Deep brain stimulation in the treatment of obesity

A review

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Obesity is a growing global health problem frequently intractable to current treatment options. Recent evidence suggests that deep brain stimulation (DBS) may be effective and safe in the management of various, refractory neuropsychiatric disorders, including obesity. The authors review the literature implicating various neural regions in the pathophysiology of obesity, as well as the evidence supporting these regions as targets for DBS, in order to explore the therapeutic promise of DBS in obesity.

The lateral hypothalamus and ventromedial hypothalamus are the appetite and satiety centers in the brain, respectively. Substantial data support targeting these regions with DBS for the purpose of appetite suppression and weight loss. However, reward sensation associated with highly caloric food has been implicated in overconsumption as well as obesity, and may in part explain the failure rates of conservative management and bariatric surgery. Thus, regions of the brain’s reward circuitry, such as the nucleus accumbens, are promising alternatives for DBS in obesity control.

The authors conclude that deep brain stimulation should be strongly considered as a promising therapeutic option for patients suffering from refractory obesity. (DOI: 10.3171/JNS/2008/109/10/0625)

Key Words • deep brain stimulation • hypothalamus • obesity • nucleus accumbens • reward

HIGH-FREQUENCY deep brain stimulation is the treatment of choice for well-selected patients with medically refractory PD. Deep brain stimulation provides significant symptomatic improvement in Parkinsonism in both animal and human studies,5,6 and at high frequencies (130–160 Hz) mimics the clinical effects of tissue lesioning.6,9,11 In contrast to stereotactic lesions, however, DBS provides the added benefit of reversibility and titratability,28 as well as a very low risk of complications.27,118 Excessive or aberrant output from the STN, currently the most favored target for DBS in PD, is postulated to play a crucial role in the pathophysiology of this disease.1 Given the remarkable improvement in Parkinsonism, high-frequency STN DBS appears to induce functional inhibition of this region.9 Indeed, some have shown that high-frequency STN DBS has an inhibitory effect on STN single unit activity.111 There is evidence that the primary effect of DBS is related to the frequency of stimulation,58 but the precise mechanism of action remains unclear, whether it be excitatory59 or inhibitory in nature.60,73,111

The success of DBS in relieving Parkinsonism has led to its application in multiple neurological diseases and more recently to treatment-resistant psychiatric conditions.59 The purpose of this paper is to motivate the neurosurgical community to consider DBS for obesity control. Obesity is a chronic disease with well-substantiated neuropsychiatric underpinnings. Appetite and satiety centers in the brain have been well-documented93 and thus represent primary areas for investigation.21,97,98 Many studies have indicated that the reward sensation associated with food intake is also largely implicated in the pathophysiology of obesity.7,44,123 In support of this concept, it was recently proposed that obesity be included as a mental disorder in the next (fifth) edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).119 Below, we review 3 potential neural targets for DBS believed to be involved in the excessive consumption of food in obesity.

Abbreviations used in this paper: BMI = body mass index; DBS = deep brain stimulation; GABA = γ-aminobutyric acid; LH = lateral hypothalamus; MCH = melanin-concentrating hormone; NAc = nucleus accumbens; OCD = obsessive-compulsive disorder; PD = Parkinson disease; 6-OHDA = 6-hydroxydopamine; STN = subthalamic nucleus; VMH = ventromedial hypothalamus; VP = ventral pallidum.
Background

Obesity, defined as a BMI > 30 kg/m², affects more than 30% of adult Americans and over 300 million people worldwide. Annual health care costs are estimated at nearly 100 billion dollars in the US alone. Obesity is associated with diminished quality of life, high risk of comorbidities, and the reduction of life expectancy by 15–20 years. Pharmacological therapies and behavioral techniques are rarely effective due to high relapse rates, explaining the more than 10-fold increase in bariatric surgeries performed over the past 8 years. Although mean weight loss after bariatric surgery ranges from ~20 to ~60%, with concomitant improvement in morbidity, complications occur in 15–55% of patients, and the perioperative mortality rate is ~1.5% even in experienced centers. Furthermore, significant weight gain occurs after the nadir weight is reached, approximately 2 years postoperatively. The failure rate due to noncompliant eating patterns in patients followed up for 10 years is as high as 20% for obese and 40% for super-obese (BMI > 50 kg/m²) patients. One follow-up study reported recurrent binge eating in 46% of patients who had undergone bariatric surgery. Thus, consideration of the neuropsychiatric basis of obesity may help explain these refractory eating habits and the significant surgical failure rate.

Deep Brain Stimulation of the Hypothalamus: Rationale

Overconsumption of calorically dense foods is a likely contributor to the rapidly progressing epidemic of obesity. Body weight results at least in part from a balance between food intake and energy expenditure, and obesity is due to an imbalance between energy input and output. The hypothalamus has been shown to be integral in maintaining this energy homeostasis. Specifically, food intake is at least in part controlled by a feeding center in the lateral hypothalamus and a satiety center in the ventromedial hypothalamus. We will discuss these regions below as potential targets of DBS.

The Lateral Hypothalamus

The LH has long been implicated in feeding behavior and energy expenditure. Its role in appetite regulation was well described in early studies of LH lesioning, which induced leanness. This impact on appetite can be partially explained by peptides expressed in the LH, such as MCH and orexins (also known as hypocretins), as well as orexin receptors. Indeed, MCH−/− mice have been shown to be lean and hypophagic, and mice with overexpression of MCH, obese and insulin-resistant. Chronic administration of an orally active MCH receptor antagonist decreased food intake, body weight, and adiposity in rodent obesity models. Injections of orexins into the LH increased feeding behavior and enhanced arousal. Indeed, upregulated expression of the orexin gene has been demonstrated in fasting rats. Other peptides shown to be critical regulators of feeding behavior and body weight include neuropeptide Y and agouti-related protein, which densely project to the LH.

Anatomy of the LH. The LH is a fairly large region of the hypothalamus, measuring approximately 6 × 5 × 3.5 mm in the largest dimensions laterally, anteroposteriorly, and dorsoventrally, respectively. The hypothalamus comprises a large number of distinct nuclei, and thus has many physiological functions not limited to appetite control, including body temperature regulation, sexual activity, reproductive endocrinology, and the fight-or-flight response. The effect of stimulating any adjacent hypothalamic region is thus associated with altering these physiological responses. Other neural structures located adjacent to the LH include the fornix and the optic nerve. Portions of the LH are just inferior to the fornix and directly superior and posterior to the optic nerve and chiasm, further complicating the targeting of this nucleus with DBS.

Stereotaxy and Stimulation of the LH. Nevertheless, targeting the hypothalamus with DBS has already been shown to be safe and potentially effective in managing patients with intractable chronic cluster headache. Furthermore, stereotactic electrocoagulation of the LH in obese humans was performed safely more than 30 years ago, resulting in significant, although transient, appetite suppression and slight weight reduction in 3 patients. Given this evidence, it was recently proposed that chronic bilateral DBS of the LH at high frequencies would mimic the results of lesion studies, just as STN DBS for PD mirrors the effect of subthalamotomy.

To test this hypothesis, Sani et al. stereotactically implanted electrodes bilaterally into the rat LH. Half of the implanted animals underwent high-frequency stimulation (stimulation parameters: 2.0 V, pulse width 100 msec, frequency 180–200 Hz), while the other half were left unstimulated. On postoperative Day 24, stimulation was associated with a mean loss of 13.8% (p < 0.001). Interestingly, no difference in food intake was found between groups. Thus, the authors concluded that the stimulation-induced weight loss seen in the stimulated group was secondary to metabolic change, although no measurements of individual animals’ metabolic profiles were made. In contrast to high frequency LH stimulation, LH stimulation at lower frequencies (50–100 Hz) elicited feeding in earlier studies. Hypothalamic stimulation at 50 Hz resulted in immediate and sustained hoarding of food in satiated rats. Similarly, unilateral LH stimulation resulted in increased feeding in cats and induced rhythmic oral activity in rabbits. Other effects of LH stimulation included exploration, as well as escape and attack behaviors associated with autonomic changes with increases in stimulation strength. These findings are consistent with those observed in canine LH stimulation at 100 Hz, which induced increases in coronary flow, blood pressure, heart rate, and other sympathetic responses. Importantly, such changes were also associated with cardiac arrhythmias.

Ventromedial Hypothalamus

Like the LH, the VMH has also been implicated in...
Deep brain stimulation in the treatment of obesity

 alimentation and the maintenance of energy homeostasis. Lesions of the VMH have been shown to induce weight gain in obese animals, and lesions resulted in substantially more carcass lipid and hyperinsulinemia in rats even if pair-fed with sham-lesioned controls, suggesting a metabolic bias toward obesity.

Anatomy of the VMH. There are various challenges to surgically targeting the VMH that need to be considered. The VMH is a small bilobed target in the vertical axis measuring approximately $2 \times 3 \times 5$ mm in the largest dimensions (Fig. 2). Although found slightly inferior to the anterior commissure in the anteroposterior plane, which may facilitate accurate localization, an intraventricular trajectory may be required given such a medial location of the VMH. Furthermore, the VMH is bounded by the optic nerve anteriorly and the mammillary body posteriorly. Deep brain stimulation of the mammillary bodies is currently under investigation as a potential target for seizure control. Due to their connections to the circuit of Papez, and given substantial evidence pointing to an important role of this circuitry in seizure propagation and expression, it is possible that the spread of stimulation from this area may induce seizures. The VMH is located just inferior and medial to the LH. The hypothalamic nuclei are well-known to be largely interconnected, and thus it is conceivable that stimulation spread to the LH may directly antagonize the effect of low-frequency DBS of the VMH.

Stereotaxy and Stimulation of the VMH. Electrical stimulation of the VMH has been reported, and stimulation at low frequencies (60–100 Hz) inhibited feeding in hungry rats, and eating resumed once the current was terminated. In goats, VMH stimulation at low frequencies (for example, 50 Hz) inhibited feeding as well. Other effects of stimulation included fear, aversion, restlessness, and attempts at escape, which may have partially accounted for the decreased feeding behavior in these animals. These effects may be related to autonomic changes due to VMH stimulation, which has been shown to increase metabolic rate. This increase in energy expenditure was associated with increased fat oxidation given a concomitant

Fig. 1. A sagittal section depicting the lateral hypothalamus adjacent to the optic nerve. The fornix is not well visualized in this section. *lateral hypothalamus (L); #optic nerve (II); ^ nucleus accumbens (Fu.st). From Schaltenbrand G, Warren W: Atlas for Stereotaxy of the Human Brain. Stuttgart: Thieme, 1977. Reprinted, with the addition of *, #, and ^, by permission.
drop in the respiratory quotient. Thus, heightened metabolism induced by VMH stimulation was sustained by utilization of fat stores, most likely due to noradrenergic turnover. Recently, VMH DBS at 4 different frequencies (25, 50, 75, and 100 Hz) in a rat was shown by means of indirect calorimetry to result in an increase in metabolism. There was a trend toward an indirect relationship between energy expenditure and increasing frequencies, suggesting that lower frequencies of stimulation drive VMH activity, while higher frequencies may have lesioning effects (A. L. Benabid, 2006, personal communication). These findings are consistent with a frequency-dependent effect of stimulation.

Deep Brain Stimulation of the Nucleus Accumbens: Rationale

Physiological states associated with energy balance, such as hunger and satiety, are strong determinants of feeding behavior. The above data support the idea that DBS of the LH or VMH at various frequencies may be able to modulate the neural regions associated with energy homeostasis. However, the assumption that feeding behavior in obesity can be effectively modulated by inhibiting appetite sensation or driving satiety may not be correct. In fact, there is a significant amount of evidence that feeding behavior is strongly influenced by palatability, or the reinforcing value of food, irrespective of appetite. For example, there is a 90% increase in food intake in mice fed a high-fat diet compared with their consumption when fed normal house chow. Such a palatable diet (45 kcal % fat) is preferred to standard house chow because of reinforcing properties believed to be mediated largely in the NAc.

Anatomy of the NAc

The NAc is a ventral striatal region located immediately inferior to the anterior limb of the internal capsule. As a DBS target, the NAc is very similar to the STN. It measures approximately 8 × 6 × 6 mm in the largest dimensions, thus making it only slightly larger than the STN, which is approximately 8 × 4 × 4 mm. The center of the NAc is located just about 3 mm anterior to the anterior commissure and approximately 6 mm lateral from the midline. To target the NAc, a trajectory can be taken just lateral to the ventricle and through the caudate nucleus; this approach has been well tolerated in reports of DBS for OCD and depression as well as DBS of the globus pallidus in PD. Certainly some cognitive deficits such as memory impairment are possible due to microtrauma to the caudate, but patients without preoperative dementia are less at risk. Some of the other nearby structures that may compromise safe targeting of the NAc include the anterior cerebral artery located just inferiorly, as well as the optic nerve found inferomedially.

The NAc is divided into 2 subregions, core and shell, based on cytoarchitectonic and neurotransmitter characteristics, as well as differences in the afferent and efferent

Fig. 2. A sagittal section depicting the ventromedial hypothalamus bounded anteriorly by the optic nerve and posteriorly by the ipsilateral mammillary body. *ventromedial hypothalamus (Vm); #mammillary body (M.m); +optic chiasm (Ch. II); ^anterior commissure (Cm.a). From Schaltenbrand G, Warren W: Atlas for Stereotomy of the Human Brain. Stuttgart: Thieme, 1977. Reprinted, with the addition of *, #, +, and ^, by permission.
connections. Anatomical tracing studies have shown that the core region connects extensively to extrapyramidal motor structures, such as the VP, the STN, and the substantia nigra. The shell region is believed to be confined to the ventromedial margins of the NAc and is embedded in a complex mesocorticolimbic circuit providing control of reward sensitivity. The NAc shell receives dopaminergic input from the ventral tegmental area, as well as afferents from the amygdala, hippocampus, prefrontal cortex, and thalamus. Efferent output projects mainly to the VP, as well as the thalamus and cingulate cortex. Recent work has implicated simultaneous involvement of the NAc shell and the VP in favorable reactions to taste in rodents (“liking”), such as tongue protrusions, whereas the NAc shell exerted independent control of food intake (“wanting”). Thus, output from the NAc shell may in part bypass the VP and project directly to the LH, suggesting that communication exists between the reward processing and feeding centers in the brain. Significant debate exists as to whether electrical stimulation of the LH alone induces rewarding sensations.

The NAc and Food Reward

The NAc is integral to the modulation of reward sensation shown to be associated with palatability of foods. Results from single-unit recordings from the NAc demonstrated that in a subset of neurons, firing rates varied significantly as a function of sucrose concentration. Furthermore, palatable food such as chow with high fat content (45 kcal % fat) was preferred to standard house chow because of reinforcing properties believed to be mediated in part by dopamine neurotransmission in the NAc. Indeed, NAc injections of dopamine antagonists suppressed feeding.
Furthermore, the levels of dopamine release were proportional to the amount ingested,\(^{66}\) and there is a significantly greater amount of dopamine released in the NAc of obese rats relative to lean rats in response to food stimuli.\(^{74,123}\)

Sensitivity to reward can vary from one person to another, but those individuals with more frequent and intense food cravings are more likely to be obese.\(^{8}\) Mice withdrawn from a highly palatable diet will endure an aversive environment to obtain preferred foods, and show a significant increase in expression of corticotropin-releasing factor associated with a stress state.\(^{110}\) Thus, we support the recent suggestion that at least some forms of obesity may be driven by an excessive motivational drive for food intake that overrides the hypothalamic circuitry normally involved in regulating food consumption.\(^{77}\) In fact, in addition to projections from the NAc to the LH,\(^{129}\) there are projections from the LH to the NAc,\(^{85}\) suggesting that signals of internal homeostasis may be relevant in modulating food reward.\(^{67}\) Studies in animal models of obesity, however, have demonstrated altered expression of many of the peptides involved in feeding behavior at the level of the LH, resulting in increased hunger for highly palatable food.\(^{57,48,125}\) Thus, hypothalamic control of intake may be impaired in obesity.\(^{47,125}\) It is conceivable that significant relapse and failure rates may be at least in part a result of a dysregulated reward system, leading to our experience to date with conservative measures and bariatric surgery.

The idea that dopamine plays a dominant role in modulating palatability has been recently called into question. Multiple neurotransmitters have been implicated in accumbal reward processes, some with potent effects on intake of high-fat diets. Injections of opioid receptor agonists into the NAc induce hyperphagia and a preference for fat consumption that was independent of dopamine neurotransmission and was blocked by co-treatment with naltrexone.\(^{79,122,131}\) The majority of corticobasal inputs to the NAc use an excitatory amino acid as their neurotransmitter. Indeed, blockade of \(\alpha\)-amino-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in the shell subregion of the NAc resulted in pronounced feeding.\(^{67}\) However, the majority of the cells in the NAc are GABAergic and therefore inhibitory, both locally and at their projection targets. In addition, there is also significant cholinergic neuromodulation of these cells. Thus, within the NAc is an extensive network of multiple neurotransmitter systems, some or all of which may be intimately involved in food reward sensation. Further study, including detailed computational modeling of the modulation of this network, will be necessary to determine the effect of DBS on specific components of this network.\(^{78,124}\)

**Evidence From Lesion Studies**

Destruction of the dopaminergic neuron terminals projecting to the NAc with a stereotactic injection of the neurotoxin 6-OHDA results in dopamine depletion in this region. The 6-OHDA lesions of NAc resulted in significant attenuation of food hoarding and weight loss in rats,\(^{53}\) and administration of levodopa restored normal hoarding behavior. While lesioning effects of DBS at high frequencies are well documented, it is difficult to predict whether DBS could mimic the effects of 6-OHDA lesions given the variety of neurotransmitter systems involved in the NAc and the differentiated anatomical projections of the accumbal subregions. N-methyl-D-aspartate lesions of the NAc core induced weight loss in rats, whereas the shell-lesion group gained weight.\(^{56}\) The authors of the study argued that the loss of weight in the core group was due to changes in motor function given the core's connections to the extrapyramidal system.\(^{29}\) It is conceivable that the core and shell have opposing effects on ingestive behavior, explaining the lack of any change in weight with large, nonspecific excitotoxic lesions encompassing both regions of the NAc. Given the functional dissociation within the NAc, further investigation is necessary to determine if modulation of reward sensation is possible with DBS, what region of the NAc is most appropriate to target, and what frequencies are necessary to obtain the desired effects. Furthermore, given the proximity of the NAc to various structures, including the globus pallidus, anterior limb of the internal capsule, VP, and caudate, rigorous stereotactic methods are necessary to ensure precise placement of the permanent electrode.

**Evidence From Neurofunctional Imaging**

Functional MR imaging studies have demonstrated activation of striatal reward areas during exposure to a high-fat stimulus, particularly in those patients with enhanced reward sensitivity.\(^{8}\) A hyperfunctioning region is known to be susceptible to the effects of DBS given the lesioning effect of high frequency stimulation of the overactive STN in PD. Positron emission tomography and autoradiographic studies have shown reductions in striatal D\(_2\) receptors, as well as elevated levels of the dopamine transporter.\(^{49,120}\) It follows that lower extracellular levels of dopamine have been found in the NAc of obese mice relative to the levels found in obesity-resistant mice, a difference that may be due to enhanced clearance.\(^{49,102}\) While heightened reward is evident in obesity associated with increased levels of accumbal dopamine release following exposure to a food stimulus, this sensation may be short-lived due to a decreased sensitivity of dopaminergic reward circuits. Thus, a need to compensate with food reinforcers in conjunction with an increased stress response to palatable food restriction may be the underlying causes for the reported high rates of recurrent binge eating and surgical failures in bariatric patients.

**Evidence From NAc Stimulation Studies**

Electrical stimulation of the NAc has been performed in rats.\(^{53,72,88}\) Multiple effects of NAc stimulation have been reported in rats, including increased sniffing, excitement, and even aggression, which were all observed at a stimulation frequency of 60 Hz.\(^{45}\) These findings have been replicated in cats,\(^{26}\) although no such effects were noted in rhesus monkeys.\(^{120}\) No consistent documentation of the response of feeding behavior to NAc DBS has been reported,\(^{49,117}\) but none of these studies included overweight or obese animals. Some evidence for the potential of NAc DBS in obesity control can be derived from its success in relieving symptoms of OCD.\(^{37}\)
Deep brain stimulation in the treatment of obesity

Reward Circuitry DBS in Other Treatment-Resistant Conditions

Bilateral NAc stimulation in a rat model of OCD has shown promise for the use of this modality in humans. Electrodes were implanted bilaterally using stereotactic coordinates similar to those previously documented. Although further investigation is required, high-frequency stimulation appeared to diminish OCD symptoms in various rat models of OCD. One explanation for these findings, as well as for the success of NAc DBS in patients with OCD, comes from a recent study in which high-frequency NAc stimulation at 130 Hz reduced the firing rate of orbitofrontal cortex neurons in rats. Indeed, metabolic hyperactivity in this region has been consistently associated with OCD symptoms.

A trial of DBS of the ventral capsule/ventral striatum site, a region that encompasses the NAc, in 10 OCD patients with long-term follow-up demonstrated a 36% decrease in disease severity and nearly a 50% improvement in global functioning. This region has been consistently implicated in OCD given its central position between the amygdala, basal ganglia, thalamus, and prefrontal cortex, all regions known to be involved in this disorder. Furthermore, the ventral striatum, and particularly the NAc, has been shown to respond abnormally to pleasurable stimuli in patients suffering from severe depression. Deep brain stimulation of the NAc provided a 42% improvement in depression severity in one study. These reports not only provide encouraging evidence for the therapeutic effect and safety of DBS, but also for its promise in modulating neural regions implicated in reward sensation associated with the pathophysiology of obesity.

Conclusions

Appetite modulation in conjunction with enhancement of the metabolic rate by means of hypothalamic lesions has been widely documented in animal models and even in humans. It appears that these effects can be reproduced by DBS, and the titratability and reversibility of this procedure, in addition to its well-established safety profile, make hypothalamic DBS an appealing option for obesity treatment. Given that palatability significantly increases food intake, however, suppressing appetite and increasing energy expenditure may prove to be inadequate, especially over the long term. Indeed, electrocoagulation of the LH in humans only transiently suppressed appetite and provided minimal weight loss. Chronic NAc DBS may allow us to modulate reward sensation and dietary preferences by interacting with the systems known to be implicated in the reinforcing properties of food. Inhibition of food reward may provide significant weight reduction over time and effectively lessen relapse rates associated with conservative and surgical treatments. Moreover, stimulation frequency may be titratable to adequate inhibition of food preference and overconsumption. Deep brain stimulation of the NAc region has already been established as safe in the treatment of patients with refractory OCD and depression. Thus, we need to consider the potential role of DBS in attenuating the reinforcing properties of highly palatable foods that have clearly contributed to the worldwide epidemic of obesity. Furthermore, established animal models of obesity exist and should be used in studies measuring the effects of DBS on weight loss.

Disclaimer

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Deep brain stimulation in the treatment of obesity


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