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Review

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Neural Control of Energy Balance: Translating Circuits to Therapies

Laurent Gautron,[1,*] Joel K. Elmquist,[1,2] and Kevin W. Williams[1,3,*]
[1]Division of Hypothalamic Research, Department of Internal Medicine
[2]Department of Pharmacology
[3]Department of Neuroscience
The University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9077, USA
*Correspondence: laurent.gautron@utsouthwestern.edu (L.G.), kevin.williams@utsouthwestern.edu (K.W.W.)
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Recent insights into the neural circuits controlling energy balance and glucose homeostasis have rekindled the hope for development of novel treatments for obesity and diabetes. However, many therapies contribute relatively modest beneficial gains with accompanying side effects, and the mechanisms of action for other interventions remain undefined. This Review summarizes current knowledge linking the neural circuits regulating energy and glucose balance with current and potential pharmacotherapeutic and surgical interventions for the treatment of obesity and diabetes.

Introduction

Obesity, diabetes, and associated disorders represent a major public health challenge for North America, Europe, and increasingly the rest of the world. Both obesity and diabetes inflict health and economic burdens that require coordinated strategies to both prevent and treat these disorders. Indeed, a major barrier in the management and prevention of obesity is that weight loss due to lifestyle changes alone is inherently difficult. For many, this means that dieting-induced weight loss initially results in tangible beneficial effects but is often followed by a return to previous energy intake and consequently a rebound weight gain.

Numerous neurobiological and physiological mechanisms that regulate energy balance exist. In particular, it has become increasingly evident that the brain plays an important role in sensing energy demands and storage in order to maintain/defend body weight within a rather tight range. Studies ranging from worms, flies, and mice to humans have identified key conserved genes and neural pathways that are critical in regulating energy balance and glucose homeostasis. Moreover, the identification of human mutations in these or analogous pathways has led to hope that it may be possible to develop rational strategies based on animal model studies that may ultimately lead to successful therapeutic intervention in humans. In this Review, we will highlight how advances in understanding the neurophysiology underlying metabolism, including an increased understanding of neural circuits, may hold promise for development of adjunct therapies in the treatment of obesity and associated co-morbidities, including diabetes. Several recent Reviews have provided more detailed information and review of the primary literature regarding the respective circuits and approaches highlighted here (Barsh et al., 2000; Cone, 2005; Deisseroth, 2012; Farooqi and O'Rahilly, 2005; Heisler et al., 2003; Myers and Olson, 2012; Powley et al., 2005; Schwartz and Porte, 2005; Wikberg and Mutulis, 2008).

A Brief Overview of Neural Circuits Regulating Feeding and Energy and Glucose Homeostasis

The central melanocortin system is comprised of neurons in the hypothalamic arcuate nucleus and brainstem that produce pro-opiomelanocortin (Pomc), the precursor polypeptide of the biologically active melanocortin receptor peptide agonist, α-melanocyte-stimulating hormone (α-MSH). Additional peptides within the arcuate nucleus that contribute to the melanocortin system include Agouti gene-related peptide (AgRP), an endogenous inverse agonist of the melanocortin 4 receptor (Mc4r), and Neuropeptide Y (NPY), which is co-expressed with AgRP. Elucidating the physiological importance of this system in regulating energy balance and glucose homeostasis brought the hypothalamic arcuate nucleus to the forefront of research aimed at understanding the neural control of energy balance (Cone, 2005; Schwartz and Porte, 2005).

Pomc and NPY/AgRP neurons are prototypical players in the regulation of energy intake and expenditure for several reasons. In particular, exogenous administration of α-MSH potently inhibits food intake via activation of central melanocortin receptor-expressing neurons (Cone, 2005; Rossi et al., 1998; Schwartz and Porte, 2005). Conversely, administration of NPY effectively stimulates food intake via action at NPY-Y receptors in the brain (Clark et al., 1984; Yulyaningsih et al., 2011). Several studies have used opto- and chemogenetic techniques to attempt to manipulate the activity of varying genetically targeted populations of neurons with a role in feeding behavior and metabolism, including but not limited to AgRP neurons (Aponte et al., 2011; Atasoy et al., 2012; Krashes et al., 2011; Krashes et al., 2013) and Pomc neurons (Aponte et al., 2010; Zhan et al., 2013). Stimulation of arcuate Pomc neurons resulted in a reduction in food intake, whereas activation of arcuate AgRP neurons resulted in increased food intake and food-seeking behaviors (Aponte et al., 2010; Krashes et al., 2011; Zhan et al., 2013). The Pomc-induced reduction in food intake was

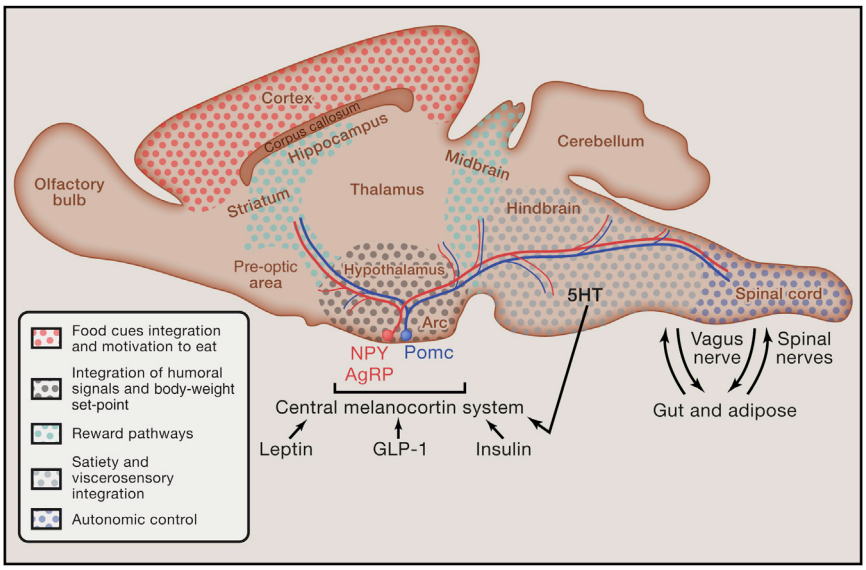

Figure 1. Integrated Model of the Central Melanocortin System and Connected Regions within the Nervous System Involved in Obesity and Diabetes

Recent discoveries highlight a circuitry within the brain that includes the hypothalamus as well as midbrain/hindbrain areas in the regulation of energy expenditure. This circuitry has also been demonstrated to have an overlapping role in the management of glucose homeostasis. Importantly, several neurotransmitters and peptides contribute to a distributed network of receptor systems within this circuit and provide potential substrates for non-surgical therapeutic intervention. Similarly, advancing technologies have raised potential surgical and non-surgical manipulation of cellular and nerve activity as a viable strategy in this circuit to combat obesity and diabetes. Abbreviations: NPY = neuropeptide Y; Pomc = pro-opiomelanocortin; AgRP = Agouti gene-related peptide; Arc = arcuate nucleus; GLP-1 = glucagon-like peptide 1.

dependent upon melanocortin receptors within the paraventricular hypothalamus (PVH), a hypothalamic nucleus that is a direct target of arcuate melanocortin neurons. Stimulation of arcuate AgRP neurons elicited feeding behavior via projections to the thalamus, the hypothalamus, and the basal forebrain (Atasoy et al., 2012). Interestingly, either the neurotransmitter GABA or NPY is required for the rapid stimulation of feeding, whereas the neuropeptide AgRP, through action on Mc4 receptors, is sufficient to induce feeding over a delayed yet prolonged period (Krashes et al., 2013). GABA from NPY/AgRP neurons of the hypothalamic arcuate nucleus may also play an important role in the regulation of feeding behaviors via direct actions within the hindbrain (Wu et al., 2009). Moreover, neurons of the nucleus of the solitary tract in the caudal medulla might counterbalance this activity (Wu et al., 2012). Neurons of the PVH also reciprocally innervate arcuate NPY/AgRP neurons, providing a regulatory loop in the control of feeding behavior (Krashes et al., 2014). Collectively, these data suggest that in addition to a core circuit, AgRP neuron projections and reciprocal innervations may reveal key modulatory circuit nodes that are gated or otherwise regulated by AgRP neuron projections (Atasoy et al., 2012). Importantly, it's currently unclear which circuits are acutely involved in other complex metabolic processes such as energy expenditure and glucose metabolism. Undoubtedly, similar parallel and redundant mechanisms involved in regulating feeding behavior will be intertwined with various aspects of metabolism.

Both NPY/AgRP and Pomc neurons are also sensitive to metabolic status (Cone, 2005; Yulyaningsih et al., 2011). In particular, NPY/AgRP neurons are activated during fasting, whereas Pomc neurons are activated following feeding and inhibited during fasting. NPY/AgRP and Pomc neurons are also well positioned to sense and integrate numerous nutrient and humoral signals (Schwartz and Porte, 2005). Indeed, many of these signals in the periphery and/or the central nervous system (CNS) have been attributed to regulating feeding behavior and energy expenditure via activity at these neurons (Figure 1). For example, increased serum levels of the adipocyte-derived anorexigenic peptide leptin activate Pomc neurons and stimulate the production as well as the release of α-MSH (Cone, 2005; Schwartz et al., 1997). Leptin inhibits NPY/AgRP neurons concomitantly suppressing the production and release of NPY and AgRP. These data and others support a primary role of arcuate Pomc and NPY/AgRP neurons as first-order neurons in the neural control of energy balance. However, it must be noted that leptin-sensitive neurons distributed across the brain may contribute to the control of feeding. For instance, loss of leptin receptors in either arcuate Pomc neurons or adjacent neurons of the ventromedial hypothalamus (VMH) results in modest increases in adiposity largely dependent upon deficits in energy expenditure (Myers and Olson, 2012). Moreover, deletion of leptin receptors in both Pomc and VMH neurons resulted in an additive effect on body weight. Among other examples, leptin receptors on GABAergic neurons of the lateral hypothalamic area (LHA) modulate the mesolimbic dopaminergic system and decrease feeding (Leinninger et al., 2009). Also, deficiency of leptin receptors in a brainstem site called the dorsal vagal complex causes hyperphagia, resulting in modest weight gain (Scott et al., 2011; Skibicka and Grill, 2009). Collectively, these data support a model of a distributed network of melanocortin- and leptin-responsive neurons contributing to the central regulation of energy homeostasis. Not surprisingly, numerous nutrient and humoral receptors are also widely distributed within the CNS, and researchers are identifying multiple divergent and redundant roles for these receptors in the regulation of metabolism.

The aforementioned evidence supports a well-defined action of the central melanocortin system in regulating food intake and body weight. However, it is less appreciated that the central melanocortin system plays an important role in regulating glucose metabolism, including insulin release and action (Farooqi and O'Rahilly, 2005; Schwartz and Porte, 2005). In fact, deficits in melanocortin signaling result in hyperinsulinemia,

fasting hyperglycemia, and frank diabetes (Berglund et al., 2014; Cone, 2005; Myers and Olson, 2012). However, restoring Mc4r expression selectively in the PVH reduces hyperphagia and largely restores deficits in body weight independent of improved glucose or insulin intolerance (Myers and Olson, 2012). In parallel, loss of Mc4rs in parasympathetic and sympathetic nuclei of the brainstem and spinal cord results in glucose and insulin intolerance largely independent of changes in food intake or bodyweight gain (Berglund et al., 2014; Myers and Olson, 2012). Thus, the wide distribution of melanocortin receptors concomitant with projection patterns of Pomc and NPY/AgRP neurons contributes to their divergent effects on energy and glucose homeostasis.

Several mutations in Mc4r have been identified and may represent the most common form of monogenic obesity in humans (Barsh et al., 2000; Farooqi and O'Rahilly, 2005). Importantly, the melanocortin system is remarkably conserved across species from zebrafish and rodents to humans (Farooqi and O'Rahilly, 2005; Sebag et al., 2013). Thus, neural circuits regulating metabolic homeostasis in the mammalian hypothalamus have an ancient origin, dating back to teleost fish. This long evolution may explain the complexity as well as some of the main anatomical and functional principles of these circuits governing energy homeostasis in the mammalian hypothalamus.

In Search of Effective Appetite Suppressants

Although dieting and balanced nutrition are key to the management of most, if not all, metabolic disorders, most dieters struggle to maintain a rigid dietary regimen. Why is dieting so difficult? There is certainly no single straightforward answer to this question; however, brain-imaging studies in humans have offered clues to neural correlates of obesity and responses to dieting. In particular, dieting in humans changes the activity of interconnected brain regions involved in the neural representations of hunger and satiety and the anticipation of reward (Rosenbaum et al., 2008). Neural activity induced by food cues also differs between obese and lean individuals in the prefrontal cortex (Zheng and Berthoud, 2008). Paradoxically, these regions are involved in the motivation to eat and are normally stimulated by dieting and starvation. Typically, the brains of obese individuals appear to react to food cues as if these individuals were in a state of negative energy balance (instead of energy repletion). Put another way, defective brain processing in response to food cues in obesity may result in inadequate reward and/or motivational processes and, ultimately, hyperphagia.

Driven by various biological and environmental factors, hyperphagia is largely responsible for the current epidemic of obesity and type 2 diabetes (T2DM). Thus, any successful weight-loss strategy must address the issue of appetite. Accordingly, many drugs approved by the US Food and Drug Administration (FDA) for the treatment of obesity directly act on the nervous system to suppress appetite (Table 1 and Figure 2) (Vetter et al., 2010). The only peripherally acting drug currently approved to treat obesity is Orlistat (trade name: Xenical or Alli), an inhibitor of lipase activity that prevents fatty-acid absorption from the diet (Bray, 2014). However, this drug commonly promotes loose stools and, due to its lack of effect on the brain, minimally reduces appetite. As the field continues to build an understanding of neural circuitry regulating appetite, it has become evident that a very large number of neural pathways and molecules are implicated in modulating appetite levels. Consequently, the neural circuits involved in metabolism offer numerous avenues for therapeutic intervention in the treatment of hyperphagia (Figure 2). Below we include a brief discussion on current appetite suppressants and promising pharmacotherapeutics, with a special emphasis on their potential mechanisms of action (Table 1 and Figure 2). Information on the clinical features and medical recommendations for the drugs presented below can be found elsewhere (Bray, 2014).

Overview of Current Anti-Obesity Drugs

Serotoninergic neurons play critical roles in the suppression of feeding (Heisler et al., 2003). Accordingly, treatments that suppress central serotoninergic signaling result in hyperphagia and weight gain in humans and rodents. Lorcaserin (trade name: Belviq), an agonist of the serotonin receptor 5-HT_{2C}R, reduces body weight largely dependent upon lowered food intake in both humans and rodents (Martin et al., 2011; Smith et al., 2010; Thomsen et al., 2008). Although 5-HT_{2C}Rs are widely expressed across the neuraxis (Julius et al., 1988), accumulating evidence in rodents indicates that 5-HT_{2C}R reduces appetite and body weight by acting on Pomc neurons (Xu et al., 2008, 2010b). Notably, Lorcaserin is currently the only FDA-approved drug monotherapy for obesity that specifically targets the brain. However, clinical trials indicate that Lorcaserin yields weight losses of 5%–10% of initial body weight after 1 year (Smith et al., 2010) and is not marketed in Europe.

The naturally occurring peptide glucagon-like peptide 1 (GLP-1) induces multiple desirable anti-diabetic and anti-obesity actions, and protease-resistant long-acting GLP-1 analogs are currently available for the treatment of T2DM (Drucker, 2006). Initial interest in the beneficial effects of GLP-1 on body weight stemmed from the observation that GLP-1 inhibits food intake (Turton et al., 1996). Both Exenatide (trade name: Byetta or Bydureon—a synthetically derived exendin-4) and Liraglutide (trade name: Victoza—a fatty acid-modified GLP-1) are long-acting GLP-1 analogs that effectively lower blood glucose in diabetic patients and are approved by the FDA (see Table 1) to treat T2DM (Juhl et al., 2002; Madsbad et al., 2004). Recent evidence further suggests that both Exenatide and Liraglutide cross the blood-brain barrier (Drucker, 2006; Hunter and Hölscher, 2012) and specifically act at the level of the hypothalamus to reduce appetite (Drucker, 2006; Secher et al., 2014; Sisley et al., 2014). Importantly, the FDA recently approved Liraglutide for the treatment of chronic weight management. In particular, Liraglutide results in sustained weigh loss of 5%–10% of initial body weight in obese patients (Astrup et al., 2009), which can be attributed to both reduced appetite (concomitant with inhibition of gastric emptying) and elevated energy expenditure in T2DM individuals (Horowitz et al., 2012). While Liraglutide is a well-tolerated drug, its long-term side effects are not well known, and some concern has been raised due to a possible risk of pancreatic cancer associated with GLP-1 agonist treatment (Cohen, 2013). Moreover, GLP-1 receptor agonists increase heart rate and blood pressure in rats by stimulating the sympathetic outflow to the cardiovascular system (Yamamoto et al., 2002).

Table 1. Select List of Current and Potential Future Therapeutics for the Treatment of Obesity and Diabetes

Pharmacology

Drug/Compound	Trade/Brand Name	Receptors/Molecular Pathways	FDA Approval	Applications(s)	Brain Area and/or Tissues Involved
Lorcaserin	Belviq	5ht2cr agonist	yes—2012	obesity	hypothalamus, cortex, midbrain, and brainstem
Liraglutide	Victoza	GLP-1r agonist	yes—2012	obesity and diabetes	hypothalamus
Topiramate/ Phentermine	Qysemia	inhibit several ionic conductances as well as carbonic anhydrase isozymes/stimulate the release of serotonin-norepinephrine-dopamine	yes—2012	obesity	hypothalamus and brainstem
Buproprion/ Naltrexone	Contrave	dopamine and norepinephrine reuptake inhibitor/opioid receptor antagonist	yes—2014	obesity	hypothalamus
D-fenfluramine	Pondimin, Ponderax, Adifax	5ht2cr agonist	withdrawn	obesity	hypothalamus and brainstem
Orlistat	Xenical and Alli	inhibit gastric and pancreatic lipases	yes—1999	obesity	gut
Sibutramine	Meridia	serotonin-norepinephrine-dopamine reuptake inhibitor	withdrawn	obesity	hypothalamus and brainstem
Ribonamant	Zimulti	CB1R antagonist	withdrawn	obesity	hypothalamus and brainstem
Mc4R agonists	N/A	Mc4R	no	obesity	hypothalamus and brainstem
Exenatide	Byetta, Bydureon	GLP-1r agonist	yes —2005	T2DM	hypothalamus
Metformin	Glucophage, Glumetza, Glucophage XR, Fortamet	suppress gluconeogenesis pathways	yes—1995	T2DM	liver
Pramlintide	Symlin	amylin receptor agonist	yes—2005	T2DM	hypothalamus and brainstem
Leptin	Metreleptin	LepRB agonist	no[b]	type 1 and 2 diabetes	hypothalamus

Device-Assisted

Device	Receptors/Molecular Pathways	FDA Approval	Application(s)	Brain Area and/or Tissues Involved
hfDBS	neuronal excitability	no[a]	obesity	hypothalamus
tDCs	neuronal excitability	no[a]	obesity	cortex
VNS	neuronal excitability	no[a]	obesity	cervical vagus nerve
VBLOC	neuronal excitability	yes—2015	obesity	gastric vagus nerve
Lap-band—laparoscopic adjustable gastric band	unknown	yes—2001	obesity	gut-brain communication
Roux-en-Y gastric bypass	unknown	N/A	obesity and T2DM	gut-brain communication
Vertical sleeve gastrectomy	unknown	N/A	obesity and T2DM	gut-brain communication

[a]Approved for indications not related to metabolic outcomes.
[b]Approved for the metabolic disorders of lipodystrophies.

Current monotherapeutic approaches in the treatment of obesity and diabetes have not been optimally effective. Emerging strategies include combination drug therapy targeting multiple signaling mechanisms. Combination therapies have been more efficacious than the aforementioned monotherapies, presumably due to the additive and synergic effects previously observed by the drugs separately. There are two combination drug therapies currently marketed in the treatment of obesity, Phentermine/Topiramate (trade name: Qysemia) and Bupropion/Naltrexone (trade name: Contrave). All four compounds have been previously approved on an individual basis by the FDA in the treatment of various neurological disorders. Phentermine and Bupropion are well-known stimulators of serotonin and norepinephrine release from nerve endings. The enhanced release of norepinephrine in sympathetically innervated tissues is likely to increase metabolism (Nedergaard and Cannon, 2014). Moreover, at high doses, these two drugs effectively reduce food intake and body weight in laboratory rodents (Roth et al., 2008; Wright and Rodgers, 2013). Topiramate is an anti-convulsant anecdotally reported to induce weight loss

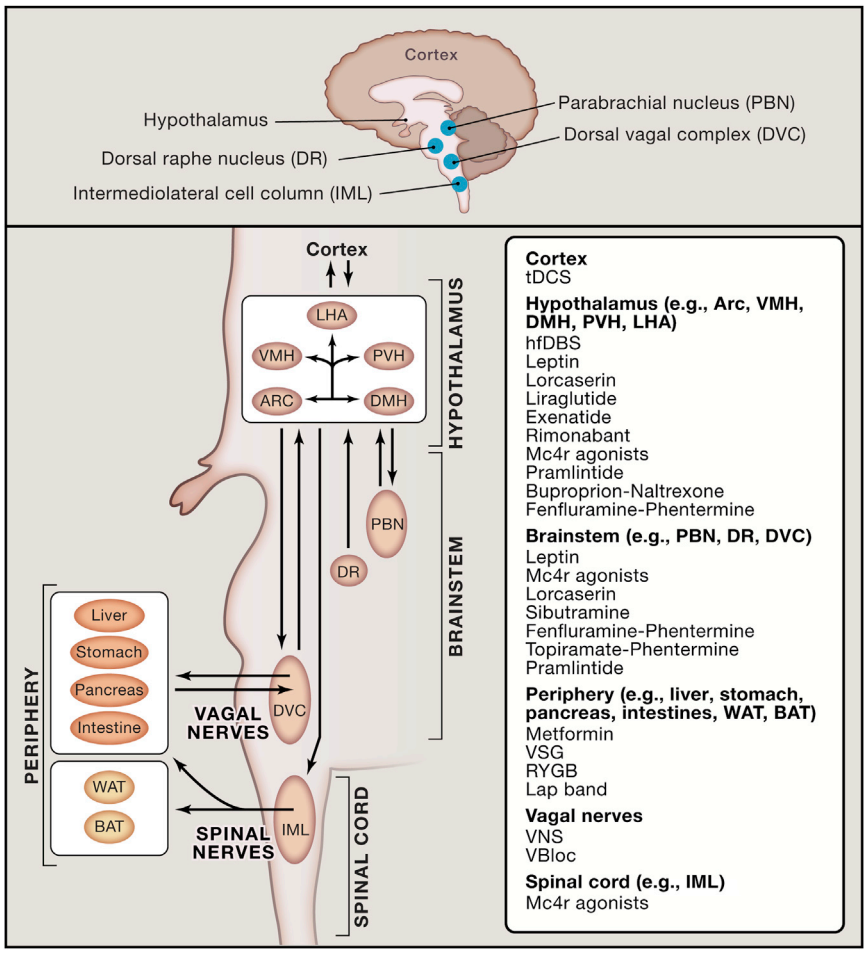

Figure 2. Selected Therapeutic Options for Treating Obesity and Diabetes by Targeting the Brain

Current and promising therapeutics in the treatment of both obesity and diabetes have targeted neural connections including the melanocortin system, via pharmacological and/or device-assisted methods. Here we summarize a select number of targets (i.e., receptors and brain regions) that have been demonstrated to regulate at least in part effects of energy balance and glucose homeostasis.

Abbreviations: hfDBS = high-frequency deep brain stimulation; VBLOC = vagal blocking; VNS = vagal nerve stimulation; Mc4r = melanocortin 4 receptor; DVC = dorsal vagal complex; PBN = parabrachial nucleus; tDCS = transcranial direct current stimulation; Arc = arcuate nucleus; VMH = ventromedial hypothalamic nucleus; LHA = lateral hypothalamic area; DMH = dorsal medial hypothalamic nucleus; PVH = paraventricular hypothalamus; DVC = dorsal vagal complex; IML = intermediolateral cell column; BAT = brown adipose tissue; WAT = white adipose tissue; DR = dorsal raphe nucleus.

(Astrup et al., 2004). Naltrexone is an antagonist of opioid receptors with little effect on food intake when administered alone (Greenway et al., 2009). Although Naltrexone may act by increasing the firing rates of Pomc neurons (Greenway et al., 2009), the exact mechanisms of action of Naltrexone and Topiramate on energy balance are unclear. Importantly, the FDA has recently approved the drug combinations Contrave and Qysemia as an adjunct for chronic weight management (Table 1) with both medications promoting weight losses of 8% to 10% of initial body weight (Allison et al., 2012; Garvey et al., 2012; Greenway et al., 2009). Interestingly, another combination medication called Empatic (trade name) that contains both Bupropion and Zonisamide (another anti-convulsant) is currently under phase 2 clinical trial (Jackson et al., 2014). Thus, with the recent FDA approval and/or promising clinical trial results, combination therapies show promise for therapeutic efficacy in the treatment of obesity.

Novel Paradigms in Anti-Obesity Pharmacotherapy

Although many compounds acting on neural pathways controlling appetite, glucose metabolism, and energy expenditure were found to induce marked body-weight loss in animal models and human clinical trials, leading to FDA approval, many of these pharmacotherapies were subsequently abandoned due to serious safety concerns (Bray, 2009) (Table 1). This was the case for D-fenfluramine (D-fen; trade name: Pondimin, Ponderax, or Adifax), a pharmacological agent that increases serotonin content by stimulating synaptic release of serotonin and blocking its reuptake into presynaptic terminals (Connolly et al., 1997). Although D-fen showed potent anorexigenic activity in humans (McGuirk et al., 1991), it was removed from the market in 1997 due to its link to the development of cardiovascular complications (Connolly et al., 1997). Other centrally acting drugs have succumbed to a similar fate, including Rimonabant (trade name: Zimulti), an antagonist of the type I cannabinoid receptor Cb1R. Rimonabant's anti-obesity actions have been attributed to altered excitability of Cb1Rs located in key hypothalamic, striatal, and brainstem neurons (Cota et al., 2006). Although Rimonabant was highly effective in reducing food intake and body weight, its development was halted in 2009 due to its serious gastrointestinal and adverse psychiatric effects. Although combinatorial approaches have already raised hope for safer ways of treating obese patients, even currently FDA-approved drugs are not without safety concerns. Another caveat of currently available drugs is their modest efficacy when compared to bariatric surgery (Colquitt et al., 2014). The issues discussed above have stimulated research aimed at identifying new classes of centrally acting appetite suppressants, some of which are presented below.

Mc4 receptors have been considered prime targets in the search for effective therapeutics managing obesity (Van der Ploeg et al., 2006; Wikberg and Mutulis, 2008). In fact, several Mc4 receptor agonists were reported to produce significant reduction in adiposity in humans and monkeys (Fehm et al.,

2001; Kievit et al., 2013; Wellhöner et al., 2012). However, Mc4 receptor agonists have not progressed to the clinic due to potential side effects, in particular those affecting the autonomic nervous system. For example, Mc4 receptor agonists such as melanotan II may result in hypertension and priapism (Greenfield et al., 2009; Van der Ploeg et al., 2002). These undesirable effects are likely caused by the stimulation of preganglionic autonomic neurons expressing Mc4 receptors (Sohn et al., 2013). However, all Mc4 receptor agonists may not similarly alter autonomic function. A small peptide, RM-493, has been demonstrated to effectively induce weight loss in non-human primates and humans with no major impact on cardiovascular function (Kievit et al., 2013). This agent is currently in clinical trials for genetic obesity. Interestingly, Mc4 receptors may also be modulated by the melanocortin receptor accessory proteins (Mrap1 and Mrap2) (Asai et al., 2013; Sebag et al., 2013). These Mraps may provide a substrate to differentially target the beneficial effects of Mc4 receptor activity on energy expenditure, glucose utilization, and other metabolic parameters while minimizing the adverse side effects. Recent work has also highlighted a potential role for the melanocortin system to regulate brown adipose tissue thermogenesis as well as the browning/beiging of white adipose tissues (Berglund et al., 2014; Dodd et al., 2015; Nedergaard and Cannon, 2014; Ruan et al., 2014; Williams et al., 2014). It's currently unclear what contribution this thermogenesis may play in the regulation of body composition and glucose homeostasis; however, these data may aid in the development of Mc4 receptor agonists to combat obesity and diabetes.

Recent efforts have also focused on exploring new ways of potentiating the efficacy of currently available appetite suppressants, including, most notably, leptin. Shortly after its discovery (Zhang et al., 1994), leptin was shown to completely reverse the hyperphagic and obese phenotype of leptin-deficient animals and humans (Farooqi and O'Rahilly, 2005; Licinio et al., 2004; Pelleymounter et al., 1995). Unfortunately, obesity is characterized by hyperleptinemia (Considine and Caro, 1996), rather than leptin deficiency. Thus, to the vast majority of morbidly obese individuals, leptin monotherapy is ineffective in lowering food intake or body weight. However, since the normal fall of leptin that accompanies weight loss is detected by the brain as a starvation signal (Ahima and Flier, 2000), it has been proposed that leptin administration during the course of dieting may amplify weight loss and reinforce compliance (Rosenbaum et al., 2008).

Several gut peptides have been demonstrated to potently enhance or restore leptin sensitivity in diet-induced obesity. Most notably, amylin, a pancreatic-derived small peptide, has been shown to successfully enhance the effects of leptin administration on energy balance in obese rodents as well as in humans (Ravussin et al., 2009; Trevaskis et al., 2008). In addition, recent advances in the synthesis of peptides with co-agonistic properties have permitted the development of a new generation of anti-obesity molecules. This includes a GLP-1::glucagon unimolecular co-agonist (Day et al., 2009). This molecule was shown to effectively reduce body weight in obese animals to almost 30% of initial body weight in only 1 month. Leptin-induced body-weight loss has also been shown to be considerably potentiated by the GLP-1::glucagon co-agonist (Clemmensen et al., 2014). The chronic co-administration of leptin and GLP-1::glucagon yielded an impressive 50% weight loss in obese mice over 1 month and normalized glucose intolerance.

Another promising co-agonistic (dual peptide) strategy consists of delivering peptide agonists with an attached (linker) small molecule. This strategy allows for the selective delivery of a complex molecule to particular target cells (Finan et al., 2012). In the first usage of this strategy, researchers capitalized on the mono-agonistic properties of GLP-1 and the sex steroid hormone, estrogen, to improve metabolic parameters of obesity and T2DM. A fully active GLP-1 agonist stably linked to estrogen consistently proved to be more efficacious in lowering body weight than either molecule alone. Additionally, these effects of the GLP-1::estrogen conjugates were independent of adverse gynecological and oncogenic outcomes. This strategy appears to uniquely combine potency with specificity; however, the molecular mechanism of these beneficial effects remains to be elucidated. Importantly, these co-agonist data suggest that the maximally achievable and sustainable body-weight loss of 10%, observed with currently available pharmaceutics, may not reflect an insurmountable physiological barrier (Day et al., 2009). Hence, co-agonistic pharmacotherapy as well as varied leptin sensitizers and new classes of chemical compounds hold promise as an efficacious approach in the management of obesity.

Finally, it must be noted that novel centrally acting molecules regulating metabolism are regularly being discovered. Among other examples, FGF21 was recently described as a potent anti-obesity factor predominately affecting energy expenditure (Bookout et al., 2013; Owen et al., 2014; Sarruf et al., 2010) and, in humans, exhibiting a marked lipid-lowering effect (Gaich et al., 2013). Based on genetic studies in rodents, the anti-obesity actions of FGF21 have been attributed to its direct action on the nervous system (Bookout et al., 2013; Owen et al., 2014; Sarruf et al., 2010). However, concurrent data indicate that the adipose tissue, rather than the nervous system, is required for FGF21 anti-obesity actions (Adams and Kharitonenkov, 2012). The regulation of glucose metabolism by FGF21 has also been attributed to direct actions on the liver (Adams and Kharitonenkov, 2012). Further work should paint a fuller picture of FGF21's activities, and overall, the field is hopeful that existing and/or novel ligands currently under development will be efficacious in the treatment of obesity.

Device-Assisted Neuromodulatory Techniques

Device-assisted neuromodulation refers to delivery of an electrical current to either a specific nerve or a particular brain region in order to influence brain activity and autonomic outflow. Devices include but are not limited to stimulators of the spinal cord, vagus nerve, and sacral nerve; deep brain stimulators; and gastric electric stimulators. Although many of these devices have not been approved by the FDA for the treatment of metabolic disorders, accumulating evidence suggests that modulation of targeted brain sites or peripheral nerve activity by device-assisted means is a valuable tool in the treatment of many chronic diseases (Famm et al., 2013).

The idea of being able to target a particular brain site is attractive, considering the unwanted effects of many pharmacological

compounds. Furthermore, peripheral nerves are increasingly recognized to play a critical role in metabolic functions (Bartness et al., 2014; Powley et al., 2005). The vagus nerve is a mixed (sensory and motor) nerve that innervates most of the thoracic and the abdominal viscera, including the entire gastrointestinal tract, pancreas, and liver (Berthoud and Neuhuber, 2000). It is well established that vagal sensory neurons convey a wide variety of signals originating from the gastrointestinal tract, including mechanical stretch, changing levels of nutrients, lipids, immune signals, and gut peptides (de Lartigue et al., 2011). Experimental observations also indicate the reduced ability of vagal afferents to respond to dietary and endogenous metabolic signals in animals fed on high-fat diets (Kentish et al., 2012). These observations strongly support the idea that the vagus nerve serves as a critical link between the gut and the brain and that this link is impaired in obesity. Based on the aforementioned literature linking vagal afferents to post-prandial functions and the regulation of feeding, stimulation of vagal afferents has been hypothesized to be a promising anti-obesity approach and a potential alternative to bariatric surgery (Powley et al., 2005). Pre-clinical studies in large animals and humans suggest that vagus nerve stimulation (VNS) might show efficacy in reducing food craving and weight gain (Pardo et al., 2007; Val-Laillet et al., 2010). A technique of vagal blocking has also been tested in pre-clinical studies (VBLOC) and recently approved by the FDA as a weight-loss treatment device in obese individuals. Briefly, this technique targets the nerve pathway between the brain and the stomach by stimulating the vagal trunks at high frequency, thus interfering with normal gastric functions and leading to early satiation (Camilleri et al., 2008). However, contradictory results have been obtained as to the benefits of this novel weight-loss approach in obese subjects, with a couple of studies suggesting a significant weight loss and reduced food craving (Camilleri et al., 2008; Shikora et al., 2013), and others finding no significant benefits (Ikramuddin et al., 2014; Sarr et al., 2012).

Central neurostimulatory techniques may also be of interest in the treatment of obesity. In particular, high-frequency deep brain stimulation (hfDBS, Table 1) has been effective at treating the symptoms associated with Parkinson's disease and other disabling neurological disorders by normalizing pathological patterns of neuronal activity (Wichmann and Delong, 2006). This technique involves the chronic implantation by stereotaxic surgery of stimulation electrodes in a targeted brain site. Electric current is delivered to electrodes connected to a pulse generator similar to a pace maker. Stimulation of the hypothalamus in humans is feasible and has been recently used in morbidly obese humans to target the LHA (Whiting et al., 2013). Stimulation of the LHA succeeded in increasing resting metabolic rate, leading to reduced binge-eating scores and/or body weight in all three test subjects. Similar results were obtained in a rat model, supporting the idea that this technique could be considered as an option for the treatment of obesity (Soto-Montenegro et al., 2014).

It should be noted that brain surgery is associated with inherent risks of hemorrhage, infection, and post-surgical complication. Less invasive strategies that target the activity of subpopulations of neurons may pose fewer concerns. In particular, transcranial direct current stimulation (tDCS) is emerging as a promising technique for non-invasive neuromodulation in a variety of clinical conditions (Dayan et al., 2013). This approach allows for the modification of neuronal excitability in regions involved in specific behaviors by delivering a weak current through the scalp (Dayan et al., 2013). Thus, tDCS is suited for cortical targets, specifically lateral and dorsomedial sectors of the prefrontal cortex that contribute to cognitive control. Importantly, this technique has shown promise for acutely reducing food craving (Fregni et al., 2008; Montenegro et al., 2012) and may be suitable for obese individuals (Boggio et al., 2009; Truong et al., 2013). Although the field embraces these novel methodologies, others are still needed in order to facilitate therapeutic opportunities in the treatment of various neurological pathologies, including those contributing to obesity.

Treating Diabetes by Targeting the Brain

Many of the currently available drugs to treat T2DM are peripherally acting compounds (Table 1). This includes molecules acting on glucose co-transporters, incretin (gastrointestinal hormone that stimulates a decrease in blood glucose levels) degradation enzymes, nuclear receptor signaling, and bile acid metabolism. The most widely prescribed anti-diabetic drug in the world is Metformin (Glucophage, Glumetza, Glucophage XR, or Fortamet), a suppressant of hepatic glucose production with few severe side effects (Garber et al., 1997). Likely due to their minimal effect on the brain, these peripherally acting agents marginally affect appetite. Overall, the popularity of each of these drugs in the medical community is largely determined by their benefit-risk profile.

Importantly, Claude Bernard's idea that mechanisms behind diabetes may have an origin in the CNS has been largely validated by modern physiological approaches (Obici and Rossetti, 2003; Pocai et al., 2005; Seeley and Tschöp, 2006). Over the past two decades, it has become apparent that many of the currently available anti-diabetic drugs also act directly in the CNS (Table 1 and Figure 2). For instance, Liraglutide and Exenatide are known to act both in the periphery and at the level of the brain (Mul et al., 2013; Sisley et al., 2014). However, one recent study demonstrates that the glucose-lowering effects of Liraglutide are independent of GLP-1 receptor signaling in the brain (Sisley et al., 2014). Instead, the GLP-1 anti-diabetic actions in the periphery have been well studied, as the naturally occurring pancreatic-derived peptide GLP-1 was initially described as an incretin-like peptide that controls blood glucose (Drucker, 2001).

Central 5-HT_{2C} receptor agonism is involved in glycemic control (Berglund et al., 2013; Nonogaki et al., 1998; Xu et al., 2010a), actions that are independent of its effects on food intake and body weight. In particular, deletion of the 5-HT_{2C}R in in mice deficient for the peptide leptin leads to synergistic impairment of glucose balance, independent of additional obesity compared to ob/ob mice (Wade et al., 2008). Furthermore, 5-HT_{2C}R signaling in the hypothalamus has also been linked to glucose metabolism (Xu et al., 2010a). It is therefore conceivable that the reported beneficial effect of Lorcaserin on T2DM (O'Neil et al., 2012) may be linked to its central actions in neurons regulating glycemia.

It is now clear that the anti-diabetic and anti-obesity actions of Mc4 receptors are independent and mediated by distinct neural

substrates. For example, humans deficient for Mc4 receptors are hyperinsulinemic, more so than would be expected from their degree of obesity alone (Farooqi and O'Rahilly, 2005). Recent genetic studies in the mouse have elegantly demonstrated that restoration of Mc4 receptors in brainstem cholinergic neurons normalizes hyperinsulinemia in an Mc4 receptor-deficient background (Myers and Olson, 2012). Conversely, the selective deletion of Mc4 receptors in the cholinergic neurons alone is sufficient to raise insulin levels (Sohn et al., 2013). However, the deletion of Mc4 receptors in both sympathetic and parasympathetic neurons is required in order to lead to hyperglycemia and insulin resistance (Berglund et al., 2014). Hence, Mc4 receptor agonism in the nervous system would appear as a promising anti-diabetic approach if these beneficial effects can be isolated from the aforementioned adverse side effects.

New experimental data indicate that targeting the brain is highly relevant to the treatment of type I diabetes (T1D). Leptin has recently been shown to normalize glucose levels in rodents with T1D, an effect that might be dependent upon leptin receptor signaling in Pomc neurons and the regulation of the hypothalamic-pituitary-adrenal (HPA) axis (Fujikawa et al., 2013; Perry et al., 2014). Surprisingly, leptin appears sufficient to prevent death and restore normoglycemia, even in the absence of insulin therapy (Fujikawa et al., 2013). Leptin has also been shown to be useful for the treatment of other metabolic disorders characterized by hypoleptinemia, which can be the result of congenital or acquired lypodystrophies involving selective loss of fat and, in some cases, severe insulin resistance, dyslipidaemia, hepatic steatosis, and diabetes (Javor et al., 2005; Oral et al., 2002; Petersen et al., 2002). The FDA has approved MYALEPT Metreleptin (trade name: MYALEPT), a synthetically derived analog of leptin, for the treatment of lipodystrophy-related metabolic disorders. Leptin monotherapy in mice (Gavrilova et al., 2000; Shimomura et al., 1999) and in patients suffering from generalized lipodystrophy results in improvements of several metabolic parameters, including lowering of triglyceride and glucose levels as well as hepatic steatosis (Javor et al., 2005; Oral et al., 2002; Petersen et al., 2002). Moreover, after just a few months of leptin therapy, many lipodystrophic patients no longer require pharmacotherapy (e.g., insulin) to regulate glucose levels.

As previously outlined, amylin is an endogenous peptide directly acting on the nervous system and able to potentiate leptin sensitivity (Ravussin et al., 2009). An amylin analog (pramlintide) is approved for T1D and T2DM in combination with insulin under the trade name Symilin (Herrmann et al., 2014). Whereas the mechanism of action of pramlintide on glucose regulation is not well documented, the involvement of the brain in its anti-diabetic actions cannot be ruled out.

At first glance, given the efficacy and large choice of currently available anti-diabetic drugs acting in the periphery, the necessity for developing centrally acting anti-diabetic compounds is not immediately clear. However, it is also evident that centrally acting agents can effectively alleviate diabetes. This may become useful when peripherally acting agents are not well tolerated in certain T2DM patients and also in subjects with poorly controlled T1D. Furthermore, centrally acting agents commonly show a broader spectrum of actions on varied metabolic functions. In particular, the ability of many central agents to simultaneously affect energy expenditure, appetite, cardiovascular function, and glucose metabolism makes them particularly relevant for the treatment of the metabolic syndrome. In summary, the brain should be (re)-considered as a prime target in designing therapeutics for diabetes, especially in individuals with multiple comorbidities.

Is the Brain Involved in the Metabolic Outcomes of Bariatric Surgery?

A number of different approaches to bariatric surgery, also known as gastric bypass, have been described (for review, see Lutz and Bueter, 2014; Stefater et al., 2012). Roux-en-Y gastric bypass is the most efficacious and frequently performed weight-loss surgery (Buchwald, 2014; Lo Menzo et al., 2014; Schauer et al., 2003). However, the use of sleeve gastrectomy has been gaining in popularity in recent years since the approval of laparoscopic sleeve gastrectomy in 2005. Patients eligible for either sleeve gastrectomy or Roux-en-Y gastric bypass can reasonably expect a near normalization of their body mass index and reversal of most co-morbidities within 2 years. Despite their remarkable efficacy, these surgeries remain costly procedures associated with many complications. Perhaps weight-loss surgeries could be simplified and their complications avoided if the biological mechanisms underlying their effects were understood. Thus, many investigators acknowledge that identifying the mechanisms underlying the beneficial effects of gastric bypass is an important challenge. There is now ample evidence that neither the mere physical restriction of the stomach nor nutrient malabsorption is sufficient to explain weight loss and glucose-metabolism improvement after bariatric surgery (Lutz and Bueter, 2014; Stefater et al., 2012). At the physiological level, a combination of modified parameters, including reduced appetite, modified food preference, and augmented energy expenditure, may collectively mediate weight loss after bariatric surgery. At the cellular level, numerous non-exclusive factors have been implicated in the benefits of bariatric surgery, including, but not limited to, elevated levels of gut peptides and bile acids secretion, enhanced intestinal growth, and changes in the microbiome composition (Lutz and Bueter, 2014). At the molecular level, farsenoid-X receptor (FXR), a nuclear receptor for bile acids, has been recently demonstrated to play a key role in mediating weigh loss after Roux-en-Y gastric bypass (Ryan et al., 2014). Interestingly, a recent study further demonstrated that intestinal FXR agonism is sufficient to attenuate diet-induced obesity and insulin resistance in the mouse (Fang et al., 2015).

The role played by the brain in mediating the benefits of bariatric surgery remains open to discussion. At the phenomenological level, the absence of compensatory hunger after bariatric surgery in the face of considerable weight loss suggests major adaptations in hunger pathways and the neural circuits involved in the regulation of body-weight set-point. Whereas the nature of these changes remains unknown, numerous experimental and clinical observations indicate that profound adaptations occur in the gut-to-brain axis after bariatric surgery: (1) Gastric bypass surgery significantly improves post-prandial functions (Borg et al., 2006; Thirlby et al., 2006), suggesting a modified functioning of the gut-brain axis. (2) Augmented c-Fos expression in the brainstem in response to gavage administration of lipid

emulsion (trade name: Intralipid) further supports the view that vagal sensory neurons may behave differently after sleeve gastrectomy (Chambers et al., 2012). (3) Following Roux-en-Y gastric bypass and sleeve gastrectomy, animals eat more frequent meals of smaller size (Stefater et al., 2010; Zheng et al., 2009); a similar phenomenon has been described in humans after Roux-en-Y gastric bypass (Laurenius et al., 2012). (4) Roux-en-Y gastric bypass in rats reduces the excitability of vagal efferents (Browning et al., 2013). Furthermore, Mc4 receptor signaling in mouse vagal efferents is required for diabetes reversal after Roux-en-Y gastric bypass (Zechner et al., 2013). (5) Destroying sensory afferents using capsaicin largely prevents the anti-diabetic actions of entero-gastro anastomosis in rats (Troy et al., 2008). (6) Indirect evidence also suggests that the activity of high-order brain sites may be modified after bariatric surgery. For instance, altered food preference (Shin et al., 2013; Wilson-Pérez et al., 2013) and increase in the risk of alcoholism after gastric bypass in humans (Ostlund et al., 2013; Suzuki et al., 2012) strongly suggest modified reward functions. Brain-imaging studies have also revealed altered dopamine receptor 2 availability after Roux-en-Y gastric bypass (Steele et al., 2010). (7) One study reported a reduced hypothalamic activity in response to food cues after gastric banding (Bruce et al., 2012). According to another study (Stefater et al., 2010), sleeve gastrectomy in the rat does not impact the expression levels of hypothalamic neuropeptides. Further research is needed to determine to what extent the vagal and brain changes discussed above may, at least in part, be causally implicated in the benefits of bariatric surgery.

Looking ahead to Unconventional Brain Therapies in Metabolism

In 1974, the stereotaxic destruction of the lateral hypothalamus was attempted in obese humans. It had been firmly anticipated that this procedure would lead to reduced appetite and weight loss, based on the previously described anorectic phenotype after lateral hypothalamus lesions in the rat. Unfortunately, the obese individuals enrolled in this trial did not respond to the procedure. Important ethical and technical constraints have limited progress in this area, and to the best of our knowledge, similar invasive neurosurgical interventions have not been attempted since. Nonetheless, the concept of altering the integrity of select brain circuits to cure obesity still garners support in the scientific community, and at least two major technical avenues for therapeutic intervention are currently being explored.

One involves cell transplantation technologies. For instance, the transplant of leptin-sensitive neurons into the hypothalamus of leptin receptor-deficient mice resulted in a diminished obesity phenotype (Czupryn et al., 2011). The other involves chemo- and optogenetics in which experimenters selectively silence or activate subtypes of neurons and their connections (Lichtman et al., 2008; Deisseroth, 2012; Urban and Roth, 2015). Unfortunately, there is no currently available experimental evidence to suggest that sustained weight loss and/or T2DM reversal could be achieved using this kind of approach, and it remains unclear whether opto- and chemogenetic techniques in their current iterations will be a viable therapeutic in the treatment of various diseases in humans. However, the following observations offer clues that the application of these technologies to the human brain may be feasible in the near future: (1) Virally mediated gene delivery has been attempted on many occasions in the non-human primate brain and at least once in the human brain. (2) Clozapine-N-oxide, an exogenous ligand commonly used in chemogenetic experiments, has been safely administered to humans. (3) The applicability of optogenetics to the non-human primate brain has been validated. Certainly, for both transplantation and acute manipulation of selectively labeled neurons, ethical and safety concerns will be an important consideration for clinical application.

Conclusions

In order for currently available drug therapies and weight-loss surgeries to be maximally effective in severely obese subjects, a careful nutritional management and monitoring of dietary habits is required. A major goal of current obesity research is to identify pharmacological compounds that would mimic the effect of bariatric surgery without the inherent complexity and potential risks of the surgery. New drugs are continuously in development, but to date, none have reached the efficacy and spectrum of action of bariatric surgery. It is admittedly disappointing that the tremendous progress in our understanding of the neural pathways regulating metabolism has not yet resulted in more clinically relevant progress and clearly not a cure for obesity or T2DM. Nonetheless, the burgeoning field of combinatorial pharmacology, device-assisted neuromodulation medicine, and chemo- and optogenetics holds promise for more effective and safer anti-obesity and anti-diabetic therapies. In parallel, it is necessary to treat the symptoms and complications of obesity with appropriate pharmacological and surgical means. The field should also address the biology underlying human preferences for hypercaloric food, especially given the constant or growing availability of these foods throughout the world. Undoubtedly, an increased understanding of the brain pathways regulating energy balance and glucose homeostasis will provide insights that will facilitate the development of multi-faceted approaches to combat both obesity and diabetes.

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