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Circuits Controlling Energy Balance and Mood: Inherently Intertwined or Just Complicated Intersections?

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Abstract

Recent reports of adverse psychiatric events from seemingly different types of weight loss therapies highlight a previously under-estimated overlap between CNS circuits that control energy balance and those that regulate mood. In this Perspective, we discuss a few potential brain sites where the homeostatic and the hedonic pathways may intersect and suggest that a better understanding of both pathways is necessary for the development of more effective and safe anti-obesity therapies.

Keywords

Weight-loss drugs; psychiatric side effects; bariatric surgeries; atypical antipsychotics; food intake; neural circuits; homeostatic; hedonic

Introduction

The rates of obesity are rising worldwide and have become a major public health problem (Must et al., 1999). Obesity is usually the result of excessive caloric intake coupled with a lack of physical activity. While life style changes such as dieting and physical exercises may provide non-pharmacological and non-surgical means towards body weight reduction, their long-term success is rather limited. As a result, development of effective medical interventions remains a goal for sustained body weight management.

The past few decades have witnessed several attempts to develop pharmaceutical weight-loss agents. A majority of these agents targeted appetite, and several were effective in reducing excessive food intake in overweight or obese patients. Unfortunately, many drugs and candidate drugs were either withdrawn from the market or rejected after preclinical

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studies. Indeed, it was not until last year that Qsymia™ (a combination of phentermine and topiramate) and Belviq™ (Lorcaserin, a selective 5-HTR_{2C} receptor agonist) became the first two FDA-approved anorectics for anti-obesity treatment after a span of nearly fifteen years. Prominent among previously failed attempts were serotonergic agents such as d-fenfluramine, a key component of the once popular diet-pill Fen-phen (Rowland and Carlton, 1986). However, this category of drugs was subsequently removed from the U.S. market after reports of adverse cardiopulmonary events due to their actions on the cardiac valves (Connolly et al., 1997). To circumvent this problem, newer classes of appetite suppressants, such as Rimonabant and Taranabant were developed with fewer cardiovascular side effects. Both compounds block the endocannabinoid system and promote sustained weight loss as well as favorable changes in cardiometabolic risk factors (Despres et al., 2005). However, new issues emerged with the use this class of drugs. In particular, an unexpected higher incidence of psychiatric problems such as depression and anxiety were noted in overweight or obese patients taking Rimonabant (Teff and Kim, 2011). Coincidentally, several recent studies found an over-representation of compulsive behaviors and even suicidality in patients following bariatric surgery (Peterhansel et al., 2013), which is currently the most effective and widely popular anti-obesity therapy.

The potential adverse psychiatric events from seemingly different types of weight loss therapies may not be mere coincidence, but more likely points to an under-appreciated area of biology. A connection between dieting and untoward psychiatric responses has been noted since 1950s (Hamburger, 1951; Stunkard and Rush, 1974). However, the underlying causes remained elusive. However, recent advances in our understanding of the neural circuitry of body weight regulation is starting to shed light on this issue. One interpretation of these reports is that approaches that induce weight loss not only target homoeostatic pathways that control energy balance, but also influence brain circuits that are involved in reward and emotional processing. The unexpected psychiatric effects, together with recent findings that commonly used atypical antipsychotic drugs (AAPDs) cause significant increase in food intake and weight gain in humans (McCloughen and Foster, 2011), reveal previously under-estimated levels of overlap between neurocircuits that regulate energy homeostasis and those that regulate emotional behaviors. That these systems are so intertwined poses a critical challenge towards the development of safe and effective anti-obesity therapies. In this Perspective, we will briefly review recent reports regarding the brain pathways regulating energy balance. We will also discuss potential intersections of these brain pathways and those regulating mood. We predict that a greater understanding of these pathways may help guide the development of safe and effective anti-obesity therapies. However, it is not our goal to provide a comprehensive review of a large literature regarding untoward neuropsychiatric effects from anti-obesity agents and surgeries. Rather, we hope that our comments will serve as a starting point for the wide readership of Cell Metabolism to think about these potentially important issues. We also hope that the points we raise leads to them digging deeper into the established literature and to think about studies that could be done to address these issues that may impede translating the explosion of basic science and translation into effective strategies to combat obesity.

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Central Control of Food Intake

Two parallel regulatory systems have been implicated in the central control of feeding behaviors (Kenny, 2011). The homeostatic system regulates food intake in response to changes in peripheral energy status and thus is essential for the regulation of hunger and satiety. The neural circuits underlying this include anatomically-defined hypothalamic and brainstem nuclei where metabolic signals such as glucose and various dietary-derived lipids are sensed and integrated to direct proper energy intake and expenditure (Elmquist et al., 2005). One key structure is the arcuate nucleus of the hypothalamus (ARH), which is made up of two distinct neuronal cell types that serve as the first-order neurons in the brain relaying peripheral nutrient and hormonal information. Neurons that produce pro-opiomelanocortin (POMC) and cocaine-amphetamine-regulated transcript (CART) peptides suppress food intake, whereas those that synthesize agouti-related peptide (AgRP) and neuropeptide Y (NPY) directly promote feeding behaviors (Aponte et al., 2011; Krashes et al., 2011). Leptin, the circulating adiposity hormone, stimulates POMC neurons while reciprocally hyperpolarizing orexigenic AgRP/NPY neurons. Years of studies have also highlighted an important role for brainstem neurons in the regulation of hunger and satiety (Grill and Hayes, 2012; Moran et al., 2006). For instance, it was recently shown that neurons in the nucleus tractus solitarius (NTS) and caudal serotonergic nuclei provide excitatory inputs to the parabrachial nucleus (PBN) and inhibit food intake (Wu et al., 2012). Furthermore, acute activation of NTS POMC neurons produces an anorexigenic effect (Zhan et al., 2013).

In addition to homeostatic regulation, central control of food intake involves other neural processes such as reward and cognition (referred to as non-homeostatic regulation). Food, especially palatable food, represents a potent reward signal that stimulates the mesolimbic dopamine (DA) pathways (Kenny, 2011). Exposure to food cues promotes the firing of DA neurons in the ventral tegmental area (VTA) resulting in an increase in DA release in the striatum (Norgren et al., 2006; Small et al., 2003). Intriguingly, decreased striatal DA signaling has been associated with reduced responsiveness to reward signals in obese patients (Geiger et al., 2008), which may perpetuate overeating through a counter-regulatory mechanism (Johnson and Kenny, 2010; Stice et al., 2008). In particular, DA neurotransmission in the striatum regulates motivational aspects of feeding behaviors and is required for food procurement and consumption. Mice deficient in DA production die of starvation due to a lack of motivation to feed, a defect that can be rescued by restoring DA in the dorsal striatum (Szczypka et al., 2001). Interestingly, a lack of motivation for palatable food or anhedonia is often viewed as one of the hallmarks of depressive symptoms. Consistently, reduced activities of mesolimbic DA system have been implicated in the pathophysiology of major depression disorder (MDD), whereas euphoria is associated with amphetamine-induced DA release in the ventral striatum (Drevets et al., 2001; Nestler and Carlezon, 2006). Together, these findings suggest that functional impairments of the mesolimbic DA system can affect both emotional and metabolic processing.

In addition to the mesoaccumbens DA circuits, other limbic [amygdala and hippocampus] and cortical [orbitofrontal cortex (OFC), anterior cingulated cortex (ACC) and insula] regions also encode the hedonic value of food cues and are responsible for the cognitive

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regulation of feeding behaviors (Pelchat et al., 2004; Simmons et al., 2005). For example, the presentation of food to fasting subjects increased metabolism in the OFC in proportion to the subjective perception of hunger and the desire to eat (Wang et al., 2004). Conversely, decreased activities were found in the amygdala, hippocampus, insula, and OFC when fasted men were asked to voluntarily inhibit their food cravings while being exposed to food cues (Wang et al., 2009). Notably, these brain sites are heavily implicated in the mood regulation, and whose malfunction could also contribute to emotional perturbations (Bachevalier et al., 2011).

Unanticipated Actions of Anti-obesity Drugs

Untoward psychiatric events may arise from the fact that several anti-obesity agents target proteins that have broad expression domains in the central nervous system. As a result, global manipulation of their activities may inevitably affect their functions in brain sites that are involved in mood regulation. Prominent examples in this regard are found in the former drugs, Rimonabant and Taranabant, antagonists of cannabinoid receptors (CB_1).

The appetite-stimulating effects of cannabis plants have been documented for centuries. However, the underlying mechanism remained unclear until the discovery of the first cannabinoid receptor (CB_1), a G-protein coupled receptor that binds delta(9)-tetrahydrocannabinol (Δ^9-THC), the principal psychotropic ingredient of marijuana (Matsuda et al., 1990). Two major cannabinoid receptors (CB_1 and CB_2) exist in the mammalian endocannabinoid system to mediate the neuromodulatory actions of endogenous endocannabinoids. While the expression of CB_2 receptors is largely enriched in the immune system, CB_1 receptors are abundant in the brain and responsible for the orexigenic actions of both natural and endogenous cannabinoid ligands (Howlett, 2002). Elevated CB_1 receptor signaling has been implicated in obesity and its comorbid metabolic syndromes (Matias et al., 2008; Osei-Hyiaman et al., 2005; Ruby et al., 2011). Rimonabant (Acomplia®, Sanofi-aventis), a selective CB_1 receptor blocker, induced significant weight loss and improved cardiometabolic risk profiles in overweight or obese patients (Despres et al., 2005; Pi-Sunyer et al., 2006; Van Gaal et al., 2005). The positive results from multiple preclinical studies led to the approval of Rimonabant in 2006 as a novel anorectic anti-obesity treatment by the European Medicines Agency (EMEA). By 2008, the drug was available in more than fifty countries. However, following its clinical introduction, adverse neuropsychiatric incidents including anxiety, depression and suicidality were noted in obese patients, leading to a growing concern regarding the psychiatric safety of this drug. Consequently, Rimonabant was removed from the global market following its suspension by the EMEA in late 2008. Meanwhile, the clinical development of similar compounds including Taranabant (Merck) and Otenabant (Pfizer) were also abandoned (Le Foll et al., 2009).

The anti-obesity effect of this type of drug is thought to be principally mediated by its anorexigenic function. Of note, when given at a sub-threshold dose, Rimonabant selectively reduces the intake of palatable food, but has no effect on the feeding of regular food, suggesting, that CB_1 receptor signaling is not only involved in the regulation of satiety, but may also influence the motivational and pleasurable aspects of eating behaviors (Simiand et al., 1998). Within the hypothalamus, one of the crossroads where CB_1 receptors regulate

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both homeostatic and non-homeostatic feeding is the lateral hypothalamus (LH) where activation of CB_1 receptors not only promotes food intake but also influences reward processing through interactions with the mesoaccumbens DA system (Jo et al., 2005; Taslimi et al., 2011). Moreover, CB_1 receptor signaling mediates the orexigenic effect of ghrelin in the PVH. Activation of CB_1 receptors diminishes the excitatory inputs on corticotrophin-releasing hormone (CRH) neurons (Kola et al., 2008) and inhibits the release of CRH (Di et al., 2003). Conversely, genetic ablation of CB_1 receptor in rodents leads to increased levels of CRH (Cota et al., 2003). In addition to its role as an anorexigenic peptide, CRH is a major regulator of the hypothalamic–pituitary–adrenal (HPA) axis. Increased levels of CRH and HPA activities have been implicated in the pathophysiologies of affective disorders including depression and suicide (Bonfiglio et al., 2011). Therefore, the actions of CB1 antagonists on CRH neurons may potentially affect emotional behaviors by altering the levels of HPA activities and stress hormones (Ashton and Moore, 2011; Cota et al., 2007).

CB_1 receptor signaling may also regulate emotional behaviors in extra-hypothalamic sites, independent of its role in the regulation of food intake. CB_1 receptors are highly enriched in the prefrontal cortex, amygdala, and hippocampus, brain regions that are critical for emotional processing (Herkenham et al., 1990). Stimulation of CB_1 receptors in these sites may serve as the neural basis for the reported feelings of relaxation, reduced anxiety and increased sociability after cannabis use (Murray et al., 2007). Conversely, pharmacological blockade of CB_1 receptors leads to increased anxiety-like behaviors and impaired stress-coping capabilities in rodents (Navarro et al., 1997; Steiner et al., 2008). It has therefore been hypothesized that a persistent endocannabinoid tone has to be maintained in certain cortical and limbic areas for normal emotional responses. In this vein, global antagonism of CB_1 receptors signaling may negatively impact emotional processing and thus contribute to the pathophysiology of affective disorders.

Unexpected Outcome of Weight loss Surgery

A growing body of literature suggests that actions of some peripheral metabolic signals do not exclusively regulate energy homeostasis, but may also directly be involved in mood regulation (Hryhorczuk et al., 2013). This hypothesis is further supported by the expression of the receptors for the circulating hormones, such as leptin, insulin and ghrelin in extra-hypothalamic sites that have been implicated in the control of mood (Plum et al., 2005; Scott et al., 2009; Zigman et al., 2006). These findings therefore raise the possibility that the increased risk of adverse psychiatric events may result from changes in the levels of circulating hormones following anti-obesity therapies. For example, bariatric surgery is currently the most effective treatment for obesity and its comorbid metabolic conditions. The surgery can help obese patients achieve not only significant long-term weight loss (40–70%), but substantial improvement in hyperlipidemia and hypertension, complete remission of diabetes, and ultimately a reduction in mortality (Mingrone et al., 2012; Schauer et al., 2012). Hundreds of thousands of Americans receive bariatric surgery each year and the number will continue to rise in the future. However, relatively few studies have been conducted to evaluate the long-term safety of this surgery especially as it relates to behavioral and psychiatric outcomes. Several studies have suggested that following surgery

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and weight loss, there is an increase in the incidence of certain maladaptive behaviors. In particular, it has been noted that some patients developed postoperative compulsive disorders such as alcoholism, gambling and compulsive shopping (Acosta et al., 2008; Wendling and Wudyka, 2011). Most alarmingly, several groups reported an increased risk of suicide among postoperative bariatric patients compared with either the general population or with obese individuals who did not have the surgery (Adams et al., 2007; Peterhansel et al., 2013; Pories et al., 1995; Tindle et al., 2010). Among these studies, Tindle et al. followed 16,683 bariatric surgery procedures performed on Pennsylvania residents over a ten-year period. The postsurgical suicide rate was 13.7/10,000 for men and 5.2/10,000 for women, compared with 2.4/10,000 for age-matched men and 0.7/10,000 for age-matched women in the U.S. general population (Tindle et al., 2010).

Other than pre- and postoperative psychological distress, the molecular mechanisms underlying the alterations in behavior and suicide rates remain unknown. A sudden decrease in serum cholesterol has been previously linked to suicide (Modai et al., 1994). Moreover, changes in the levels of peripheral derived neuropeptides including leptin, GLP-1, PYY and ghrelin have all been described following the surgery (Ionut et al., 2013). Ghrelin, a 28-amino acid peptide, is synthesized and secreted primarily by the epithelia cells of the fundus (Kojima et al., 1999). Depending on the type of the surgery, the fundus can be either isolated or removed during the procedure leading to a significant reduction in serum ghrelin levels (Fruhbeck et al., 2004). In addition to its role as an orexigenic peptide, a growing body of literature indicates that ghrelin, acting through its receptors in the brain, regulates emotional behaviors (Chuang and Zigman, 2010). For example, plasma ghrelin level rises upon various types of stress and may serve as a neuroprotective mechanism against stressed-induced anxiety and depression (Lutter et al., 2008). Consistent with these findings, ghrelin produces an anti-depressant-like effect in rodents, which may be associated with adult neurogenesis in the hippocampus (Chuang and Zigman, 2010). Therefore, lower serum ghrelin levels in postoperative bariatric patients may lead to increased vulnerability and susceptibility to depression and suicide ideation. Further studies are clearly needed to directly address this hypothesis. In addition to ghrelin, leptin receptors are highly enriched in the hippocampus, amygdala and VTA (Scott et al., 2009). Leptin administration reduces the firing rates of dopaminergic neurons within the VTA, suggesting leptin actions on DA neurons may directly regulate mesolimbic DA activity and DA-modulated behaviors (Fulton et al., 2006; Hommel et al., 2006). Reduced levels of striatal dopamine D2 receptors have been found in drug-addicted subjects (Volkow et al., 2007). Interestingly, Dunn et al. found a similar reduction of D2 receptor availability in post-operative bariatric patients accompanied by a significant decrease of plasma levels of insulin and leptin (Dunn et al., 2010). It remains to be determined whether changes in peripheral-derived hormones such as leptin have a direct impact on mesoaccumbens DA signaling and if they contribute to the observed maladaptive behaviors. Relevant to the reports of depression, lower levels of plasma leptin have been observed in depression patients and in rodent models of depression (Lu et al., 2006). Conversely, systemic leptin administration produce an anti-depressant –like effect and dose-dependently improves mice performance in both forced swim and tail suspension tests (Kraus et al., 2001; Lu, 2007). However, it is unclear whether a drop in postoperative leptin

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levels ultimately contributes to the altered emotional processing and the pathophysiologies of depression and suicide.

Finally, the increased risks for adverse neuropsychiatric events could be the result of altered gut-brain signaling following bariatric surgery (Berthoud et al., 2011). It is well known that the metabolic actions of several gut-derived neuropeptides and transmitters including CCK, PYY, GLP-1, ghrelin and 5-HT are mediated, in part, through the vagal afferents (Moran, 2009). The vagus nerve is the tenth cranial nerve that arises from the brain stem and innervates key visceral organs including the entire gastrointestinal tract. Various visceral signals collected by the vagal sensory neurons are initially integrated in the nucleus of solitary tract (NTS) in the brain stem and ultimately reach the cerebral cortex via parabrachial-thalamic and other ascending pathways (Saper, 2002). It has long been proposed that visceral inputs are integrated with emotional experience and can potentially affect psychiatric functioning (Stellar, 1954). Moreover, vagal nerve stimulation has been clinically used to combat treatment-resistant depression. However, much of the mechanisms underlying the beneficial effects of vagal stimulators remain poorly understood. Recently, Tellez et al., reported that lipid-sensing by vagal afferents can influence the striatal release of dopamine and dopamine-modulated feeding behaviors (Tellez et al., 2013). Both ventral and dorsal branches of the gastric vagus nerves are severed during Roux-en-Y gastric bypass (RYGB) surgery. It is therefore important to investigate whether the surgery-associated gastric vagotomy may contribute to these potential maladaptive behavioral responses.

Body Weight Effects of Psychiatric Agents

Excess weight and obesity are associated with mood disorders (Petry et al., 2008). A large number of epidemiologic and clinical studies indicate obese patients are more susceptible to psychiatric illnesses, raising the possibility that metabolic abnormalities may precipitate mental illness (Faith et al., 2011). On the other hand, a broad range of psychotropic agents, including various anti-depressants, mood stabilizers and antipsychotics can cause significant weight gain. Among different psychiatric agents, abnormal weight gain is most prominent within individuals taking atypical antipsychotic drugs (AAPDs). AAPDs are second generation antipsychotic agents, and despite their metabolic side effects, are frequently prescribed to treat several psychiatric conditions including depression, bipolar disorder, and schizophrenia. Standard doses of AAPDs can cause rapid weight gain of more than 4 kilograms over a 10-week period (Allison and Casey, 2001). In addition, other metabolic impairments including hyperglycemia, hypertension, hypertriglyceridemia and low HDL-cholesterol, are also prevalent among patients taking AAPDs (Bergman and Ader, 2005). The risks for developing metabolic syndromes vary between individual AAPDs, among which clozapine and olanzapine have the greatest side effects (Teff and Kim, 2011). Moreover, children and young adults seem to be the most susceptible to developing metabolic abnormalities and tend to gain more weight during AAPD treatment (Almandil and Wong, 2011). The mechanism underlying AAPD-induced weight gain remains unknown. However, an increase in food cravings has been consistently reported following Olanzapine and Clozapine administration (Kluge et al., 2007), suggesting that AAPDs cause weight gain through actions on neurocircuits that regulate appetite.

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AAPDs exert their psychotropic actions by antagonizing receptors for biogenic amines including dopaminergic, adrenergic, muscarinic, histaminergic and serotonergic receptors (Bymaster et al., 1999), many of which have been directly or indirectly implicated in feeding regulation. Previous work has focused on the central histamine system and showed that AAPDs' binding affinity for the histamine H1 receptor (H1R) were significantly correlated with body weight gain (Kroeze et al., 2003). Furthermore, pharmacological and genetic ablation of H1Rs results in hyperphagia and obesity (Masaki et al., 2004). In addition to the H1R signaling, AAPDs-induced weight gain is associated with polymorphisms in the 5-HT_{2C}R gene (Reynolds et al., 2002; Templeman et al., 2005). Global deletion of 5-HT_{2C}Rs causes hyperphagia and obesity in mice (Nonogaki et al., 1998; Tecott et al., 1995). Our lab has recently identified the POMC neuron in the ARH as one of the physiologically important sites where 5-HT_{2C}R regulates food intake. Furthermore, selective re-expression of physiological levels of 5-HT_{2C}Rs only in POMC neurons is sufficient to normalize hyperphagia and obesity in 5-HT_{2C}R null mice (Xu et al., 2008). Conversely, 5-HT_{2C}Rs expression in POMC neurons is required to effectively regulate energy balance and glucose homeostasis (Berglund et al., 2013). To this end, it will be interesting to investigate whether AAPDs-induced hyperphagia and weight gain involves antagonism of 5-HT_{2C}Rs in POMC neurons.

Perspectives

The neural control of energy balance and emotional behaviors are both complex physiological processes that involve coordinated actions of multiple brain structures and neurotransmitter systems. Therefore, it is not surprising that common pathways have "dual" functions and contribute to both metabolic and emotional regulation. A prime example of "shared pathways" is the mesolimbic DA system that not only encodes for the hedonic value of palatable food, but is heavily implicated in the pathophysiology of emotional disorders such as schizophrenia and depression. Consistently, impairments in mesolimbic DA signaling can cause both obesity and anhedonia, a major clinical symptom of depression. Within the hypothalamus however, accumulating evidence suggests that several neuronal populations influence emotional processing independent of their roles in the homeostatic regulation of energy balance. For example, the CRH neurons in the PVH play a crucial role in regulating circulating levels of glucocorticoid hormones which are elevated in response to stress and in patients with major depression (Manji et al., 2001). Additionally, LH orexin neurons modulate motivation by direct innervation and stimulation of DA neurons in the VTA (Narita et al., 2006). Within the arcuate nucleus, β-endorphin, another splicing product of POMC, has been implicated in major depression (Hegadoren et al., 2009). Moreover, a recent study highlighted a role for AgRP neurons in the regulation of midbrain DA neuron activities and DA-associated reward behaviors (Dietrich et al., 2012).

Without a doubt, these recent findings strongly suggest that neural pathways that regulate metabolism and those that regulate emotional behaviors are intimately intertwined and are not easy to target in isolation. In fact, many think that untangling this intimate relationship is not feasible and drugs that target the CNS "feeding circuits" are often non-starters as potential candidates. Whether this is the case or not remains to be seen. Nonetheless, these findings provide fuel to a widely held notion that anti-obesity therapies that directly or

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indirectly affect the central nervous system (CNS) are likely to carry inherent risks for negative psychiatric events. Optimizing the benefit/risk profile remains a key challenger for the development of safe and effective anti-obesity therapies. In this regard, the adverse neuropsychiatric events associated with recent anti-obesity therapies provide valuable lessons for new drug development. We argue that developing protocols that allow for the early pre-clinical detection of adverse psychological effects are imperative for the development of future CNS targeted anti-obesity agents. On the other hand, a revisit of the peripheral functions of several existing pharmacological targets may be necessary so that it is possible to develop periphery-restricted anti-obesity agents without incurring CNS related side effects. For example, studies suggest that many of the metabolic benefits of CB_1 receptor antagonists (potentially the anorexic effects) can be mediated through their actions on peripheral CB_1 receptors (Gomez et al., 2002). These findings raise the possibility of developing novel peripherally restricted CB_1 receptor antagonists to circumvent the neuropsychiatric complications that are certainly mediated by the CNS.

Regardless of the aforementioned issues, at the end of the day we posit that a better understanding of the neurocircuits that control energy balances and those regulating emotional behaviors, as well as how these pathways interact remains essential for identifying novel and more refined targets for pharmacological intervention. Notably, several new approaches that allow for targeted drug delivery and selective nerve stimulation are being developed so that only anatomically-defined feeding circuits and pathways are affected by these therapies. For example, Finan et al., recently described a new combinatorial approach that used a glucagon-like peptide-1 (GLP-1)-estrogen conjugate to selectively activate estrogen receptors only in GLP-1 targeted tissues (Finan et al., 2012). Using this approach, the authors were able to improve obesity, hyperglycemia and dyslipidemia in diet-induced obese mice while minimizing the side effects that are commonly associated with traditional estrogen therapies. It remains to be seen whether similar approaches can be utilized to direct other pharmacological agents to specific populations of CNS neurons. Furthermore, several groups have demonstrated the feasibility of inhibiting food intake in rodents by selectively stimulating or inhibiting distinct hypothalamic and brainstem circuits via either optogenetic or pharmacogenetic means (Aponte et al., 2011; Krashes et al., 2011; Wu et al., 2012; Zhan et al., 2013). As well, hypothalamic deep brain stimulation (DBS) has been tried in both primates and humans and shown to be effective in reducing food intake and body weight (Torres et al., 2012; Whiting et al., 2013). It is therefore expected that with an improved understanding of central pathways regulating food intake and mood, these new approaches will significantly enhance the specificity of current treatments and facilitate the development of future anti-obesity therapies.

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