Review Article

pISSN 1738-6217 • eISSN 2765-6608

J Korean Stereotact Neurosurg 2021;17(1):14-23
<https://doi.org/10.52662/jksfn.2021.00059>

Received: May 28, 2021

Accepted: June 14, 2021

Address for correspondence:

Jong Hyun Kim, MD

Department of Neurosurgery, Korea
University Guro Hospital, 148 Gurodong-
ro, Guro-gu, Seoul 08308, Korea
Tel: +82-2-2626-1178

Fax: +82-2-863-1684

E-mail: jhkimns@gmail.com

ORCID: <https://orcid.org/0000-0002-8300-9486>

Deep brain stimulation for obesity or binge-eating behavior: an overview

Haewon Roh, MD^{1,2,3}, Jong Hyun Kim, MD³

¹Department of Neurosurgery, Armed Forces Capital Hospital, Seongnam, Korea

²Trauma Center, Armed Forces Capital Hospital, Seongnam, Korea

³Department of Neurosurgery, Korea University Guro Hospital, Seoul, Korea

Obesity is a global epidemic, leading to huge burdens on both individuals and society. Non-invasive approaches, such as lifestyle modification or medication, have been regarded as a first-line treatment. However, these have shown only limited success. For patients with medically refractory obesity, surgical options (e.g., gastric bypass or sleeve gastrectomy) have been attempted, although they also have a high rate of recurrence and may cause nutritional complications. Beyond body weight itself or peripheral systems that control body weight, recent evidence has suggested that obesity or binge eating behavior is closely associated with the hedonic properties of highly palatable food, which is mediated by the dopamine system in the brain reward circuit. In this context, deep brain stimulation for medically refractory obese patients has gained attention as a novel treatment that challenges the traditional paradigm of treatment for obesity. In this review article, we summarize the evidence from animal experiments and human studies dealing with deep brain stimulation for obesity or binge-eating disorder. We also explain the theoretical background of obesity as it relates to the reward circuit and introduce current ongoing human trials for obesity.

KEY WORDS: Binge eating, Deep brain stimulation, Hypothalamus, Nucleus accumbens, Obesity, Reward

INTRODUCTION

Obesity is an increasingly prevalent condition, especially in developed countries, causing 3.4 million deaths per year worldwide [1]. According to a global national survey in 2014, there has been a 10% increase in overweight populations (body mass index [BMI] > 25 kg/m²) between 1980 and 2013. Furthermore, the number of children with overweight has been rapidly increasing up to 23% in developed countries, indicating a significant health concern [1,2]. Given the numerous comorbidities of obesity such as osteoarthritis, stroke, certain types of cancer, financial burdens affecting individuals and whole societies are also to be expected. The medical costs associated with obesity are estimated to have risen to \$147 billion from \$78.5 over the span of 10 years [2-4]. In the United States, if the current increase in the obese population continues, all adult Americans will be overweight by the year 2048 [5].

There are only limited treatment options available for obese patients. The current available anti-obesity drugs can be divided into two classes; central acting

and peripheral acting. However, owing to a number of factors including misuse of the agents, abusive commercialization of pharmaceutical galenic preparations and less emphasis on classic treatment counselling, the long-term effect of these anti-treatment drugs is controversial yet. Furthermore, the vast majority of these focus on body weight alone, leading to a high rate of treatment failure [6].

Bariatric surgery is usually reserved for patients with a BMI > 40 kg/m² or a BMI > 35 kg/m² in the presence of significant comorbidities and most commonly involves laparoscopic gastric banding or laparoscopic Roux-en-Y gastric bypass [6]. Although bariatric surgeries have been regarded as a primary weight loss strategy for medically refractory obese patients, it has various limitations, including a high incidence of both recurrence and complications [6,7]. Even if bariatric surgery leads to weight loss and improvement in morbidity reduction, considerable weight gain often recurs approximately 2 years after surgery with a failure rate of up to 46% [2]. Moreover, as Roux-en-Y gastric bypass surgery enables the bypass of 95% of the stomach, the entire duodenum, and 150 cm of the jejunum, the risk of micronutrient deficiency, such as in calcium and various minerals, is high and patients need to be treated with life-long supplementation [2]. Considering that the fundamental cause of obesity or binge eating behavior is related to psychiatric disease linked to the reward center of the brain, the limitation of gastric bypass surgery is apparent. The primary focus should be put on a more fundamental treatment that targets the cerebral networks of the reward system [2,6,7].

The present study has two purposes: 1) to review findings from the recent literature on deep brain stimulation (DBS) for obesity or binge eating behavior and 2) to introduce a persuasive theoretical hypothesis by which DBS works for obesity. It is not meant to be an extensive review of obesity, but rather a summary of contemporary theories and practical information, which stem from animal experiments, human studies, and ongoing human trials.

REWARD SYSTEM AND KEY STRUCTURES

Many cerebral regions are known to be involved in the mechanism of eating disorders [8]. It is widely accepted that there is “bottom-up” emotion generation emerging from subcortical, limbic neural structures and “top-down” emotion regulation by dorsal prefrontal cortical regions. An imbalance between these can result in abnormal behavior. Increased activity of the “bottom-up” stream, which means increased activity in emotion generation to external stimuli, may contribute to altered reward processing such as binge eating behavior [8,9]. Key neurotransmitter in this reward system is dopamine. The regulation of eating behavior or addiction is modulated by multiple peripheral and central systems

that deliver information to the dopamine center in the reward system [10-15]. The brain dopamine reward circuitry increases the probability that behaviors that activate it (food consumption) will be repeated when encountering the same reinforcer [15]. Hence, with repeated access to highly palatable food, some individuals may exceed the inhibitory process that signals satiety and begin to compulsively consume large amounts of food, frequently leading to repulsion in this behavior [2,11-15]. Three cerebral structures have been identified through lesioning studies to have a critical role in the reward circuit, leading to excessive food consumption: the lateral hypothalamus (LH), nucleus accumbens (NA), and ventral tegmental area (VTA) [2,7]. We will discuss the individual structures in the next section.

THE LATERAL HYPOTHALAMUS, NUCLEUS ACCUMBENS, VENTRAL TEGMENTAL AREA

The LH has been shown to mediate appetitive and feeding-related behaviors [12]. GABAergic neurons from the LH disinhibit dopamine neurons in the VTA and result in increased dopamine levels in the NA, leading to motivated behaviors (Fig. 1A) [14]. As a response to this increase in dopamine levels in the NA, the lateral NA predominantly disinhibits dopamine neurons in the lateral VTA, increasing dopamine levels in the NA (indirect feedback). However, the medial GABAergic inhibitory pathway from the NA to dopamine neurons in the medial VTA is much stronger (direct feedback), thus resulting in the net inhibition of VTA dopaminergic neurons (Fig. 1B) and consequently leading to a decreased dopamine concentration in the NA [16]. This feedback loop between these three structures (LH-VTA-NA) has been widely accepted as a fundamental background in reward systems, especially for eating behaviors [16].

DEEP BRAIN STIMULATION TARGETS IN ANIMAL EXPERIMENTS

Previous findings from animal studies on DBS for obesity or binge eating behavior are summarized in Table 1 [11,17-24]. Many studies have confirmed that the NA can be divided into two substructures, core and shell, which both mediate reward cue-driven consumptive behaviors [25-27]. However, the effect of DBS in the NA core and shell is dissociable based on the aspects of motivated behavior, “wanting” vs. “liking [28].” In a study to identify the differences in the effect on eating behavior between the two, stimulation of the NA core before binge eating (not during binge eating) induced a decrease in high-fat food intake, whereas stimulation of the NA shell during binge eating (not

Fig. 1. (A) Model representing the GABAergic projection from the LH onto GABA cells in the ventral tegmental area (VTA). Activation of the GABAergic LH-VTA projection leads to disinhibition of VTA dopamine (DA) neurons, thereby increasing DA release in the nucleus accumbens (NA). (B) Model representing direct and indirect feedback loops in the VTA and NA. Since the MED GABAergic inhibitory pathway in the NA to DA neurons in the MED VTA is much stronger (direct feedback) than the LAT NA to VTA pathway, the activation of the NA to VTA GABAergic pathway results in net inhibition of VTA dopaminergic neurons. GABA_A represents GABA receptor subtype A. MED: medial, LAT: lateral.

before) affected behavior [20]. Given that “wanting” is responsible for cravings (i.e., in anticipation before binge eating) and “liking” is the pleasurable feeling of using the potentially incentive substance (during binge eating), it is plausible that NA core stimulation might modulate the process of “wanting” and that the NA shell might be involved in the process of “liking.” The NA shell can further be divided into two sub-nuclei, based on their distinct functional role in food intake (medial NA shell vs. lateral NA shell) [21]. However, even if the same target of the NA shell is stimulated, conflicting results have also been reported: increased food intake in normal-weight rats following DBS of the medial NA shell but a decrease in food intake in obese rats [21,24,29]. Despite this inconsistency, these results indicate that the NA shell is associated with food intake and body weight, further highlighting the NA shell as an interesting target of DBS to modulate eating behavior [21]. As a potential mechanism by which DBS on the NA shell may modulate such behavior, Halpern et al. [11] suggested the hypothesis that DBS in the NA shell may lead to local release of dopamine, which in turn binds to dopamine-2-receptor (D2R), blocking the hedonic valence of the high-fat diet [24,30]. However, the efficacy was found to diminish with continuous stimulation. In addition, in some cases of behavioral context changes (e.g., other behaviors of palatable food consumption such as diet-induced obesity or a binge

relapse model), DBS of the NA shell appears to be less effective [11,18]. With regard to this failure in a relapse model, Doucette et al. postulated that the decreased efficacy of NA DBS may stem from an increased motivation to consume the palatable food, which had been proven in many studies showing that “incubation of craving” during prolonged abstinence can drive a more enhanced response to specific material when animals are re-exposed to previously associated cues [18,31,32]. In addition, a recent study by Casquero-Veiga et al. [17] supported a new hypothesis that NA DBS can also decrease metabolism in the striatum and thalamus, suggesting that this induced hypometabolism may alleviate the hyperactivated status of the striatum and thalamus, which is a characteristic pathology in obesity.

Given that the LH is an anatomical hub linking the arcuate nucleus in the ventromedial hypothalamus (VMH) (in which various peripheral signals are delivered throughout fenestrated capillaries) and multiple limbic structures, its effect on obesity or binge eating disorder has received significant attention [22]. Sani et al. [22] reported that stimulation of the LH leads to weight loss without any change in food or water intake, suggesting that LH stimulation may induce metabolic changes rather than modulate eating behavior. However, in other studies, LH stimulation showed different efficacies between diet-induced obese rats and normal rats [24]. Previ-

Table 1. Summary of findings from previous animal experiments on DBS in obesity or binge eating models

Study	Animal	Sample size	Disease	Devices (1. Electrode/2. Generator/3. Output monitor)	Target+coordinates (mm)	Parameter	Outcome measurement	Conclusion	Comments
Doucette et al. [18] (2015)	Sprague-Dawley rats	12 (DBS) vs. 6 (control)	BE	1. Plastics, Roanoke 2. S11, Grass instruments 3. PSIU6, Grass Technologies	NA core, Bilateral; 1.2 (A), 2.8 (L), 7.6 (V) 4° from bregma	Monophasic, continuous 60 µsec, 50 Hz, 150 µA	1. Binge size change (%)	1. Reduction of binge size in DBS group	Relapse model; No significant improvement in binge size
Halpern et al. [11] (2013)	Mice (male, C57BL/6J)	NA shell (n = 12) vs. dorsal striatum (n = 14) vs. control (n = 7)	BE	1. Custom bipolar tungsten electrode 2. SD9 Square Pulse Stimulator, Grass Technologies 3. CT3684, Cal Test/TPS2000B, Tektronix	NA shell Unilateral; 1.34 (A), 0.6 (L), 4.25 (V) Dorsal striatum 1.34 (A), 1.5 (L), 2.2 (V) from bregma	Monophasic, continuous 60 µsec, 160 Hz, 150 µA	1. High-fat diet (kcal) 2. Activity 3. c-Fos-IR in the NAS and ILC 4. Pharmacological effect (D1R, D2R)	1. Decrease in high-fat diet intake 2. No activity change 3. Increased c-Fos-IR in the bilateral NA 4. Only D2R antagonist attenuated the effects of DBS	NA DBS can produce behavioral change (reducing high-fat diet intake) via the D2R pathway
Sani et al. [22] (2007)	Sprague-Dawley rats	8 vs. 8 (DBS vs. sham)	BE	1. 0.25 mm bipolar product (Plastic) 2. Medtronic products	LH Bilateral; 2.3 (P; bregma), 2 (L; sagittal), 8.6 (below dura)	Continuous 100 msec, 180–200 Hz, 2.0 V	1. Body weight 2. Food intake 3. Water intake	1. Significant weight reduction in stimulated rats 2. No change in food or water intake 3. Water intake	Stimulation of LH might reduce metabolic rate, rather than modulating appetite control
Prinz et al. [21] (2017)	Sprague-Dawley rats (female)	6 vs. 6 (DBS vs. sham)	Normal	1. platinum/iridium wire with 70 µm diameter 2. Implantable stimulator 3. None	Medial NA shell; Unilateral; 1.44 (A), 3.0 (L), 7.3 (V) 18°	Biphasic 130 Hz, 100 µA for 7 days	1. Food/water intake 2. Weight gain 3. Behavior	1. High trend of an increase in weight gain in DBS group 2. No changes in food intake and behavior	Day time food intake > night food intake (DBS group) Reduction of satiation
Zhang et al. [24] (2015)	Sprague-Dawley rats	1. DIO (DBS, n = 8) vs. control (sham, n = 8) 2. Normal (DBS, n = 8) vs. control (sham, n = 8)	2 groups; 1. DIO rats 2. Normal rats	1. CBRU30 (FHC) 2. Master 8 (AMPI) 3. NA	Left NA shell; Unilateral; 1.2 (A), 0.7 (L), 7.4 (V) from bregma	90 µsec, 130 Hz, 500 µA	1. Body weight/food intake 2. D1/2 receptor mRNA 3. DA/DOPAC	1. Significant weight loss and food intake reduction in DIO-DBS rats 2. Increased D2R mRNA expression in DIO-DBS rats 3. Increased dopamine levels in DIO-DBS rats but no significant change in DOPAC level was noted	DBS has effect only in DIO rats No significant change in weight loss (or food intake) and dopamine-related activity was noted in normal rats

(Continued to the next page)

Table 1. Continued

Study	Animal	Sample size	Disease	Devices (1. Electrode/2. Generator/3. Output monitor)	Target+coordinates (mm)	Parameter	Outcome measurement	Conclusion	Comments
Torres et al. [23] (2012)	Monkeys (<i>Macaca fascicularis</i>)	4 (DBS) vs. 1 (sham)	Normal	1. 1.5 mm/400 contact or 3.0 mm/one contact (specific information about products is not shown)	VMH, Anterior to 3rd ventricle; Unilateral	30–130 Hz	1. Body weight and body fat 2. Fat intake 3. Glucose and leptin 4. Locomotion	1. Significant reduction in body weight and body fat in DBS monkeys 2. No significant change in fat intake during stimulation 3. No change in glucose or leptin level during stimulation 4. Increased velocity during stimulation	Only 80 Hz stimulation showed anti-obesity effect No hormonal change during stimulation and no change in serum leptin levels during weight loss
Oterdoorn et al. [20] (2020)	Wistar rats	7 (NA core) vs. 7 (NA lateral shell) vs. 7 (NA medial shell)	BE	Not specified	NA core vs. NA shell; Coordinates were not specified; Unilateral	60 μ sec, 140, 50, 10 Hz, 250 μ A (or 150 μ A in cases with side effects)	High-fat food intake	NA core–stimulation before binge eating produced significant decrease in high-fat food intake NA lateral shell–stimulation during binge eating led to suppression of high-fat food intake	Different mechanism on binge eating between NA core and NA shell; wanting vs. liking Stimulation of medial NA shell led to major side effect (e.g., fear and escape behavior)
Casquero-veiga et al. [17] (2018)	Zucker rats	6 (NA core) vs. 9 (sham)	Obesity model (leptin-resistant model)	1. Platinum-iridium electrodes (MS303/8-AIU/Spoc, Bilaney Consultants GmbH, Germany) 2. CS 120 81 (CIB-ERTEC S.A., Spain)	NA core; 1.2 (P), 1.5 (L) from bregma, –8.2 from dura; Unilateral	Biphasic, continuous, 100 μ sec, 130 Hz, 150 μ A	1. Glucose metabolism using FDG-PET 2. Weight 3. Food and water intake	1. Alteration in glucose metabolism in DBS rats; decreased metabolism in the NA, thalamic and pre-tectal nuclei, and increased metabolism in the cingulate-retrosplenial-parietal association cortices 2. No significant change in weight and food intake.	Over-activated striatum and thalamus in obese rats can be counteracted by NA DBS since it reduced glucose metabolism in the striatum and thalamus No significant weight loss in DBS rats can indicate that NA-DBS cannot resolve imbalance caused by the lack of leptin signaling in the hypothalamus
Melega et al. [19] (2012)	Göttingen	4 (DBS) vs. 4 (non-DBS)	Obesity	1. A miniature DBS (custom-made, NuMED Inc., Hopkinton, NY) 2. Genesis, 8-Channel #3608 (ANS, Plano, TX)	Bilateral VMH; Navigation-assisted	Monopolar 507 μ sec, 50 Hz, 0.5 mA	1. Weight gain 2. Blood glucose level 3. Behavioral change	1. Significantly lower in stimulated-VMH 2. No difference	

DBS: deep brain stimulation, NA: nucleus accumbens, DIO: diet-induced obese, BE: binge eating, A: anterior, L: lateral, V: ventral, LH: lateral hypothalamus, P: posterior, VMH, ventromedial hypothalamus, c-Fos-IR: c-Fos immunoreactivity, NAS: nucleus accumbens shell, ILC: infralimbic cortex, D1R: dopamine receptor 1, D2R: dopamine receptor 2, DA/DOPAC: dopamine/dihydroxyphenylacetic acid.

Table 2. Summary of previous studies on DBS in obese humans

Study	Sample size	Devices (1. Electrode/ 2. Generator)	Target+coordinates (mm)	Parameter	Outcome measurement	Conclusion	Significance or comments
Whiting (2013) et al. [44]	n = 3	1. Model 3389 (Medtronic) 2. Soletra (Medtronic)	LH; Bilateral; 6.5 (L), 3 (I) to intercommissural line, 4.5 (P) to AC ± adjustment in relation to fornix	Monopolar or bipolar; 90 µsec; 185 Hz	1. Psychological tests 2. Biochemical analysis 3. Energy metabolism 4. Body weight	1. Improvement in Binge Eating score (1/3), cognitive restraint subscale (1/3), hunger scale (2/3), body shape questionnaire (2/3) 2. No changes in biochemical analysis 3. Significant increase in RMR 4. Significant weight loss in 2/3 and stable weight in 1/3	Parameters that appeared to augment RMR induce significant weight loss in 2/3 patients Contact 1 (most closely located to mid-LH) increased RMR in 2/3 Contact 3 produced increased activity and increased arousal in all patients
Whiting et al. [45] (2019, follow-up study)	n = 2 (one patient was excluded due to lead breakage)	1. Model 3389 (Medtronic) 2. Soletra (Medtronic)	LH; Bilateral	Various settings were tested to identify optimal setting	1. Optimal setting for increasing RMR	Patient 1: contact 2 with pulse width of 60 msec and a frequency of 185 Hz Patient 2: contact 0 with pulse width of 90 msec and a frequency of 60 Hz	No significant adverse effects This different optimal setting might indicate the activation of different nuclei and regions Long-term investigations of weight loss and metabolic rate at optimized settings are mandatory
Mantione et al. [46] (2010)	n = 1 (OCD patient with obesity; BMI 37 kg/m ² (107 kg)	1. Model 3389 (Medtronic) 2. Soletra (Medtronic)	NA; Bilateral	Monopolar; 90 msec; 185 Hz; 3.5 V	1. Various psychiatric battles 2. Weight loss 3. Smoking cessation	1. Significant improvement in various tests for OCD, depression, and anxiety 2. Significant reduction in weight 3. Success in smoking cessation	Compulsions, smoking, and excessive food intake have a shared pathophysiology that can be improved by NA modulation
Harat et al. [47] (2016)	n = 1 (hypothalamic obesity due to earlier craniopharyngioma surgery)	Not shown	NA; Bilateral	208 µsec; 130 Hz; 2 mA (increases to 3.5 mA)	1. Various psychiatric tests 2. Weight control	1. Significant improvement in various psychiatric tests 2. Significant weight reduction	Modulation of the immediate brain reward system can treat hypothalamic obesity

DBS: deep brain stimulation, OCD: obstructive compulsive disorder, BMI: body mass index, LH: lateral hypothalamus, L: lateral, I: inferior, P: posterior, AC: anterior commissure, NA:

ous studies have shown that impaired dopamine neurotransmission in diet-induced obese leads more obsession with high-energy food to compensate for the weak dopaminergic input and this altered system of dopamine neurotransmission in obesity is believed to result in this difference [24,33,34]. Consistent with this, Zhang et al. [24] reported that DBS of the LH can induce an anorexic effect caused by the activation of D2Rs only in diet-induced obese rats (not in normal rats), implying that DBS-induced higher upregulation of dopamine can account for this selective efficacy.

In addition to these targets directly related to the reward circuit, it is worth noting that neuromodulation of the VMH can also lead to weight reduction [2,10,13]. The VMH, which contains the ventromedial nuclei and arcuate nuclei, is a critical structure in regulating glucose levels and energy homeostasis [35]. There is a long-lasting consensus suggesting that the VMH can reduce weight gain by altering the metabolic rate, rather than affecting eating behavior [36,37]. Being modulated by positive signals of nutritional resources such as glucose (insulin) and leptin, the VMH not only reduces hepatic glucose output and increases peripheral glucose metabolism but also regulates appetite regulation as the satiety center of the brain [2,13]. The interaction between the VMH and structures of the reward system is schematically depicted in Fig. 2. Receiving projections from brain regions that maintain homeostasis (VMH), nuclei in the LH send projections to the reward center (VTA and NA) where they promote motivated behaviors [38]. Accordingly, in contrast to the mechanism related to dopamine levels in the reward system when the LH or NA is stimulated, the effect of VMH stimulation is likely associated with hypermetabolism, which increases basal energy con-

sumption [23,39]. In a study by Torres et al. [23], a significant reduction in body weight and body fat was observed without any changes in hormone levels after chronic DBS stimulation of the VMH. In addition, an increase in animals' movement velocity facilitating a higher metabolic rate during acute stimulation was noted. The authors also suggested that chronic DBS was effective only at 80 Hz stimulation, which might indicate selective inhibition of the orexigenic LH [23]. In addition, low-frequency DBS of the VMH can induce a significant reduction in weight gain without any behavioral change in minipigs, providing preclinical evidence in support of low-frequency VMH DBS as a treatment for obesity [19].

DEEP BRAIN STIMULATION FOR HUMANS WITH OBESITY OR BINGE EATING DISORDER

Ventromedial hypothalamus

The findings of recent studies dealing with DBS for humans are summarized in Table 2 and 3. Since a growing body of evidence has revealed that posterior hypothalamic DBS can induce weight loss in various diseases (i.e., cluster headache and refractory aggressiveness disorder), bilateral VMH DBS has emerged as a potential intervention for patients who fail bariatric surgery or for those preferring a reversible surgery [40-42]. In a study by Hamani et al. [41], morbidly obese patients treated with bilateral ventral hypothalamus DBS showed a 6% weight loss over 5 months with low-frequency stimulation, without any change in behavior. Currently, a single-cohort, open-label, and non-masked study of DBS of the VMH with low frequency (50 Hz) is ongoing. The role of

Fig. 2. Interaction between the ventromedial hypothalamus (VMH) and structures of the reward system. LH: lateral hypothalamus, VTA: ventral tegmental area, NA: nucleus accumbens.

Table 3. Ongoing trials of DBS for patients with obesity

Study	RCT numbers	Inclusion & estimated sample size	Target	Parameters	Outcome measurements	Current status
De Salles et al. [43] (BLESS study, 2018)	NCT 02232919	BMI > 40 kg/m ² or > 35 kg/m ² with therapeutic failure Sample size: 6 patients	VMH; Bilateral	Low frequency (50 Hz)	1. Various psychiatric batteries 2. Weight changes 3. Indirect calorimetry and dual-energy X-ray absorptiometry (DEXA 62) 4. Food intake	Recruited
Wu et al. [48] (DBSLOC, NCT 03868670 2020)		BMI 40–60 kg/m ² Sample size: 6 patients	NA; Bilateral	RNS [®] system (closed-loop DBS); Stimulation setting is not specified.	1. Adverse events 2. Decrease in loss of control episodes	Recruiting

DBS: deep brain stimulation, RCT: randomized controlled trial, BMI: body mass index, VMH: ventromedial hypothalamus, NA: nucleus accumbens.

VMH DBS in refractory obese patients will be elucidated in the near future in the BLESS trial (NCT 02232919) (for more detailed information, see Table 3) [43].

Lateral hypothalamus

The first pilot study of LH DBS for obesity was published in 2013 [44]. In a pilot study in which bilateral DBS electrodes were implanted in the LH of three obese patients who showed no improvement after bariatric surgery, significant weight loss with increased resting metabolic rate (RMR) was observed in two of these patients. Since the DBS effect on RMR was observed at contact 1 of model 3389 (Medtronic, Inc., Minneapolis, MN, USA), which was located more closely to the mid-LH, the authors postulated that the nearby nuclear structures around the mid-LH might play a critical role in the regulation of metabolic rate. However, in a follow-up study to identify optimal stimulation settings for increasing RMR, opposite DBS settings between two participants for the maximal increase in RMR were found: high-frequency of 185 Hz vs. low-frequency of 60 Hz [45]. This difference is assumed to be caused by different regions being activated by LH stimulation, suggesting that long-term investigation of weight loss and RMR at the optimized DBS settings is mandatory in each LH-DBS patient [45].

Nucleus accumbens

During the treatment of a patient for medically refractory obsessive-compulsive disorder with DBS of the NA, a non-intended reduction in food intake was observed [46]. Although a sustained weight loss occurred 10 months after DBS surgery when most of her obsessive-compulsive disorder symptoms had disappeared, this case report suggests the possibility that compulsion, addiction, and food consumption have a shared pathophysiology in the reward circuit and that these behavioral disorders can be treated with neuro-

modulation of the NA. In the case of hypothalamic obesity patients, bilateral NA DBS also showed a significant effect on weight reduction with improvement in various psychiatric tests [47].

However, since the effects of DBS on excessive food intake may not be sustained over time and may even affect other social behaviors, closed-loop NA DBS, in which stimulation is delivered only when specific physiological fluctuations associated with abnormal behavior are detected in the NA, has been receiving significant attention. A randomized, early feasibility study of closed-loop NA DBS was designed to study this in more detail (DBSLOC; NCT 03868670, currently recruiting) [48].

CONCLUSIONS

Although the exact mechanism to explain the effects of DBS on obesity or binge eating behavior has not been elucidated, an increasing number of studies have consistently revealed promising results on the clinical utility of DBS for medically refractory obesity.

The currently ongoing human trials are expected to further elucidate the role of neuromodulation in the treatment of obesity. Furthermore, other novel less-invasive methods such as optogenetics will hopefully emerge as an effective treatment in the near future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT):

NRF-2017R1D1A1B03036357.

REFERENCES

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;384:766-81
2. Kumar R, Simpson CV, Froelich CA, Baughman BC, Gienapp AJ, Sillay KA. Obesity and deep brain stimulation: an overview. *Ann Neurosci* 2015;22:181-8
3. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer- and service-specific estimates. *Health Aff (Millwood)* 2009;28:w822-31
4. Girardet C, Butler AA. Neural melanocortin receptors in obesity and related metabolic disorders. *Biochim Biophys Acta* 2014;1842:482-94
5. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. *Obesity (Silver Spring)* 2008;16:2323-30
6. Pisapia JM, Halpern CH, Williams NN, Wadden TA, Baltuch GH, Stein SC. Deep brain stimulation compared with bariatric surgery for the treatment of morbid obesity: a decision analysis study. *Neurosurg Focus* 2010;29:E15. doi: 10.3171/2010.5.FOCUS10109
7. Halpern CH, Wolf JA, Bale TL, Stunkard AJ, Danish SF, Grossman M, et al. Deep brain stimulation in the treatment of obesity. *J Neurosurg* 2008;109:625-34
8. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biol Psychiatry* 2003;54:515-28
9. McClelland J, Bozhilova N, Campbell I, Schmidt U. A systematic review of the effects of neuromodulation on eating and body weight: evidence from human and animal studies. *Eur Eat Disord Rev* 2013;21:436-55
10. Brobeck JR. Mechanism of the development of obesity in animals with hypothalamic lesions. *Physiol Rev* 1946;26:541-59
11. Halpern CH, Tekriwal A, Santollo J, Keating JG, Wolf JA, Daniels D, et al. Amelioration of binge eating by nucleus accumbens shell deep brain stimulation in mice involves D2 receptor modulation. *J Neurosci* 2013;33:7122-9
12. Hoebel BG, Teitelbaum P. Hypothalamic control of feeding and self-stimulation. *Science* 1962;135:375-7
13. Mobbs CV, Moreno CL, Poplawski M. Metabolic mystery: aging, obesity, diabetes, and the ventromedial hypothalamus. *Trends Endocrinol Metab* 2013;24:488-94
14. Nieh EH, Vander Weele CM, Matthews GA, Presbrey KN, Wichmann R, Leppla CA, et al. Inhibitory input from the lateral hypothalamus to the ventral tegmental area disinhibits dopamine neurons and promotes behavioral activation. *Neuron* 2016;90:1286-98
15. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev* 2013;14:2-18
16. Yang H, de Jong JW, Tak Y, Peck J, Bateup HS, Lammel S. Nucleus accumbens subnuclei regulate motivated behavior via direct inhibition and disinhibition of VTA dopamine subpopulations. *Neuron* 2018;97:434-49. e4
17. Casquero-Veiga M, García-García D, Pascau J, Desco M, Soto-Montenegro ML. Stimulating the nucleus accumbens in obesity: a positron emission tomography study after deep brain stimulation in a rodent model. *PLoS One* 2018;13:e0204740. doi: 10.1371/journal.pone.0204740
18. Doucette WT, Khokhar JY, Green AI. Nucleus accumbens deep brain stimulation in a rat model of binge eating. *Transl Psychiatry* 2015;5:e695. doi: 10.1038/tp.2015.197
19. Melega WP, Lacan G, Gorgulho AA, Behnke EJ, De Salles AA. Hypothalamic deep brain stimulation reduces weight gain in an obesity-animal model. *PLoS One* 2012;7:e30672. doi: 10.1371/journal.pone.0030672
20. Oterdoom DLM, Lok R, van Beek AP, den Dunnen WFA, Emous M, van Dijk JMC, et al. Deep brain stimulation in the nucleus accumbens for binge eating disorder: a study in rats. *Obes Surg* 2020;30:4145-8
21. Prinz P, Kobelt P, Scharner S, Goebel-Stengel M, Harnack D, Faust K, et al. Deep brain stimulation alters light phase food intake microstructure in rats. *J Physiol Pharmacol* 2017;68:345-54
22. Sani S, Jobe K, Smith A, Kordower JH, Bakay RA. Deep brain stimulation for treatment of obesity in rats. *J Neurosurg* 2007;107:809-13
23. Torres N, Chabardes S, Piallat B, Devergnas A, Benabid AL. Body fat and body weight reduction following hypothalamic deep brain stimulation in monkeys: an intraventricular approach. *Int J Obes (Lond)* 2012;36:1537-44
24. Zhang C, Wei NL, Wang Y, Wang X, Zhang JG, Zhang K. Deep brain stimulation of the nucleus accumbens shell induces anti-obesity effects in obese rats with alteration of dopamine neurotransmission. *Neurosci Lett* 2015;589:1-6
25. Avena NM, Bocarsly ME. Dysregulation of brain reward systems in eating disorders: neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology* 2012;63:87-96

26. Burton AC, Nakamura K, Roesch MR. From ventral-medial to dorsal-lateral striatum: neural correlates of reward-guided decision-making. *Neurobiol Learn Mem* 2015;117:51-9
27. Richard JM, Castro DC, Difeliceantonio AG, Robinson MJ, Berridge KC. Mapping brain circuits of reward and motivation: in the footsteps of Ann Kelley. *Neurosci Biobehav Rev* 2013;37:1919-31
28. Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol* 2016;71: 670-9
29. van der Plasse G, Schrama R, van Seters SP, Vanderschuren LJ, Westenberg HG. Deep brain stimulation reveals a dissociation of consummatory and motivated behaviour in the medial and lateral nucleus accumbens shell of the rat. *PLoS One* 2012;7: e33455. doi: 10.1371/journal.pone.0033455
30. Sesia T, Bulthuis V, Tan S, Lim LW, Vlamings R, Blokland A, et al. Deep brain stimulation of the nucleus accumbens shell increases impulsive behavior and tissue levels of dopamine and serotonin. *Exp Neurol* 2010;225:302-9
31. Counotte DS, Schiefer C, Shaham Y, O'Donnell P. Time-dependent decreases in nucleus accumbens AMPA/NMDA ratio and incubation of sucrose craving in adolescent and adult rats. *Psychopharmacology (Berl)* 2014;231:1675-84
32. Marchant NJ, Li X, Shaham Y. Recent developments in animal models of drug relapse. *Curr Opin Neurobiol* 2013;23:675-83
33. Alsiö J, Olszewski PK, Norbäck AH, Gunnarsson ZE, Levine AS, Pickering C, et al. Dopamine D1 receptor gene expression decreases in the nucleus accumbens upon long-term exposure to palatable food and differs depending on diet-induced obesity phenotype in rats. *Neuroscience* 2010;171:779-87
34. Geiger BM, Behr GG, Frank LE, Caldera-Siu AD, Beinfeld MC, Kokkotou EG, et al. Evidence for defective mesolimbic dopamine exocytosis in obesity-prone rats. *FASEB J* 2008;22:2740-6
35. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000; 404:661-71
36. Lehmkuhle MJ, Mayes SM, Kipke DR. Unilateral neuromodulation of the ventromedial hypothalamus of the rat through deep brain stimulation. *J Neural Eng* 2010;7:036006. doi: 10.1088/1741-2560/7/3/036006
37. Stenger J, Fournier T, Bielajew C. The effects of chronic ventromedial hypothalamic stimulation on weight gain in rats. *Physiol Behav* 1991;50:1209-13
38. Hurley SW, Johnson AK. The role of the lateral hypothalamus and orexin in ingestive behavior: a model for the translation of past experience and sensed deficits into motivated behaviors. *Front Syst Neurosci* 2014;8:216. doi: 10.3389/fnsys. 2014. 00216
39. Bielajew C, Stenger J, Schindler D. Factors that contribute to the reduced weight gain following chronic ventromedial hypothalamic stimulation. *Behav Brain Res* 1994;62:143-8
40. Franzini A, Ferroli P, Leone M, Broggi G. Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. *Neurosurgery* 2003;52: 1095-9; discussion 1099-101
41. Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, et al. Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Ann Neurol* 2008;63:119-23
42. Torres CV, Sola RG, Pastor J, Pedrosa M, Navas M, García-Navarrete E, et al. Long-term results of posteromedial hypothalamic deep brain stimulation for patients with resistant aggressiveness. *J Neurosurg* 2013;119:277-87
43. De Salles AAF, Barbosa DAN, Fernandes F, Abucham J, Nazato DM, Oliveira JD, et al. An open-label clinical trial of hypothalamic deep brain stimulation for human morbid obesity: BLESS study protocol. *Neurosurgery* 2018;83:800-9
44. Whiting DM, Tomycz ND, Bailes J, de Jonge L, Lecoultre V, Wilent B, et al. Lateral hypothalamic area deep brain stimulation for refractory obesity: a pilot study with preliminary data on safety, body weight, and energy metabolism. *J Neurosurg* 2013;119:56-63
45. Whiting AC, Sutton EF, Walker CT, Godzik J, Catapano JS, Oh MY, et al. Deep brain stimulation of the hypothalamus leads to increased metabolic rate in refractory obesity. *World Neurosurg* 2019;121:e867-74
46. Mantione M, van de Brink W, Schuurman PR, Denys D. Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: therapeutic and research implications: case report. *Neurosurgery* 2010;66:E218; discussion E218. doi: 10.1227/01.NEU.0000360570.40339.64
47. Harat M, Rudaś M, Zieliński P, Birska J, Sokal P. Nucleus accumbens stimulation in pathological obesity. *Neurol Neurochir Pol* 2016;50:207-10
48. Wu H, Adler S, Azagury DE, Bohon C, Safer DL, Barbosa DAN, et al. Brain-responsive neurostimulation for loss of control eating: early feasibility study. *Neurosurgery* 2020;87:1277-88