptinaemic and exogenous leptin has a negligible effect on suppressing appetite to lower body weight [3]. This insight gave rise to

the hypothesis of 'leptin resistance' as a phenomenon that may play a crucial role in the proximate perturbations in energy homeostasis that ultimately lead to obesity [4]. However, whether or not the inability of leptin to suppress feeding in the face of obesity is a consequence of cellular 'leptin resistance' remains subject to debate and is beyond the scope of this current review. Irrespective of this dispute, amplifying leptin responsiveness may hold the key to unlocking the potential of leptin as a powerful anti-obesity drug.

Whereas it is well established that leptin can be used to correct neuroendocrine and metabolic abnormalities in patients with acquired or congenital leptin deficiency and lipodystrophy [5–7], overcoming resistance to the effects of leptin therapy on energy metabolism in common obesity continues to challenge us. Intriguingly, in recent years, novel approaches have surfaced to show that leptin resistance is a reversible condition. Indeed, preclinical studies have identified several 'leptin sensitisers', that may hold therapeutic promise. These leptin sensitisers target distinct neuroendocrine systems, all of which have been linked to leptin signalling pathology, including endoplasmic reticulum (ER) stress [8], hypothalamic inflammation [9] and multiple nodes of the leptin signalling cascade [10–13]. In addition, a growing body of evidence suggests that gastrointestinal-derived peptides and a series of already approved pharmacotherapies can amplify the weight-lowering actions of exogenous leptin [14–19], re-positioning leptin as a relevant agent in combination therapies for the treatment of obesity.

In this review we present an overview of emerging strategies for restoring or enhancing the energy metabolic actions of leptin in the leptin-resistant state. We summarise the proposed cellular and molecular underpinnings of these novel leptin-enhancing precision medicines and we provide an outlook on the translational prospects and challenges and, accordingly, the rational for employing leptin in future polypharmacy to treat common obesity.

Targeting leptin responsiveness with pharmacology

Whether the inadequacy of hyperleptinaemia to correct obesity reflects a diet-induced defect in leptin action or whether the predominant physiological role of leptin is to defend against reductions in body fat remains a topic of discussion and ongoing investigations [20, 21]. Separately from this debate, a growing body of evidence supports the thinking that distinct pharmacological interventions can act as applicable leptin sensitisers in the obese leptin-resistant state (see Text box). This notion of pharmacotherapy-induced 'turbocharging' of leptin signalling is contributing to a paradigm shift, positioning leptin as a possible adjunctive agent in future polypharmacological anti-obesity interventions. In the following sections, the most promising strategies to enhance leptin responsiveness in obesity are reviewed.

ER stress The ER is a dynamic organelle regulating the synthesis, folding and maturation of proteins. An imbalance between the loading and folding capacities of the ER results in a condition known as ER stress. Pioneering studies have demonstrated a causal link between hypothalamic ER stress, leptin signalling and obesity [22, 23] (Fig. 1). Corroborating this theory, preclinical studies found that specific overexpression of molecular ER components can prevent dietary inhibition of leptin signalling [22]. Accordingly, pharmacological application of the chemical chaperones tauroursodeoxycholic acid (TUDCA) and 4-phenyl butyric acid (4-PBA) can alleviate hypothalamic ER stress to reverse diet-induced leptin resistance [22–24]. These chemical chaperones stabilise protein folding by decreasing the formation of abnormal protein aggregates, which reduces ER stress. In support of the hypothesis that ER stress may be directly involved in diet-induced leptin resistance and obesity progression, the non-steroidal anti-inflammatory drug (NSAID) flurbiprofen was recently shown to alleviate ER stress, and lower body weight in diet-induced obese (DIO) mice [25, 26].

The beneficial effects of the chemical chaperones in rodents suggest that they may enhance leptin action in obese individuals [27]. TUDCA was recently tested in obese insulin-resistant patients in a 4-week treatment study [28]. Although the treatment induced moderate improvements in insulin sensitivity, it exhibited no ability to lower body weight. Discouragingly, ER stress markers did not appear to be affected in peripheral tissues, and the relative weak capacity of these chaperones to improve ER function [29] may limit their clinical utility.

An in silico screening to identify novel small molecules acting on ER stress was recently performed [8]. This study led to the identification of a small molecule (celastrol) with potent anorectic and body weight-lowering effects in DIO mice. Importantly, compared with celastrol monotherapy, co-treatment of celastrol and leptin amplified weight loss in leptin resistant DIO mice, indicative of celastrol-induced restoration of leptin action. Supporting the interplay between celastrol administration and leptin, in obese mice with genetically disrupted leptin signalling (*ob/ob* and *db/db* mice), celastrol treatment showed negligible effects on energy metabolism. While the effects of celastrol to correct hyperleptinaemia and obesity coincided with changes in hypothalamic STAT3 phosphorylation and a reduction in ER stress markers, a more recent study showed that celastrol induces an HSF1–PGC1α axis to control thermogenic and mitochondrial gene programs in adipocytes and myocytes [30]. Independent of the primary site of action of celastrol, future investigations will undoubtedly explore safety and translational efficacy of celastrol and/or celastrol mimetics to treat obesity.

Inflammation Diet-induced obesity promotes chronic low-grade inflammation in both peripheral tissues and in the brain

Pharmacological leptin sensitisers			
Compound	Metabolic effects	Mechanism of action	Species
4-PBA	FI & BW ↓ Insulin sensitivity ↑	ER stress ↓ p-PERK ↓	Mouse
TUDCA	FI & BW ↓ Insulin sensitivity ↑	ER stress ↓ p-PERK ↓	Mouse
Flurbiprofen	BW & adiposity ↓	ER stress ↓ Protein aggregation/ inflammation ↓	Mouse
Trodusquemine	FI, BW & adiposity ↓	LepR signalling ↑ PTP1B ↓	Mouse
Celastrol	FI & BW ↓ EE ↑ Glucose tolerance, insulin sensitivity ↑	ER stress ↓ p-PERK, SERCA2B ↓ HSF1–PGC1α ↑	Mouse
Amylin	FI, BW & adiposity ↓	LepR signalling ↑ p-STAT3 ↑	Rat and human
Exendin-4	FI, BW & adiposity ↓ Glucose tolerance ↑	Exogenous leptin action ↑	Mouse
FGF21	BW & adiposity ↓ Glucose tolerance ↑	Exogenous leptin action ↑	Mouse
GLP-1/Glucagon	FI, BW and adiposity ↓ Glucose tolerance ↑	Exogenous leptin action ↑	Mouse
Clusterin	FI & BW ↓	Exogenous leptin action ↑ LepR signalling ↑ LepR binding ↑	Mouse
Metformin	FI, BW & adiposity ↓ Insulin sensitivity ↑	Exogenous leptin action ↑ LepR signalling ↑ Leptin transport across the BBB ↑	Rat
mCPP	BW ↓	Exogenous leptin action ↑ LepR signalling ↑ p-STAT3 ↑	Mouse
PYY(3–36)	FI & BW ↓	Exogenous leptin action ↑	Rat
CCK	FI ↓	LepR signalling ↑	Mouse

BBB, blood–brain barrier; BW, body weight; CCK, cholecystokinin; EE, energy expenditure; ER, endoplasmic reticulum; FGF21, fibroblast growth factor 21; FI, food intake; GLP-1, glucagon-like peptide-1; HSF1, heat shock transcription factor 1; LepR, leptin receptor; mCPP, meta-chlorophenylpiperazine; PBA, 4-phenyl butyric acid; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PGC1α, peroxisome proliferator-activated receptor-gamma coactivator 1alpha; PTP1B, protein tyrosine phosphatase 1B; PYY, peptide YY; PVN, paraventricular nucleus of the hypothalamus; SERCA2B, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; STAT3, signal transducer and activator of transcription 3; TUDCA, tauroursodeoxycholic acid

[31]. In the hypothalamus, the amplified immune response to excess nutrients may play a causal role for pathogenesis of diet-induced leptin resistance and adiposity [32, 33] (Fig. 1). Excess dietary fat activates TLR4–MyD88-dependent IKKβ/NF-κB signalling, which in turn leads to the production and release of proinflammatory cytokines to impair hypothalamic leptin signalling [24, 34, 35]. Moreover, diet-induced induction in proinflammatory cytokines triggers an immediate response in non-neuronal hypothalamic cells (microglial and astroglial populations) [33, 36, 37]. Corroborating a role for proinflammatory cytokines in leptin signalling pathology, central administration of TNF-α impairs leptin sensitivity, possibly by increasing the levels of SOCS3 and PTP1B, which act as negative regulators of

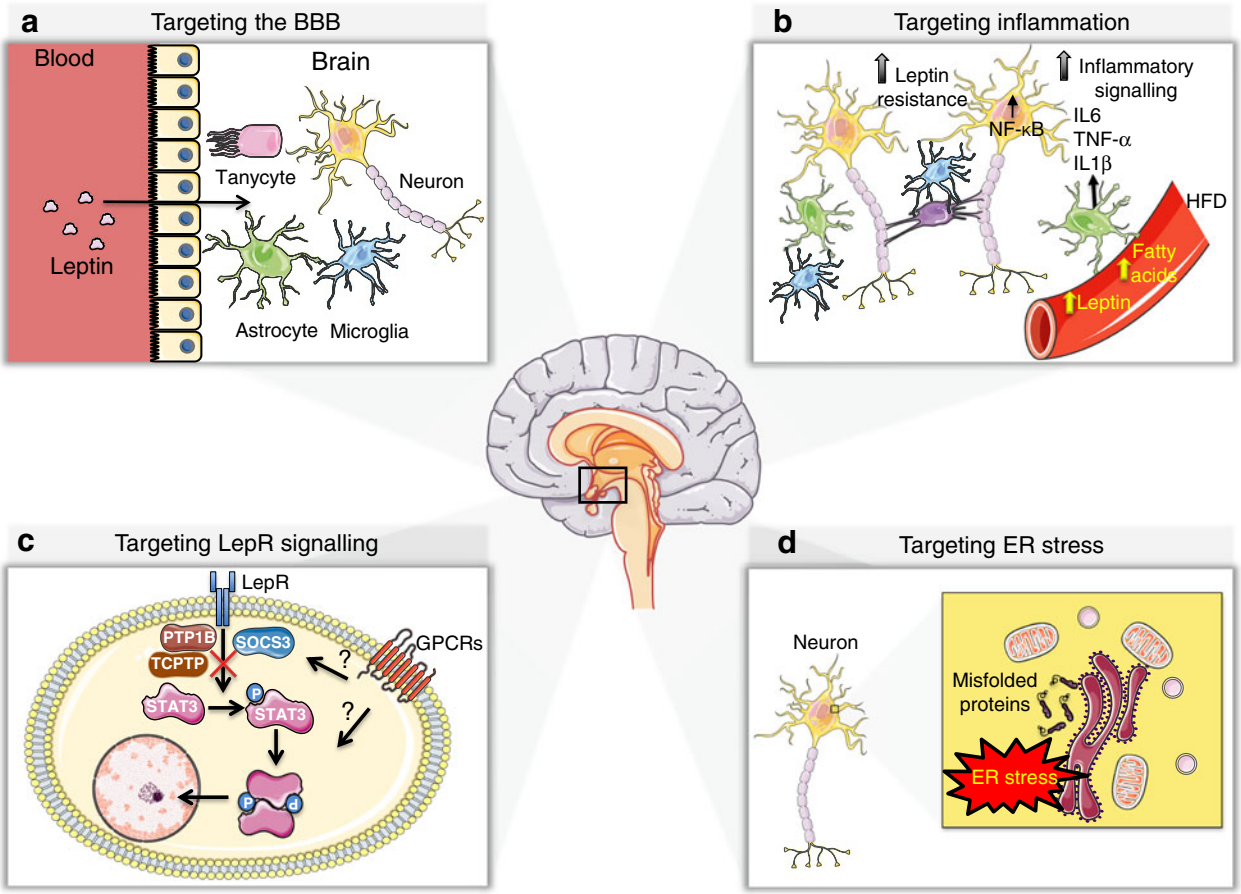

Fig. 1 Schematic overview of potential therapeutic strategies to enhance leptin action. (**a**) Agents that facilitate increased leptin transport across the blood–brain barrier and/or tanycytes may provide enhanced leptin access to hypothalamic target cells. (**b**) Targeting hypothalamic inflammation in neurons or glial cells may reverse diet-induced perturbations in cytokine signalling and NF-κB signalling to restore leptin sensitivity. (**c**) Negative regulators of leptin receptor (LepR) intracellular signalling, including the protein tyrosine phosphatases PTP1B, TCPTP and SOCS3 may be relevant targets to increase the maximal signalling capacity downstream of LepR. Multiple G protein-coupled receptors (GPCRs) are intertwined with leptin signalling. Indeed, peripheral administration of several approved GPCR-targeting pharmacotherapies can enhance leptin responsiveness in leptin-resistant obesity. (**d**) Correction of imbalances in neuronal protein folding, i.e. ER stress, via application of chemical chaperones, might increase central leptin sensitivity and restore energy homeostasis. HFD, high-fat diet; TCPTP, T Cell PTP. The figure was produced using Servier Medical Art (www.servier.com)

leptin receptor signalling [9, 11, 38]. Although causality is not clear, there is considerable evidence to support the existence of a vicious cycle between excess nutrients, hypothalamic inflammation, leptin resistance and obesity [39]. Of note, glial leptin receptor signalling was recently reported to control feeding [40]. However, the relative contribution of astrocyte leptin signalling to diet-induced leptin resistance, hypothalamic inflammation and obesity is to date uncharted.

Several studies have explored the potential of pharmacological intervention targeting hypothalamic IKKβ/NF-κB signalling to reverse diet-induced metabolic perturbations. Teasaponin, a naturally derived inhibitor of NF-κB, has been reported to reduce body weight and improve leptin sensitivity in DIO mice [41]. IKKβ/NF-κB inhibitors have been found to reduce food intake and lower body weight via increasing leptin sensitivity in some, but not all studies, indicating that the application of this strategy needs further evaluation [32, 42–45].

Future studies investigating the mechanistic interplay between diet-induced molecular perturbations in glial cells, hypothalamic inflammation-like processes and the development of leptin resistance are urgently needed. Furthermore, the role of neuronal-supporting cell types such as tanycytes in this pathology, e.g. through controlling leptin entry across the blood–brain barrier, deserves additional attention (Fig. 1). Insights into these cell type-specific processes and their interconnectedness could potentially facilitate the discovery of novel drug candidates that reverse leptin resistance.

Metformin Treatment with the glucose-lowering drug metformin disproportionally decreases circulating leptin levels in obese and healthy individuals [46–48] and, in DIO rats, reverses leptin resistance [16]. In addition to restoring leptin

responsiveness in DIO leptin-resistant rats, metformin treatment also enhances the anorectic effect of exogenous leptin in lean rats. The efficacy of metformin to restore leptin sensitivity may be multi-factorial and involve enhanced transport of leptin across the blood–brain barrier, increased leptin receptor expression and/or induction of the STAT3–POMC signalling pathway [16, 49]. Furthermore, metformin directly inhibits leptin secretion in rat adipocytes [50]. Studies in obese leptin-resistant humans are needed to evaluate whether metformin is able to restore the weight-lowering activity of exogenous leptin and, thus, if metformin and leptin co-treatment can reduce body weight synergistically and should be considered as a relevant anti-obesity combinatorial strategy. Of note, despite the fact that metformin has been widely used as a type 2 diabetes therapy for many years, its mechanisms of action remain poorly defined. Uncovering the cellular metabolic actions of metformin may, in parallel, provide important hints for its application as a leptin-sensitising agent.

Amylin A landmark study by Roth and colleagues demonstrated that pretreating obese humans or rodents with the pancreatic polypeptide amylin restored the responsiveness to exogenous leptin in terms of weight-lowering [14]. In DIO leptin-resistant rats, co-administration of leptin and amylin led to a greater body weight loss than monotherapy. Importantly, the efficacy of amylin in restoring the weight-lowering efficacy of leptin was confirmed in obese and overweight patients subjected to energy restriction and pramlintide (amylin analogue) and metreleptin (leptin analogue) as combination therapy [51, 52]. At the molecular level, amylin was shown to restore leptin sensitivity by potentiating leptin-stimulated phosphorylation of STAT3 in the arcuate nucleus and the ventromedial hypothalamus (VMH). Additionally, complementary neuronal signalling in the area postrema, and the mesolimbic reward pathway between amylin and leptin has been reported [53, 54]. Although only mild and transient adverse effects were reported with the combination of pramlintide and metreleptin, in 2011, Amylin Inc. decided to halt the development of this combination therapy because of potential safety issues. Whether this relates to metreleptin-induced generation of antibodies with neutralising activity remains speculative, however, in the meantime, metreleptin has been approved for treating leptin deficiency in patients with congenital or acquired lipodystrophy [55–57].

Glucagon-like peptide 1 and fibroblast growth factor 21 In 2012, Müller and colleagues reported that pharmacologically induced restoration of leptin responsiveness is not a feature unique to amylin, but that fibroblast growth factor 21 (FGF21) and exendin-4 (glucagon-like peptide 1 [GLP-1] receptor agonist) can also restore sensitivity to the catabolic actions of exogenous leptin when co-administered [15]. In this study, a site-specific PEGylated leptin was used to enhance bioavailability relative to native leptin. Although FGF21 and exendin-4 act via distinct metabolic pathways, the efficacy of exogenous leptin to amplify the pharmacologically induced weight loss was, for both compounds, not achieved until ~25% weight loss had occurred, suggesting a threshold for the restoration of leptin sensitivity. One caveat to FGF21- and exendin-4-mediated restoration of leptin responsiveness was the necessity of a concomitant dietary switch to a low-fat diet upon treatment initiation. Strikingly, energy restriction-induced weight loss to ~25% alone did not restore leptin responsiveness, suggesting that both weight loss pharmacotherapy and leptin receptor activation are required to restore the metabolic action profile of leptin (Fig. 1).

Corroborating the differential effect between pharmacologically-mediated and energy restriction-mediated weight loss, a recent study demonstrated that GLP-1R agonism, but not energy restriction, drives a reduction in nutrient-induced hypothalamic inflammation [36]. However, further investigations are required to establish whether the ability of GLP-1R agonism to amplify leptin sensitivity is causally linked to a reversal in diet-induced microgliosis.

GLP-1 receptor/glucagon receptor co-agonism Recent progress in biotechnology has helped facilitate the generation of a series of single-molecule compounds that combine and integrate different modes of pharmacological action [58]. In 2009, this strategy was used to show that a molecule with balanced action at the glucagon receptor and the GLP-1 receptor (GLP-1R), synergistically orchestrates distinct biological pathways to exhibit a coordinated effect on energy metabolism in rodents [59]. This GLP-1R/glucagon receptor co-agonist was recently found to act as a powerful leptin sensitiser in leptin-resistant DIO mice [60]. Indeed, animals who received co-treatment with GLP-1/glucagon and leptin exhibited superior weight loss relative to each monotherapy. Importantly, and in contrast to treatment with exendin-4 and FGF21 [15], the GLP-1R/glucagon receptor co-agonist restored leptin responsiveness in DIO mice chronically exposed to a high-fat, high sucrose diet. While it remains to be uncovered how exactly the dual agonist activating glucagon- and GLP-1 receptors alleviates leptin unresponsiveness, the anti-obesity properties of concerted GLP-1R and glucagon receptor co-agonism translates to humans [61, 62], and several pharmaceutical companies are now pursuing GLP/glucagon co-agonism for the treatment of obesity [58].

Conclusions and future directions

While the discovery of leptin as a governing anorectic signal did not immediately lead to the development of an influential anti-obesity drug, it triggered massive interest in delineating the neuronal circuitries underling the central control of energy

homeostasis. Some 20 years later, there is a much deeper understanding of the neuronal machinery involved in the control of feeding behaviour and systemic substrate metabolism. However, despite major parallel advances in biotechnology, synthetic chemistry and information technology, these efforts have yet to be translated into safe and efficacious anti-obesity pharmacotherapies.

One way of overcoming such frustrating complexity of energy homeostasis regulation may be offered by simultaneous targeting of several distinct biological mechanisms. Specifically, novel poly-agonism molecules may offer unprecedented potential to overcome severe diet-induced energy metabolic perturbations and offset redundant counter-regulatory processes. Importantly, as outlined in this review, leptin may serve a key role in next-generation anti-obesity polypharmacy. While major efforts continue to be invested in understanding and refining ways of re-sensitising the neuronal circuitry to the weight-lowering properties of leptin, focus on the feasibility of targeting these pathways with translational pharmacology should be pursued with equal determination.

Engineering mixed small and large molecule co-agonists could represent another viable strategy to specifically deliver abundant concentrations of leptin sensitisers into hypothalamic target cells. We published the first proof-of-concept showing that peptide hormones can be exploited to selectively target steroid hormones in a cell-specific manner governed by the peptide receptor expression pattern [63]. A stable GLP-1–oestrogen conjugate was thus developed to selectively deliver oestrogen to GLP-1R-expressing cell populations, including the hypothalamus. The specific targeting of oestrogen amplified the anorectic properties of each co-agonist constituent without the hallmark toxicities of oestrogen actions in non-GLP1R-expressing cells. This conceptual approach could be evolved to decorate GLP-1 or other macromolecules with leptin-sensitising small molecules targeting ER stress or inhibiting inflammation.

There is reason for optimism. Our knowledge on the molecular basis of leptin signalling has never been greater, and if we continue to work hard on translating emerging molecular insights into therapeutic strategies we may, in the near future, be able to sensitise leptin signalling in obese individuals. As one example for key areas warranting intense future studies, major efforts will be necessary to understand how cell types such as tanycytes, microglia and astrocytes interact with neurons to meaningfully integrate existing knowledge of leptin biology with neuroendocrine pathologies resulting from—and driving—metabolic disease. Importantly, for leptin to (re)enter clinical studies as anti-obesity therapy, previously reported adverse effects associated with leptin administration, including hypertension and immunogenicity, will have to be carefully assessed [64, 65].

Nevertheless, we may currently be witnessing a shift in the anti-obesity pharmacology paradigm. Recent biotechnological advancements have pushed the development of single-molecule biologics with engineered mixed-agonism as well as next-generation small molecule screens resulting in the identification and validation of potent novel leptin sensitisers. By overcoming leptin insensitivity, such approaches appear to offer some of the most promising strategies yet to reverse and prevent diet-induced obesity, insulin resistance and type 2 diabetes.

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

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