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Invited Review

The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight

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Abstract

Early researchers found that lesions of the ventromedial hypothalamus (VMH) resulted in hyperphagia and obesity in a variety of species including humans, which led them to designate the VMH as the brain's "satiety center." Many researchers later dismissed a role for the VMH in feeding behavior when Gold claimed that lesions restricted to the VMH did not result in overeating and that obesity was observed only with lesions or knife cuts that extended beyond the borders of the VMH and damaged or severed the ventral noradrenergic bundle (VNAB) or paraventricular nucleus (PVN). However, anatomical studies done both before and after Gold's study did not replicate his results with lesions, and in nearly every published direct comparison of VMH lesions vs. PVN or VNAB lesions, the group with VMH lesions ate substantially more food and gained twice as much weight. Several other important differences have also been found between VMH and both PVN and VNAB lesion-induced obesity. Concerns regarding (a) motivation to work for food and (b) the effects of nonirritative lesions have also been addressed and answered in many studies. Lesion studies with weanling rats and adult pair-tube-fed rats, as well as recent studies of knockout mice deficient in the orphan nuclear receptor steroidogenic factor 1, indicate that VMH lesion-induced obesity is in large part a metabolic obesity (due to autonomic nervous system disorders) independent of hyperphagia. However, there is ample evidence that the VMH also plays a primary role in feeding behavior. Neuroimaging studies in humans have shown a marked increase in activity in the area of the VMH during feeding. The VMH has a large population of glucoresponsive neurons that dynamically respond to blood glucose levels and numerous histamine, dopamine, serotonin, and GABA neurons that respond to feeding-related stimuli. Recent studies have implicated melanocortins in the VMH regulation of feeding behavior: food intake decreases when arcuate nucleus pro-opiomelanocortin (POMC) neurons activate VMH brain-derived neurotrophic factor (BDNF) neurons. Moderate hyperphagia and obesity have also been observed in female rats with damage to the efferent projections from the posterodorsal amygdala to the VMH. Hypothalamic obesity can result from damage to either the POMC or BDNF neurons. The concept of hypothalamic feeding and satiety centers is outdated and unnecessary, and progress in understanding hypothalamic mechanisms of feeding behavior will be achieved only by appreciating the different types of neural and blood-borne information received by the various nuclei, and then attempting to determine how this information is integrated to obtain a balance between energy intake and energy output.

Keywords: Ventromedial hypothalamus; Ventral noradrenergic bundle; Paraventricular nucleus; Arcuate nucleus; Lateral hypothalamus; Amygdala; Autonomic nervous system; Feeding behavior; Melanocortins; Brain-derived neurotrophic factor; Body weight

Contents

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1. Introduction

For researchers investigating satiety mechanisms in feeding behavior and body weight regulation, the ventromedial hypothalamus (VMH) was once the center of the universe. Between 1940 and 1980, there were hundreds of published studies of the effects of VMH lesions and stimulation or of knife cuts in and around the VMH. Then, almost as fast as you can say paraventricular hypothalamic nucleus (PVN), the VMH disappeared from many feeding researchers' vocabulary. Today, the VMH is not even included in some leading anatomists' schema of hypothalamic nuclei involved in feeding behavior [101,312] and is barely mentioned in some reviews of the central (brain) control of feeding behavior (e.g., [352,415]). Some biopsychology textbooks dismiss a role for the VMH entirely (e.g., [61,315]). This paper reviews (in chronological order) the rise and fall of the VMH in feeding research, and after addressing the major issues that led to its demise, concludes that dismissal of a role for the VMH in feeding behavior and body weight regulation was premature.

Some researchers use the term ventromedial hypothalamus to refer either to a general area (e.g., [80,117]) or to the ventromedial hypothalamic nucleus and arcuate nucleus (ARC) combined (e.g., [240]). In this paper, VMH refers only to the VMH nucleus, its capsule (shell), and dendritic branches. When the ARC was purposely included in a study, or the target (of lesions or stimulation) was not the VMH nucleus itself but instead was the basomedial hypothalamus (i.e., the ventral and medial portion of the hypothalamus, hereafter referred to as the VMH area), that will be specifically indicated. The abbreviation "VMH" (rather than VMN) follows the nomenclature of the widely used stereotaxic atlas by Paxinos and Watson [310].

2. The rise

2.1. Fröhlich's syndrome and early experimental studies

An obesity syndrome in humans that was associated with abnormalities of the basomedial hypothalamus was reported as early as 1840 [277]. This was initially attributed to endocrine imbalances due to dysfunction of the pituitary gland [17,124] and eventually came to be known as Fröhlich's syndrome. The belief that the obesity was due to pituitary dysfunction remained the prevailing view through the mid-1930s (e.g., [25,82,104,195]).

The first challenge to the idea that Fröhlich's syndrome was due to pituitary abnormalities came from Erdheim [115], who observed that obesity was often observed in people with tumors at the base of the brain near, but not extending into, the pituitary. Later studies showed that hypophysectomy did not result in obesity unless there was additional damage to the basomedial hypothalamus [14,57,58,59]. The first real experimental study of the effects of hypothalamic lesions came from the lab of Bailey and Bremer in 1921 [20]. In a study of diabetes insipidus, they reported that lesions of the basomedial hypothalamus in dogs resulted not only in polyuria and polydipsia, but often hyperphagia and obesity as well. Smith [374,375] and Hetherington [160], both of whom used rats, similarly reported that basomedial hypothalamic lesions produced obesity, whereas hypophysectomy without additional hypothalamic damage did not.

2.2. Stereotaxic lesions in rats

One could argue that the modern era of brain research in feeding behavior began with the adaptation of the Horsley-Clarke stereotaxic instrument for the use with rats in 1939. Among the first to use the new instrument was Albert Hetherington, who in a series of studies, examined the effects on body weight of lesions placed throughout the hypothalamus [161–166]. Lesions of the medial and/or lateral preoptic area, or lesions just anterior (anterior hypothalamus) or dorsal (dorsomedial hypothalamus) to the VMH, did not result in obesity. Obesity did result when there was damage to the VMH, particularly when the lesions destroyed "the capsule of tissue immediately surrounding that nucleus, especially on its lateral and ventrolateral aspect" [165,p. 489]. Brobeck [43] and Kennedy [198] similarly observed that "relatively small lesions placed on the ventrolateral borders [of the VMH] and extending to the base of the brain are singularly effective" [43,p. 547] for evoking weight gain. Anand and Brobeck [6] later reported that obesity could be produced by either VMH lesions or by small