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Glutamate and GABA in lateral hypothalamic mechanisms controlling food intake

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ABSTRACT

By the 1990s a convergence of evidence had accumulated to suggest that neurons within the lateral hypothalamus (LH) play important roles in the stimulation of feeding behavior. However, there was little direct evidence demonstrating that neurotransmitters in the LH could, like electrical stimulation, elicit feeding in satiated animals. The present paper is a brief review in honor of Bartley Hoebel's scientific contributions, emphasizing the evidence from my lab that the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter gamma aminobutyric acid (GABA) in the LH mediate feeding stimulation and feeding inhibition respectively. Specifically, we summarize evidence that LH injection of glutamate, or agonists of its N-methyl-D-aspartate (NMDA) and non-NMDA receptors, elicits feeding in satiated rats, that NMDA receptor antagonists block the eating elicited by NMDA and, more importantly, that NMDA blockade suppresses natural feeding and can reduce body weight. Conversely, $GABA_A$ agonists injected into the LH suppress feeding and can also reduce body weight, while $GABA_A$ receptor antagonists actually elicit eating when injected into the LH of satiated rats. It is suggested that natural feeding may reflect the moment-to-moment balance in the activity of glutamate and GABA within the LH.

1. The lateral hypothalamus and feeding–reward

The lateral hypothalamus (LH) has long been a focal point of research on control of food intake. This area was first implicated in control of food intake by evidence that LH lesions suppress eating and that electrical stimulation within the LH may elicit eating [1,2]. It was further shown that animals will learn behaviors, typically pressing a lever, and will rapidly and incessantly repeat that behavior when it produces a depolarizing electrical stimulation in the LH, a phenomenon frequently termed self-stimulation. Findings such as these linked the LH to both feeding control and to reward. Importantly, as shown by some of Bart Hoebel's earliest research, in LH regions where electrical stimulation also elicits feeding, the rewarding value of self-stimulation appears to mirror the rewarding value of food. Specifically, food deprived subjects will work intensely for electrical stimulation of the LH, whereas satiated animals may actually work to avoid such stimulation, hence the concept of feeding–reward [3–5]. In honor of Bart's legacy of seminal contributions, the current mini-review is focused on some of my lab's contributions to understanding the LH and feeding behavior, along with some of our most current work focused on expanding our understanding of the linkages between the LH and the nucleus accumbens.

2. Neuropeptide Y and hypothalamic stimulation of eating behavior

After completing graduate work in Bart Hoebel's lab, I became a postdoctoral fellow with Sarah Leibowitz and starting in 1984 she and I published a series of papers demonstrating that the then newly discovered peptide, neuropeptide Y (NPY), elicited substantial and sustained feeding when injected directly into the paraventricular hypothalamus (PVN, e.g., Ref. [6]). However, our efforts to precisely localize NPY's site of action within the hypothalamus were fruitless, until, with the development of a more anatomically specific technique for central injection, we showed that the most effective site for NPY to elicit feeding was the perifornical LH [7]. The subsequent discovery of a NPY pathway(s) originating in the arcuate nucleus that projected to both the perifornical LH and the PVN [8,9] provided an endogenous substrate for the feeding effects of NPY and was seminal in establishing critical hypothalamic components of eating and body weight regulatory mechanisms. Stemming from the localization work suggesting that NPY acts in the perifornical LH, I refocused on the LH, a brain area I had learned most about and become interested in during my 4 years (1978–1982) as a graduate student in Bart Hoebel's laboratory at Princeton University.

3. Glutamate injected into the LH elicits eating

From the early 1970s' until 1998, substantial skepticism existed about whether neurons originating within the LH actually played significant roles in neurocircuits controlling eating behavior. Those

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concerns stemmed from the possibility that the effects of lesions and electrical stimulation on eating might have been consequent to effects on axons passing through the LH, rather than to actions on neurons originating within the LH, or that their effects might have been secondary to behaviorally non-specific actions [10–12]. One approach to address these concerns is to determine whether or not neurotransmitters and receptor agonists or antagonists, which have little or no effect on axons, might, like electrical stimulation, elicit eating with microinjections directly into the LH.

Using this approach, we initially focused on glutamate, which, despite being one of the most abundant neurotransmitters in the brain, had not been studied as a neurotransmitter in food intake control. Glutamate is the major excitatory neurotransmitter in the mammalian brain and most neurons respond to exogenously applied glutamate, reflecting their expression of glutamate receptors and synaptic or extrasynaptic input from glutamatergic neurons [13]. Importantly, immunohistochemical and electrophysiological studies showed that glutamate exists within the synaptic vesicles of many hypothalamic neurons and that they are depolarized by glutamate [14,15].

We tested glutamate by injecting it directly into the LH of satiated rats and measuring their consequent food intake. We found that glutamate produced a dose-dependent eating response beginning within minutes of injection [16]. Towards determining the receptor subtypes mediating the eating response elicited by glutamate, we tested the feeding stimulatory effects of N-methyl-D-aspartate (NMDA), D,L-alpha-amino-3-hydroxy-5-methyl-isoxazole propionic acid (AMPA), and kainic acid, the prototypical agonists of glutamate receptors of the same name. All three agonists were effective in rapidly eliciting marked eating responses when injected directly into the LH, supporting a feeding stimulatory role for LH glutamate and also suggesting that multiple glutamate receptor types might mediate its effects [16]. Indeed, follow up studies focused on the receptor subtypes mediating glutamate's feeding stimulatory effects provided further evidence for the involvement of NMDA, kainate and AMPA receptors in the mediation of eating [16–19].

Given that substances administered centrally may diffuse away from the injection site, leaving open the possibility of actions at sites remote from the LH site of injection, we next performed a cannula-mapping study. In this experiment, we compared the effectiveness of the glutamate and its receptor agonists in eliciting feeding in the LH, as opposed to bracketing sites anterior, posterior, medial, lateral and dorsal to the LH. The cannula-mapping work showed that glutamate (see Fig. 1) and all three of the glutamate receptor agonists were maximally effective in the LH, with most producing little or no feeding when injecting into sites bracketing the LH at distances of less than 2 mm [20]. That an excitatory neurotransmitter elicited intense feeding, specifically when injected directly into the LH, strongly supports the hypothesis that stimulation of subsets of neurons originating within the lateral hypothalamus is sufficient to elicit eating behavior. These findings also argue that the effects of lesions and electrical stimulation on eating behavior were not solely the result of effects on axons passing through the LH. This conclusion was popularized and the underlying mechanisms specified by a number of seminal findings published in 1998. These studies showed that the LH was virtually the sole source of neurons containing the feeding related peptide neurotransmitters orexin or melanin-concentrating hormone (MCH), and that LH neurons receive feeding related synaptic input from leptin-sensitive NPY and proopiomelanocortin (POMC) neurons originating from the arcuate nucleus [8,9,21–23].

Another concern with the early LH lesion and electrical stimulation studies was that the effects on feeding might have been an artifact of behaviorally nonspecific effects [10–12]. Indeed, this potential issue was also a concern in our LH glutamate agonist studies, as the injections frequently produced behavioral arousal or even frank hyperactivity. To address this possibility, we used intracerebral microdialysis, a technique I had learned in Bart Hoebel's lab from Luis Hernandez [24]. More specifically, using this technique we were able to apply NMDA to the LH in orders of magnitude lower concentrations than were effective with central injections, and could do so remotely, without disturbing the rats. Using continuous reverse dialysis applications of NMDA for 10 min, we found that the sleeping rats awoke, typically spent several minutes

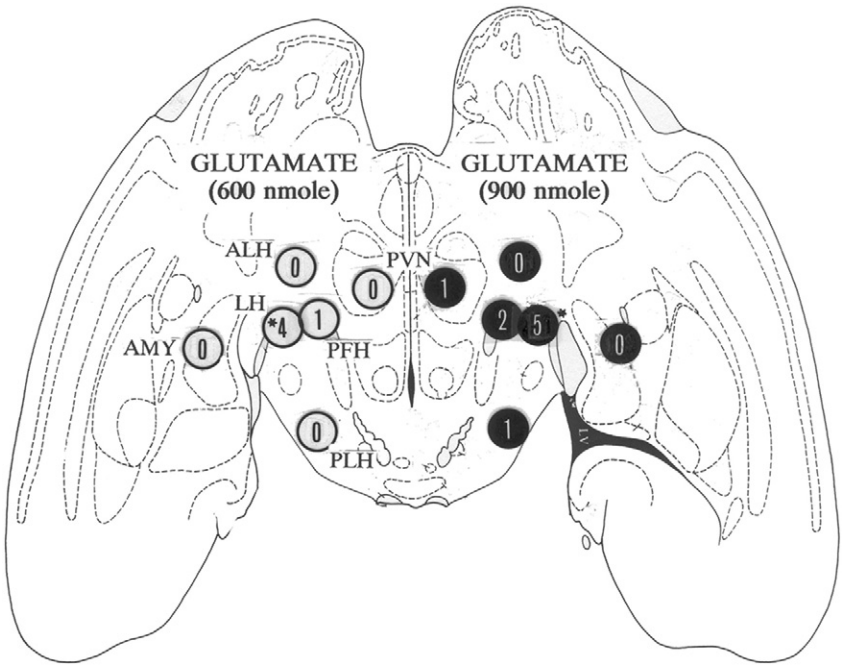

Fig. 1. Elicited eating as a function of glutamate dose (600 nmol, open circles on the left; 900 nmol, filled circles on the right) and injection site in the horizontal planes. The encircled numbers represent food intake in grams rounded down to the nearest whole number and the placement of each circle represents the histologically-determined mean location of the corresponding injection site. *$P<0.05$ versus vehicle by t-test for paired means. Abbreviation: LH = lateral hypothalamus; ALH = anterior LH; PLH = posterior LH; PFH = perifornical hypothalamus; PVN = paraventricular hypothalamus; AMY = amygdala.
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