Obesity Research & Clinical Practice xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

journal homepage: www.elsevier.com/locate/orcp

Review

Deep brain stimulation as a therapeutic option for obesity: A critical review

Cécile Bétry[a,b,*], Stéphane Thobois[c,d,e], Martine Laville[f,g], Emmanuel Disse[f,g]

[a] Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France
[b] The Medical School, University of Nottingham, Nottingham, UK
[c] Hospices Civils de Lyon, Hopital Neurologique Pierre Wertheimer, Service de neurologie C, Lyon, France
[d] Université de Lyon, Université Claude Bernard Lyon 1, Faculté de médecine Lyon Sud Charles Merieux, Lyon, France
[e] CNRS, Institut des Sciences Cognitives Marc Jeannerot, UMR 5229, Bron, France
[f] Service d'Endocrinologie-Diabétologie-Maladies de la nutrition, Centre Intégré de l'Obésité, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France
[g] Unité INSERM 1060, Laboratoire CARMEN, CENS-Centre Européen pour la Nutrition et la Santé, Centre de Recherche en Nutrition Humaine Rhône-Alpes., Université Claude Bernard Lyon 1, Pierre Bénite, France

ARTICLE INFO

Article history:
Received 5 July 2017
Received in revised form 29 January 2018
Accepted 6 February 2018

Keywords:
Nucleus accumbens
Hypothalamus
Weight loss
Energy metabolism
Bariatric surgery

ABSTRACT

Despite a better understanding of obesity pathophysiology, treating this disease remains a challenge. New therapeutic options are needed. Targeting the brain is a promising way, considering both the brain abnormalities in obesity and the effects of bariatric surgery on the gut-brain axis. Deep brain stimulation could be an alternative treatment for obesity since this safe and reversible neurosurgical procedure modulates neural circuits for therapeutic purposes. We aimed to provide a critical review of published clinical and preclinical studies in this field. Owing to the physiology of eating and brain alterations in people with obesity, two brain areas, namely the hypothalamus and the nucleus accumbens are putative targets. Preclinical studies with animal models of obesity showed that deep brain stimulation of hypothalamus or nucleus accumbens induces weight loss. The mechanisms of action remain to be fully elucidated. Preclinical data suggest that stimulation of nucleus accumbens reduces food intake, while stimulation of hypothalamus could increase resting energy expenditure. Clinical experience with deep brain stimulation for obesity remains limited to six patients with mixed results, but some clinical trials are ongoing. Thus, drawing clear conclusions about the effectiveness of this treatment is not yet possible, even if the results of preclinical studies are encouraging. Future clinical studies should examine its efficacy and safety, while preclinical studies could help understand its mechanisms of action. We hope that our review will provide ways to design further studies.

Contents

Abbreviations: BMI, body mass index; DBS, deep brain stimulation; VMH, ventromedial hypothalamus nucleus; LH, lateral hypothalamus area; GLP1, glucagon-like peptide 1; 5-HT, serotonin.

* Corresponding author. Current address: Department of Diabetology, Pôle DigiDune, Grenoble University Hospital, Grenoble Alpes University, Grenoble, France.
E-mail address: cbetry@chu-grenoble.fr (C. Bétry).

https://doi.org/10.1016/j.orcp.2018.02.004
1871-403X/

Introduction

Obesity, defined by a body mass index (BMI) >30 kg/m^2, is a major public health problem [1]. During the last fifty years, obesity prevalence has dramatically increased in parallel with changes in lifestyle. Even if obesity is often thought as a simple problem, namely the result of an imbalance between food intake and energy expenditure, the former excessive and the latter insufficient, the problem of common obesity is far from solved. For example, some brain abnormalities, especially in the reward system, could explain why people with obesity overeat despite a positive energy balance [2]. Furthermore, the medical management of obesity, based on a decrease in food intake and an increase in physical activity, induces moderate weight loss, which is usually not sustained over the long-term [3]. Adaptive phenomena, including a decrease in resting energy expenditure, contributes to limit the weight loss [4].

Targeting the brain to treat obesity is not recent. With the exception of orlistat, which induces fat malabsorption, all the anti-obesity drugs currently approved by the Food and Drug Administration target the central nervous system [5,6]. Nevertheless, targeting the brain remains a pharmacological challenge. It can explain, why most of the anti-obesity drugs do not have optimal efficacy and safety ratio. Furthermore, in the mid-seventies, three subjects were treated for obesity by cerebral lesions of the hypothalamus. In this study, it was reported a decreased perception of hunger, a slight decrease in food intake but no significant effect on body weight [7]. This inconclusive study and, above all, the further development of bariatric surgery put an end to the use of neurosurgery to treat obesity. Bariatric surgery is so far the most effective treatment of obesity in terms of weight loss, quality of life, and comorbidity improvements [8–10]. It was expected to induce food restriction and/or malabsorption. However, it also modulates eating behaviour. Recent researches have highlighted the role of gut-brain axis in this effect [11]. In particular, the level of many gut hormones that target the brain, such as peptide YY, Glucagon-like peptide 1 (GLP1), ghrelin or cholecystokinin, is altered by bariatric surgery [11–13]. These changes are involved in the subjective decrease of hunger and reward value of high-energy density food and are determinant for the success of weight loss [11,12,14]. Thus, an insufficient change in gut hormone levels could be one of the factors of weight regain or poor weight response after bariatric surgery [12]. According to a recent review, between five and eight percent of patients experience failure of bariatric surgery defined by insufficient weight loss or weight regain [15]. Failure of bariatric surgery is highly dependent on the type of surgical technique with a higher failure rate for laparoscopic-adjustable gastric band than gastric bypass and sleeve gastrectomy [9,16–19]. Beyond the type of surgery, the factors associated with failure of bariatric surgery remain to be fully determined, even if it is an active research topic [20]. In any case, patients tend to regain weight after bariatric surgery in the long-term follow-up [9,21]. Thus, bariatric surgery might not be the panacea to solve the obesity problem, and, alternative treatments are required, especially after its failure.

Targeting the brain to treat obesity with a more efficacious and safer treatment than pharmacological treatments is an attractive therapeutic option. Deep brain stimulation (DBS), which is routinely used in movement disorders, including Parkinson's disease, could be a valuable option [22,23]. DBS has been proposed as a potential treatment for obesity since 2008. It has been assessed in a few clinical trials and in several preclinical studies The aim of this review is to provide to obesity specialists the basic knowledge of DBS and a comprehensive view of DBS to treat obesity. For this purpose, we critically reviewed the published preclinical and clinical studies and we compared the two potential brain targets, namely the hypothalamus and the nucleus accumbens.

Deep brain stimulation: an overview

DBS is a neurosurgical treatment, which has been developed over the last 30 years. Since it is reversible and, less invasive than the conventional functional neurosurgery, based on brain lesioning, it has become a valuable alternative. It is one of the validated treatments for severe movement disorders [22,24]. The most frequent targets of DBS are the ventral intermediate nucleus of the thalamus for essential tremor and the subthalamic nucleus for Parkinson's disease. Since then, DBS has been assessed in a wide range of neurological disorders, when conventional treatments are poorly efficacious (e.g., Gilles de la Tourette syndrome [25], epilepsy [26], cluster headache [27] or Alzheimer's disease [28]). DBS is also under investigation for psychiatric disorders (e.g., major depressive disorder [29], bipolar disorder [29], obsessive-compulsive disorders [30] or anorexia nervosa [31]). Nevertheless, the body of evidence supporting the use of DBS in most of these diseases remains low, the majority of published studies being open-label trials with a small effective size.

DBS is based on the implantation of one or more electrodes to stimulate directly or indirectly a specific brain area involved in the pathophysiology of the disease of interest. Electrode implantation is performed with or without electrophysiological recordings, with or without perioperative clinical test and under local or generalised anaesthesia [32–35]. The implanted electrodes are connected to an implantable pulse generator placed under the skin [36]. Although adverse events can occur, DBS is nonetheless considered safe with a mortality rate below 0.3% [37,38]. The rate of serious complications remains low with a mean incidence rate of haemorrhage of 5% (symptomatic in 3.1% of patients) and skin infection of 5.7% [37,39]. Short-term adverse outcomes were below 5% in a cohort of 650 people with Parkinson's disease. However, people with obesity had higher risks of postoperative complications in this study [40].

The neurological bases underlying the therapeutic effect of DBS remain to be fully elucidated and are dependent on both the disease of interest and the stimulated brain area. Stimula-

Please cite this article in press as: Bétry C, et al. Deep brain stimulation as a therapeutic option for obesity: A critical review. Obes Res Clin Pract (2018), https://doi.org/10.1016/j.orcp.2018.02.004