ANNALS
MINI REVIEW

Obesity and deep brain stimulation: an overview

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ABSTRACT

Deep brain stimulation (DBS) has been employed to treat a variety of disorders such as Parkinson disease, dystonia, and essential tremor. Newer indications such as epilepsy and obsessive-compulsive disorder have been added to the armamentarium. In this review, we present an initial summary of current methods in the management of obesity and then explore efforts in neuromodulation and DBS as a novel modality in the treatment of obesity disorders.

KEYWORDS: Restorative neuromodulation, Deep brain stimulation, DBS, Obesity, Eating disorders

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doi: 10.5214/ans.0972.7531.220310

Introduction

Obesity is an increasingly prevalent condition in both developed and developing countries. According to Ng et al., estimates suggest 3.4 million deaths per year attributable to obesity worldwide with around 4% of both years of life lost and disability-adjusted life-years.[1] Between 1980 and 2013, the adult population has seen around a 10% increase in the proportion of overweight individuals (BMI ≥25 kg/m^2). However, obesity has also begun to emerge as a significant health concern in the child and adolescent population with around 23% of children in developed countries being overweight or obese. In developing countries, the prevalence of overweight and obesity in children has risen by around 5% to 13% in the same 33 year period.[1]

According to the United States Centers for Disease Control and Prevention (CDC), over 35% of US adults are obese.[2] While this rate varied by state, no state had an obesity rate less than 20%. Even more alarming is the ascendant trend of the incidence of obesity in the US: in the year 2000, no state had an obesity rate higher than 30%, while as of 2010, at least 12 states had a rate of 30% or higher with many other states approaching that number.[2]

Obesity is associated with diminished quality of life, numerous comorbidities, and decreased life expectancy by as much as 20 years.[3–5] Considering the numerous comorbidities of obesity, such as osteoarthritis, heart disease, stroke, type 2 diabetes, and certain types of cancer, financial burdens are to be expected.[6] However, not only is the individual but the society as a whole is affected. Yach et al. reported that the medical and treatment costs for diabetes alone siphon considerable resources from health systems.[7] In 2008, it was estimated that medical costs associated with obesity had risen to $147 billion from $78.5 billion ten years prior.[8]

When the increased rates in obesity throughout the years are compared with the increased cost of health care for obese patients, the data "suggests that the increased prevalence of obesity is driving increases in total medical spending."[8] Finkelstein et al. also found that, "obese beneficiaries, on average, cost Medicare over $600 per beneficiary per year more compared to normal-weight beneficiaries."[8] The per capita medical spending for the obese is about 42% higher than for a person of normal weight.[8] Wang et al. proposes that if current trends in the rising incidence of obesity continues, all adult Americans will by overweight by the year 2048 and "total health-care costs attributable to obesity/overweight would double every decade to 860.7–956.9 billion US dollars by 2030, accounting for 16–18% of total US health-care costs."[9]

Significant weight variation—notably, weight loss—as a secondary effect of DBS treatment for Parkinson's Disease (PD), has been well-documented in the scientific literature.[10–18] Similarly, DBS treatment of cluster headaches has been shown to cause secondary weight loss.[19,20] In addition, neuromodulation has been proven to elicit weight change in several animal studies.[21–26] Because of the few pharmacological treatments for obesity and their success rates of only moderate weight loss, most patients with refractory obesity must rely on bariatric surgery, which has a high rate of success but can have potentially severe adverse effects, possible problematic recovery, and carries a risk of causing nutritional deficiencies.[27]

The possibility of using brain surgery to treat obesity is highly intriguing. DBS has been proven safe with a high rate of documented successes in the treatment of many other disorders (PD, OCD, and tremor). However, the exact mechanism of action for neuromodulated weight variation is not completely known. In this review, we examine traditional treatments for refractory obesity and assess possible targets for neuromodulation to assist patients with weight loss.

Current management of obesity

Treatment and management of obesity often includes diet, exercise, medications, new technology, and various surgical treatments involving both the brain the and gastrointestinal system. In the following section, we present a brief overview of these modalities and their roles in treating and managing the patient with obesity.

Diets

Common modes of weight loss considered when first attempting to lose weight are diet and exercise. Although the combination of these two components contributes to a higher possibility of success, diet modification is generally the first

attempted course of action. In the clinical setting, current medical nutritional therapy for patients with obesity includes both low calorie diets (i.e., calorie deficit of 500–1000 kcal/d) and very-low calorie diets (800 kcal/d or less). The very-low calorie diet necessitates medical supervision throughout the weight loss period by means of electrolyte monitoring and supplementation of vitamins and minerals. These two diets describe caloric intake but do not factor in the composition or source of these calories.[28,29] Prescribed diets may also restrict dietary composition, regarding components such as fat and carbohydrates.

Historically, registered dietitians promote a low-fat diet, as fat is calorically dense and reductions in fat-intake have been shown to benefit those at risk of heart disease. A low-fat diet is typically comprises of 55–65% carbohydrates, 10–15% protein, and 30% fat, no more than 10% of which should come from saturated fats, 10% from monounsaturated fatty acids, and 10% from polyunsaturated fatty acids.[30] Low-fat diets should also contain foods high in fiber, given its low glycemic index and beneficial role in heart health. With adherence to caloric restriction, this low-fat diet results in weight loss and concurrently provides favorable reduction in total cholesterol and LDL cholesterol values.[31,32]

Carbohydrate restriction is another common method of weight loss. A low carbohydrate diet is one that limits daily carbohydrate intake to less than 30% of total energy intake. Low carbohydrates diets have become more popular as a means for weight loss but were originally employed to treat disorders such as epilepsy and polycystic ovarian syndrome.[32–35] Short-term low carbohydrate diets result in a higher percentage weight-loss than the low-fat diet; in the long-term, however, patients lost similar percentages of weight on both diets but compliance was higher with the low-fat diet.[32] Weight lost while on the low carbohydrate diet was associated with decreased triglyceride level and an increase in HDL levels.[32] Weight loss is a short-term consequence of low carbohydrate diets though it is not always successfully maintained.[32,36–42]

Carbohydrates can be further restricted to comprise only 10% of total energy intake. These very low carbohydrate diets such as the Atkin's diet are designed to place the body in a state of ketosis and drive β-oxidation to fuel gluconeogenesis. Despite any resulting weight loss that may correspond with this diet, it still raises some concerns due to associated halitosis and increased LDL levels due to production of ketone bodies.[32] Use of long-term very low carbohydrate diets are contra indicated, as carbohydrates are required for serotonin synthesis and their deficit places the patient at risk of depression. Additionally, very low carbohydrate diets are usually associated with low fiber and calcium intake, which can lead to constipation and bone demineralization respectively. Deficiencies in water-soluble vitamins secondary to low fruit intake can lead to anemia and scurvy; patients on these restrictive diets often require supplements.[32,43]

Studies that examined the efficacy of fat diets noted many test subjects had difficulty complying with the prescribed diet. Many test subjects ended up dropping-out of the study because these diets are often difficult to follow.[36,44] This highlights issues with diets in general and indicates the need for a modification of lifestyle.

Exercise

There is no doubt that exercise is very valuable in maintaining physical fitness along with cardiovascular health. In a study by Slentz et al., a relationship between amount of weekly exercise and amount of weight change was observed.[45] Garrow et al. state that, "the changes in fitness and body composition which accompany physical training in people of normal weight would be very valuable in the treatment of obesity."[46] However, many obese patients experience exercise intolerance, which would limit them from performing these activities to bring about the desired result of weight loss. While it has been suggested that exercise may confer benefits to the obese person by reducing voluntary food intake, there is no solid evidence to support this claim.[46]

Medical Treatment

The use of medications has been a popular option for patients with obesity, but most obesity medications have not been efficacious. The effects of most obesity medications on weight loss is only about 3–8% of original body weight.[47] In fact, Britain's National Institute for Health and Clinical Excellence recommends that weight-loss medication treatment be discontinued if a 5% loss in weight has not occurred by 3 months.[48] At present, the only FDA-approved weight-loss drug for obesity management is tetrahydrolipstatin (Orlistat), which works by inhibiting pancreatic lipase and can cause adverse effects, such as fatty stools, increased number of bowel movements, oily spotting, liquid stools, and fecal urgency.[47] Other prescription drugs being used are phentermine (Apidex-P), diethylpropion (Tepanil), benzphetamine (Didrex), and phendimetrazine tartrate (Adipost).[47] There are also limitations on candidacy for treatment with weight-loss drugs: a patient must have a BMI over 27 (if there are co-morbidities such as type 2 diabetes, hypertension, heart disease, sleep apnea, or metabolic syndrome) or over 30 without comorbidities.[47] Studies have shown that with the use of Orlistat, 21% of subjects in studies reviewed lost at least 5% of their body weight and 12% of the subjects lost 10% or more.[47]

Though the weight loss results with Orlistat show promise, the FDA is currently investigating its safety due to adverse effects. One study has reported cases of patients taking Orlistat developing serious liver damage.[47] As with other past medications that had their FDA-approval withdrawn, weight-loss drugs that have caused serious problems, fenfluramines or "phen-fens",[47] which was withdrawn from the market in 1997 due to valvular regurgitation.[47] Use of non-prescription weight-loss supplements are also common; however, over 74% of weight-loss supplements contain stimulants such as ephedra which can drastically effect health in some individuals with co-morbidities such as hypertension and heart disease.[47]

Technology

Researchers are now beginning to turn their attention to the use of technology for weight reduction by controlling and modifying behavior. Spence et al. highlight many of these technological advancements, such as cognitive conditioning in the form of notifications of caloric and speed of intake.[49] One example of such technology is a sensor-rich spoon that has been developed to vibrate if it detects that the person is eating too quickly which, in turn should provide encouragement to the person to eat more slowly and hopefully less. In addition, the HAPIfork, an eating tool that is designed to measure how long a person eats, how long between each mouthful, and how many bites a person takes has been developed to vibrate and help facili-

tate cognitive conditioning. The data has designed to give feedback to a person on his or her eating habits and allow online viewing of these results and trends. While the jury is still out on the devices' effectiveness on weight loss and lacking FDA approval in weight loss for use in weight loss, these tools do indeed represent a "promising, not to mention important, area for future research."[49]

Surgical treatment of the Gastrointestinal System

Bariatric surgery has been used in many patients to attempt to treat their obesity. However, considering obesity as a neuropsychiatric disease (multiple studies have shown a correlation with the reward centers in the brain and food intake), bariatric surgery will only be a temporary fix to the problem. Halpern et al. found that pharmacological and behavioral therapies are seldom effective because of high relapse rates, which is a possible explanation for the more than 10-fold increase in bariatric surgeries in the last 8 years.[50] While bariatric surgery is initially effective in allowing for a mean weight loss of 20–60%, roughly 15–55% of patients experience complications (33.4%) with a mortality rate of 1.5%.[27,50] Even if the risk-laden bariatric surgery results in weight loss and improvement in morbidity, considerable weight gain occurs at about 2 years after surgery with a failure rate (recurrent binge eating) up to 46%.[50]

Mechanisms of surgical treatment of the gastrointestinal system work by either restricting the capacity of the stomach or by promoting malabsorption; in some cases, a combination of both are employed. Malnutrition often exists presurgically for the bariatric candidate; they are in a state of hypercaloric malnutrition, experiencing a deficit in key vitamins and minerals secondary a lifetime of poor nutritional choices, which may also be an indicator of compliance with post-procedure supplementation.[51] Protein malnutrition is the most severe macronutrient complication. Problems exist in performing surgery on the super obese (BMI >60 kg/m^2) if the patient has low serum albumin levels, which often delays necessary surgery until these levels improve. Parenteral nutrition is sometimes needed to prep candidate patients for surgery.

Rouxen-Y gastric bypass surgery results in the bypass of 95% of the stomach, the entire duodenum, and 150 cm of the jejunum. Patients who have undergone gastric bypass surgery can experience micronutrient deficiency as a lifelong concern and will need to be treated with lifelong supplementation of iron and other micronutrients that would normally be absorbed in the duodenum. Duodenal bypass patients have a high risk of osteoporosis because of calcium malabsorption. Decreased calcium levels are also observed in patients prescribed hypocaloric diets because their diets are generally not broad enough to provide an appropriate level of calcium.[52] Vitamin D levels may also be low in both of these patients and should be supplemented.[52–54] It is also thought that there may be a deficiency in both selenium and zinc despite little published data supporting this claim.

Vitamin B12 (cobalamin) requires an accessory factor known as intrinsic factor that is produced by the lower stomach and is required for vitamin B12 absorption in the duodenum. If the stomach has been altered or the small intestine has been bypassed, then either intrinsic factor or the appropriate section of intestine responsible for absorbing B12 is unavailable, resulting in a B12 deficiency. B12 monitoring and supplement shots are thus standard.[30,52,54,55] Folic acid is often malabsorbed because the gastrointestinal tract bypasses the jejunum.[54] Vitamin B1 (thiamine) may also be limited in patients with jejunum resections/bypasses or in patients experiencing severe emesis.[52,54] Water is often an overlooked nutrient, and has not been studied extensively on a population-wide scale.[56] Mild dehydration (–1% to –2% body mass) is common in most individuals in America, even the sedentary. Dehydration has been implicated in cancer development, kidney stones, and coronary heart disease.[57–66]

Psychological assessment has essentially become standard of care for routine pre-operative bariatric evaluation.[67] The National Institutes of Heath (NIH) issued a consensus statement in 1991 making psychological assessment a mandatory procedure for pre-operative care.[68] More recent practice guidelines have relaxed psychological assessment as a requirement, but continue to recommend evaluation as an integral part of a multidisciplinary evaluative process.[69] The purpose of the psychological evaluation is multifactorial and may include an assessment of presence of Axis I or Axis II psychiatric history, substance use, relevant lifestyle and eating habits, social and family support, patient knowledge of surgery procedures and consent capacity, surgical expectations, and motivational factors.[70,71] While no best practice guideline exists, assessment of these factors is typically completed via thorough structured or semi-structured diagnostic interview and a combination of psychometric instruments. Initial BMI was not a significant predictor of post-operative weight loss. These findings support the use of psychometric measures to assess the role of personality and psychopathological factors in weight loss surgery. However, further investigation of specific scale profiles is warranted.

Psychological factors

One area that has received relatively less attention in the weight loss literature has been neurocognition and its relation to weight loss treatment. Several studies have identified significant correlations between obesity/increased BMI and cognitive dysfunction, including memory, attention, processing speed, and executive function.[72–74] Yet, fewer studies have focused efforts on patients undergoing surgical weight loss treatment. Gunstad et al. evaluated a sample of 190 patients (141 patients for bariatric surgery and 49 obese controls) and found cognitive impairment in 4.6% to 23.9% in their sample.[75] Interestingly, the authors reported improved cognitive functioning in some surgical patients. However, the gains on performance-based cognitive tests were unrelated to medical conditions or weight changes. Alosco et al. documented gains in memory and other cognitions at both brief (12 weeks) and sustained (2 year) intervals.[76] These findings are compelling and warrant follow-up, as they suggest effective weight loss that may lead to gains in areas other than general health or medical status.

Neurosurgery and weight modulation

Anatomy and animal studies

Halpern et al. identified three potential neural targets that are believed to be associated with excessive food consumption: the lateral hypothalamus, the ventromedial hypothalamus, and the nucleus accumbens.[50] While these targets were generally discovered via lesioning studies, they may provide the best leads for future studies with DBS. In addition, animal studies have provided keen insights into the role of these structures in modulating weight through various mechanisms.

The lateral hypothalamus (LH) has been implicated in feeding behavior, energy expenditure, and appetite regulation. Quaade et al. in 1974 found that stereotactic electrocoagulation of the lateral hypothalamus of obese patients resulted in a significant—albeit temporary—suppression of appetite.[77] Three patients in the study were also found to have slight reduction in weight. Animal studies involving modulation of the lateral hypothalamus have also found a relationship to appetite. Sani et al found that high frequency stimulation of 180 to 200 Hz of the lateral hypothalamus resulted in weight loss in rats.[26] In their study, 16 rats were put on a high-fat diet with daily food intake measured for 7 days, at which point the rats underwent a stereotactic placement of 0.25-mm-diameter bipolar stimulating electrodes bilaterally in the lateral hypothalamus. On the seventh post-operative day, 8 of the rats started to receive continuous stimulation of the LH while the remaining 8 rats were left unstimulated. The unstimulated group resumed a linear weight gain curve while the stimulated group failed to show weight gain throughout the study.[26] On post-operative day 24, the unstimulated group had a mean weight gain of 13.8%, while the stimulated group had a 2.3% weight loss average.[26] With these results, Sani et al. concluded that bilateral electrical inhibition (high frequency stimulation) of the LH is indeed effective in causing noteworthy and sustained weight loss in rats.[26] Conversely, low frequency stimulation of 50–100 Hz was associated with increased feeding, further establishing a connection of the lateral hypothalamus in appetite control.[78–81]

The ventromedial hypothalamus (VMH) has also been implicated in the regulation of appetite regulation in animal studies[82,83] and is considered the satiety center of the brain.[82,83] Lesions of the ventromedial hypothalamus in already obese animals have been found to induce further weight gain and resulted in more carcass lipid and hyperinsulinemia.[84,85] Some studies found that low frequency stimulation of 60 to 100 Hz inhibited feeding in hungry rats.[86–88] These studies also found that feeding resumed as soon as the stimulation was terminated. Low frequency stimulation of 50 Hz of ventromedial hypothalamus also inhibited feeding in goats.[89,90] A more recent study by Covalin et al. suggested an association between stimulation in the 25 to 100 Hz range increased expenditure of energy while resting.[91] While these animal studies appear promising, adverse events, such as fear, aversion, restlessness, and attempts at escape were associated with stimulation of this part of the brain.[86,88,89] This fear response could have been responsible for the decreased feeding behavior. Non-human primate studies of VMH DBS using "floating" electrodes inserted into the third ventricle have shown reductions in both food intake and weight during acute (24 hours) and chronic (8–10 weeks) stimulation at 80 Hz.[92] Furthermore, use of smaller (1.5 mm versus 3.5 mm) electrode led to an additional 6% weight loss. It is well-known that accurate anatomical targeting of the hypothalamus is important in preventing spreading of the electric field and stimulation effects to neighboring regions, such as the antagonistic LH. In addition, the intermediate frequencies used in this intraventricular approach to VMH stimulation may be "sufficiently high to provoke certain inhibition in [the] orexigenic [LH]."[92]

The nucleus accumbens (NA) mediates the value of food regardless of appetite with studies suggesting it as another target for potential weight-related neuromodulation.[86,93,94] It is believed that food value may be related to similar mechanisms at the root of obsessive-compulsive disorder (OCD). High-frequency stimulation has been found to diminish symptoms of OCD in various rat models.[95,96] A significant body of evidence that feeding behavior may be influenced by palatability, irrespective of appetite exists. A recent study by Volkow et al. provided evidence that food and drug addictions may have the same underlying pathology as some disorders of obesity.[97] It was shown that drugs act on the reward and ancillary circuits, but all lead to dopamine increases in the nucleus accumbens.[97] Similarly, comparable dopaminergic responses are linked with food reward, and these mechanisms likely have a role in excessive food consumption and obesity.[97] Halpern et al. highlight a 90% increase in food consumption in mice when they were fed a high-fat diet as opposed to mice fed normal food.[50] The high fat diet is believed to be preferred due to reinforcing properties mediated by dopamine neurotransmission in the nucleus accumbens.[50,86,93,94] When rats underwent nucleus accumbens injections of dopamine antagonists, feeding was suppressed and the levels of dopamine release were proportional to amount ingested.[50,94,98] There is also a considerably greater amount of dopamine released in the nucleus accumbens of obese rats compared to lean rats in response to food stimuli.[50] Mice studies have also suggested D2 receptor modulation as the underlying effect of DBS of the nucleus accumbens shell (NAS). Furthermore, chronic NAS DBS was found to "acutely reduce caloric intake and induce weight loss".[23] Therefore, targeting the mesolimbic dopamine system to attenuate overconsumption contributing to obesity appears a viable candidate in DBS.

Thus, three neural targets are largely being considered for placement of electrodes for DBS in obesity: the hypothalamus (lateral or ventromedial) and the accumbens. The lateral and ventromedial hypothalamus are considered neural targets based on an assumption that feeding behavior can be modulated by inhibiting appetite sensation or driving satiety. The accumbens plays a central role in reward pathways and reinforcement learning. However, as a multifactorial and complex disease, obesity and its attempted control through DBS may be influenced by unforeseen mechanisms. For instance, hormonal axes, namely the hypothalamic-pituitary-adrenal axis, and inflammatory mediators may also be responsible for some of the effects of DBS in treating obesity. Rat studies have shown that DBS can alter levels of TNF-alpha, IFN-gamma, corticosterone, and IL-1-beta.[99] Therefore, future efforts in studying DBS in the treatment of obesity will need to consider a wide host of mechanisms and effectors.

Past and present human trials

A single 420 pound patient was treated for obesity by the use of DBS by Dr. Lozano at the University of Toronto. While the long-term weight loss was unsuccessful, the patient had very detailed memories triggered by the stimulation which has lead to more research in the use of DBS for Alzheimer's patients.[100]

Ohio State University is recruiting participants for a new study led by Dr. Rezai. The purpose of the study is to investigate the safety and efficacy of DBS as a treatment option for treatment-refractory obesity. Patients must be at least 24 months post Roux-en-Y gastric bypass surgery without evidence of a sustained improvement in BMI after gastric bypass surgery for at least 6 months. The primary outcome measure of the study was the percent of excess weight loss. All of the participants

who enroll in the study will undergo DBS implantation to an unspecified neural target. The study is estimated to end in January 2018.

In their study sponsored by the Allegheny Singer Research Institute, Whiting et al. have shown safety of continuous DBS of the lateral hypothalamic area (LHA) in three patients with intractable obesity.[101] After a mean follow-up of 35 months, no serious adverse effects were noted in addition to "promising weight loss trends" using monopolar stimulation rather than traditional settings in movement disorders programming.[101] Given the small size of the LHA, stimulation was applied at specific contacts which increase resting metabolism as determined by respiratory chamber studies. Though the study was not meant to gauge efficacy, two of the three patients showed "significant" weight loss with the other achieving a "stable weight."[101] It has been suggested that increased voltages (>5V) on the deepest contact centralized in the LHA may be responsible for minor side effects of LHA DBS, such as nausea, anxiety, and panic attacks. These side effects are believed to be due to current spread from the LHA into the VMH.[101]

Hospital do Coração is conducting a study on DBS of the VMH led by Dr. Gorgulho. Their team is a conducting a safety study of VMH DBS in the treatment of obese patients with body weight, composition, and food intake as secondary outcomes.

Future

Optogenetics

Optogenetics refers to "the integration of optics and genetics to achieve gain- or loss-of-function of well-defined events within specific cells of living tissue.[102] Optogenetics is currently being utilized by numerous scientists to probe how the brain works and have learned such information as which cells in the brain's reward pathway become hijacked by cocaine, as well as how deep brain stimulation relieves the symptoms of PD.[103] Williams et al. stated that "in the brief time since the introduction of optogenetics, this technique has found widespread use in neuroscience, including studies that range from expanding our understanding of basic neuroscience principles to investigating neuropsychiatric disorders such as Parkinson's disease."[104] Obesity presents another area to focus the use of optogenetic techniques. Gradinaur et al. stated that "optogenetics, in principle, could be used to systematically probe specific circuit elements with defined frequencies of true excitation or inhibition in freely behaving parkinsonian rodents."[105]

Optogenetics has been used to study obsessive-compulsive behavior in rats, a disorder which may be treated by DBS. In the study, a drop of water was dropped onto the rodents' noses after a tone was sounded due to the fact that OCD rats tend to over-groom.[106] While the normal mice learned that the water droplet would not come until after the tone was sounded, the OCD rats continued to groom immediately after the tone was sounded.[106] Through the use of optogenetics, the MIT team found that "these mutant animals fail to keep the firing of so-called medium spiny neurons (MSNs) in check, because they're apparently deficient in fast-striking striatal interneurons (FSIs)" and "demonstrated that normal inhibitory activity and normal grooming behavior could be restored almost immediately."[106] The researchers commented on the results saying that the study would allow them to hone in on the role of corticostriatal circuits in OCD pathology and treatment.[106]

Optogenetics is also being used to discover the brain's role in obesity. A recent study in optogenetics has found that stimulation of pro-opiomelanocortin (POMC) and agouti-related peptide (AGRP) neurons acutely regulates feeding behavior in mice.[104] It has been found that the POMC neurons play an important role in "maintaining normal feeding behavior and energy homeostasis."[107] When the POMC was activated by light, it resulted in a frequency-dependent decrease in food intake, which required downstream melanocortin receptor activity and light activation of AGRP neurons, and resulted in an acute, frequency-dependent increase in food intake that was independent of melanocortin signaling.[104] These findings support the previously identified role of GABA in mediating acute starvation, and recent work also found that selective deletion of the vesicular GABA transporter (Vgat) from AGRP neurons using *Cre-loxP* resulted in mice that are lean and resistant to high-fat diet-induced obesity with no major effect on food intake.[104]

In addition to studies of the POMC and AGRP using optogenetics to understand their link to obesity, a study by Calu et al. recently employed optogenetics to evaluate inhibition of dorsal medial prefrontal cortex (mPFC) and its effects on stress-induced food seeking in rats.[22] It was determined that intracranial light delivery disrupted mPFC neural activity that plays a role in stress-induced food seeking in rats.[22] Further research by Thanos et al. has shown that positron emission tomography can be employed as an adjunct to optogenetic stimulation to monitor connectivity in the awake rodent brain.[108] The research team used this method to evaluate changes in regional brain glucose metabolism in response to optogenetic stimulation of the NAc.[108]

Thus, as a robust research technique with proven use in the study of neural disorders, optogenetics will likely become a mainstay of obesity research. Understanding the mechanisms underlying disorders of obesity is essential to developing targeted therapies, such as DBS and stem-cell therapy. With explosive growth across the research spectrum on obesity, it is imperative to maintain research momentum and focus on developing and refining the neurosurgical approaches and techniques in the potential treatment of obesity.

Conclusion

With the large impact of obesity both on the health of individuals and the healthcare system, novel therapies targeting underlying pathology must be developed and explored. Current methods of obesity management can have several drawbacks. Several investigations using neuromodulation and deep brain stimulation (DBS) have yielded encouraging results, warranting further investigation the treatment of humans. Currently, three human trials (Table 1) are ongoing and will likely represent the fullest evidence on the role of DBS in the human treatment of obesity at the time of their respective completions. In addition to DBS, other methods such as optogenetic may be employed in the future as the ability to selectively modulate subpopulations of neurons. With growing advances in uncovering the neural and homeostatic mechanisms underlying disorders of obesity, novel treatments including neuromodulation and DBS will hopefully emerge as effective tools in armamentarium against these disorders.

Acknowledgments

The authors would like to thank Jean Laboe, Gray McClatchy, Mallory Roberts, Semmes-Murphey, and the Restorative

Table 1

Author	Clinical Investigations of DBS in Obesity		
	Target	**Primary Outcome [time frame]** **(n = expected enrollment)**	**Completion**
Rezai (2012)	Unknown	Percentage of excess weight loss [2 years] (n = 5)	Jan. 2018
Whiting (2013)	LHA	Weight loss [1 year] Change in metabolic rate [1 week] (n = 3)	Dec. 2015
Gorgulho (2014)	VMH	Identification of possible adverse events related to stimulation [1 year] (n = 6)	Apr. 2017
Luming (2014)	Unknown	Body weight [1 year] (n = 8)	Dec. 2018
Damiani (2014)	HA	Waist and mid−upper arm circumference [6 months] Resting energy expenditure [6 months] Body mass index [6 months] Number of participants with adverse events as a measure of safety and tolerability [3 and 6 months] (n = 6)	Oct. 2016

Neuroscience Foundation for their assistance.

Authorship contributions

Rahul Kumar, Constance V Simpson, Clifford A Froelich, Brandon C Baughman, Andrew J Gienapp, Karl A Sillay contributed equally to prepare the manuscript.

The article complies with International Committee of Medical Journal editor's uniform requirements for manuscript.

Competing interests: None.
Source of Funding: None.

Received Date: 7 October 2014; Revised Date: 27 February 2014; Accepted Date: 18 March 2015

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