Nucleus accumbens receives gastric vagal inputs

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ABSTRACT

AIM: To localize and characterize the response of single accumbal neurons to electrical stimulation of the gastric vagal fibers. **METHODS:** Unitary responses to electrical stimulation of the ventral and dorsal gastric vagal fibers which serve the proximal stomach were recorded extracellularly in the nucleus accumbens in anesthetized cats. **RESULTS**: The evoked units recorded in the nucleus accumbens consisted of phasic and tonic responses, with a mean latency of (396±43) ms. Convergence of ventral and dorsal gastric vagal inputs onto single phasic and tonic accumbal units was observed. For tonic inhibitory responses, convergence was exhibited when stimulation applied to both the ventral and dorsal gastric vagal branches resulted in a significantly longer inhibitory period than did stimulation of a single gastric vagal branch. Comparing the gastric vagally evoked accumbal unitary responses to the neuronal responses recorded in the nucleus tractus solitarius, parabrachial nucleus and hypothalamus in our previous studies, our data showed a higher percentage of single spike responses and shorter response duration's in the nucleus accumbens than in the other nuclei. This suggests that the synaptic drive from the gastric vagal inputs to the nucleus accumbens is less powerful than in the other structures. **CONCLUSION**: The present study localized and characterized gastric vagally evoked responses in the nucleus accumbens, which suggest that the nucleus accumbens may process gastric signals concerned with the ingestive process.

INTRODUCTION

The stomach is connected to the central nervous system (CNS) by the vagus nerve which contains predominantly sensory fibers[1]. Neurons have been identified in the nucleus tractus solitarius of the rat and the cat which respond to electrical stimulation of gastric fibers traveling in the vagal trunk[2,3]. Vagal afferent fibers that serve the proximal part of the stomach join the ventral and dorsal gastric vagal branches. In the cat, stimulation of the ventral and dorsal gastric vagal fibers evoked unitary responses in the parabrachial nucleus[4] and the medial and lateral hypothalamus[5].

The nucleus accumbens is a forebrain region that has been described as a functional interface between the limbic and motor system[6]. For example, activation of dopaminergic receptors in the nucleus accumbens produced a marked increase in locomotion[7]. The role of the accumbens in food-related activities has also been studied. Bakshi and Kelley showed that microinjection of a dopamine antagonist into the nucleus accumbens altered food consumption[8], and Mucha and Iversen observed that microinjection of morphine into

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the accumbens stimulated feeding[9]. Other investigations demonstrated that injection of morphine into the nucleus accumbens potentiated the rewarding effects of hypothalamic stimulation[10]. These and other studies (see Discussion) suggest that the nucleus accumbens might be involved in central autonomic regulation. The present study was undertaken to localize and characterize the response of single accumbal neurons to electrical stimulation of the ventral and dorsal gastric vagal fibers serving the proximal stomach.

MATERIALS AND METHODS

Experiments were conducted on 17 adult cats, weighing between 2.3 and 4.0 kg. An anesthetic mixture of halothane and nitrous oxide supplemented with oxygen was used for initial surgical procedures. For data collection, alpha-chloralose (65 mg/kg) in 0.9 % NaC1 solution was administered intraveneously while the gaseous anesthesia was gradually terminated. Supplemental doses of alpha-chloralose were given throughout the experiment to maintain appropriate levels of surgical anesthesia. Heart rate and blood pressure were monitored during the experiments. The animals were mechanically ventilated (modified Bourns Infant Ventilator, model LS 104-150) and pancuronium bromide was administered (initially 0.25 mg/kg iv, supplemented as needed to keep animal paralysed). The cats were positioned in a stereotaxic unit (Trent Wells). A dorsal midline skin incision was made over the skull, and a trephine was used to remove the bone sections above the recording area.

A pair of spring electrodes and a cuff electrode were placed respectively on the ventral and dorsal gastric vagal branches, which served the proximal stomach. The nerves were stimulated with single or paired (10 ms interval) pulses of 300-500 μA for 0.3 ms at a frequency of 0.5 Hz by a Grass stimulator (model S11) coupled to a stimulus isolation unit (Grass Model SIU7). The stimulus intensity was approximately 1.5 times that required to produce maximal amplitude of the nerve action potentials.

Evoked unitary responses were recorded extracellularly in the nucleus accumbens with platinum-blacked tungsten microelectrodes. The nucleus accumbens was probed in an area extending from 15.5-17.5 mm anterior to the inter-aural line, 1.0-3-5 mm lateral and 1.5-(-2.0) mm according to the cat diencephalons atlas of Jasper and Ajmone-Marsan[11]. At the onset of each tract, the microelectrode was stereotaxically positioned on the surface of the cerebral cortex and the craniotomy was filled with agar which had been cooled to body temperature. The search for evoked responses in the nucleus accumbens was conducted by electrically stimulating the ventral and dorsal gastric vagal brances while advancing the recording microelectrode in micron steps. When an evoked response was identified, the microdrive was stopped. In some experiments, unitary responses in the medial and lateral hypothalamus were recorded for comparison purposes. Data signals were amplified by a Grass preamplifier, monitored on a Tektronix storage oscilloscope and an audio system, and recorded on a Honeywell 5600C FM tape recorder.

Electrolytic lesion of the recording site was induced by passing current through the recording electrode at 10 μA for 15-30 s. At the conclusion of the experiment the animal was transcardially perfused with heparinized saline followed by 10 % buffered formalin. The brain was removed and serially passed through solutions of 10 %, 20 %, and 30 % sucrose in 10 % buffered formalin. Sectioning was done at 25 microns in a cryostat (Reichert-Jung 2800), and the sections were stained with luxol fast blue and cresyl violet. Location of unitary responses in the nucleus accumbens was determined histologically.

RESULTS

A total of 102 evoked unitary responses, to electrical stimulation of the ventral and dorsal gastric vagal fibers, were recorded extracellularly in the nucleus accumbens. These accumbal units consisted of phasic and tonic responses. Eighty-eight units were phasic responses, which exhibited either single or multiple spikes, or a short train of discharges (Fig 1). The remaining 14 units were tonic responses, including 2 tonic excitatory responses and 12 tonic inhibitory responses.

The mean latency of the evoked responses was (396±43) ms (mean±SD). Fig 2 is a frequency histogram of the latencies of nucleus accumbens unitary responses to ventral and dorsal gastric vagal branch stimulation. Stimulation of ventral and/or dorsal gastric vagal branches did not change the latency significantly.

Convergence of ventral gastric input and dorsal gastric vagal input onto single neurons in the nucleus accumbens was observed. Excitatory convergent responses were shown in 11 phasically responding units. For these responses, simultaneous stimulation of both

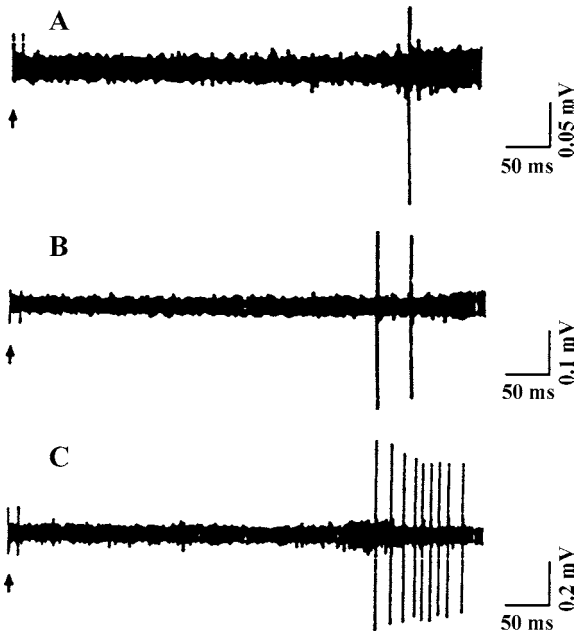

Fig 1. Three different accumbal units responding to simultaneous electrical stimulation of the ventral and dorsal gastric vagal branches. (A) A single spike response. (B) Double spike response. (C) A short train response. Arrow=stimulus artifact.

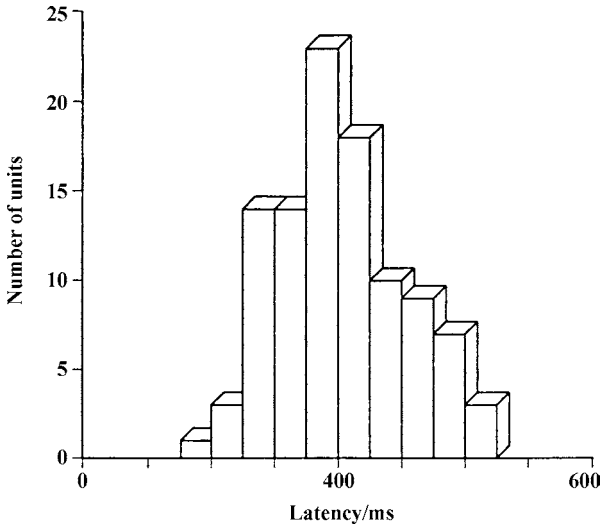

Fig 2. Frequency distribution of the latencies of 102 nucleus accumbens unitary responses activated by simultaneous electrical stimulation of the ventral and dorsal gastric vagal branches serving the proximal stomach.

ventral and dorsal gastric vagal branches caused more accumbal unitary discharge spikes than did stimulation of any single gastric vagal branch. Convergent inhibitory responses were observed in 6 tonic accumbal units. As shown in Fig 3, stimulation of both the ventral and

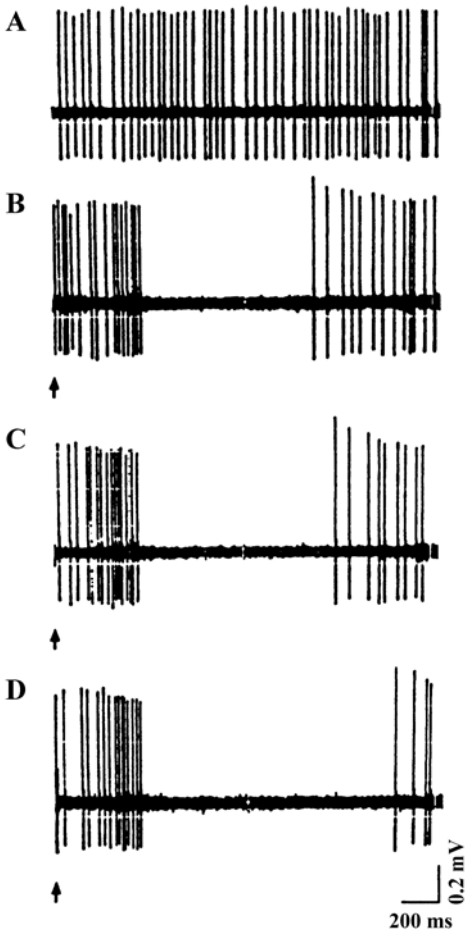

Fig 3. Convergence in a tonic inhibitory unit recorded in the nucleus accumbens. (A) Control, spontaneous activity. (B) This cell responds to electrical stimulation of the ventral gastric vagal branch, with an inhibitory period of 809 ms. (C) The same unitary recording after stimulation of the dorsal gastric vagal branch, with an inhibitory period of 916 ms. (D) The same unit responding to simultaneous stimulation of both ventral and dorsal gastric vagal branches, displaying a significantly longer (1229 ms) inhibitory period. This suggests that convergent inhibitory input from both ventral and dorsal gastric vagal fibers impinged onto a single neuron, resulting in a substantially longer inhibitory period than when only one gastric vagal branch was stimulated. Arrow=stimulus artifact.

dorsal gastric vagal branches caused a significantly longer inhibitory period than did stimulation of any single gastric vagal branch.

DISCUSSION

In our previous studies, unitary responses to gastric vagal stimulation have been recorded in the nucleus tractus solitarius[2], parabrachial nucleus[4], and medial and lateral hypothalamus[5]. In this study, some characteristics of the accumbal unitary responses were com-

pared to the characteristics of responses in the other previously studied structure(s).

Latency The mean latencies of the unitary responses recorded in the nucleus tractus solitarius, parabrachial nucleus, hypothalamus, and accumbens were (291±48) ms, (349±38) ms, (370±43) ms, and (396±43) ms, respectively. The mean latency of the gastric vagally evoked responses recorded in the nucleus accumbens was approximately 26 ms longer than that in the hypothalamus. The estimated distance between the nucleus accumbens and the hypothalamus is six millimeters. Assuming that there is a direct connection between the two structures, the estimated conduction velocity is <9.25 m/s.

Based on previous studies, the gastric vagal inputs from the proximal stomach impinge on neurons in the medial subnucleus of the nucleus tractus solitarius in the caudal brainstem. The parabrachial nucleus may serve as a pontine relay for processing ascending gastric afferent information from the caudal brainstem. Gastric vagal inputs further extend to the hypothalamus, a major autonomic regulatory center. We postulate that some of the gastric related signals processed in the hypothalamus are transmitted to the nucleus accumbens. In this scenario the nucleus accumbens could then contribute to the integration of gastric signals related to the ingestive process. However, in our experimental conditions, it is not possible to distinguish whether the signals from the hypothalamus are conveyed directly or indirectly to the nucleus accumbens.

Spontaneous neuronal activity Spontaneously active neurons that did not receive gastric vagal inputs were recorded in the nucleus accumbens. The number of these spontaneously discharging units recorded in the nucleus accumbens was fewer in number per experiment than the number recorded in the hypothalamus in previous studies. In 5 randomly chosen experiments in this study, the number of spontaneously discharging units recorded in the nucleus accumbens per experiment was approximately 40 % less than the number recorded in the hypothalamus.

Phasic response spike number and response duration The spike number and duration of multiple spike responses recorded in the nucleus accumbens were compared to the spike number and response duration of the unitary responses in the other areas where evoked responses to gastric vagal inputs were recorded. The higher spike number and longer response duration of the phasic unitary responses reflect the greater magnitude of the excitatory effects on these cells. It is a logical inference that the nucleus tractus solitarius and the hypothalamus receive strong gastric afferent signals, because the nucleus tractus solitarius receives primary gastric vagal inputs, and the hypothalamus is a principal autonomic regulatory center. Our data support this hypothesis by showing that a significantly higher percentage of greater than two-spike responses occur in the nucleus tractus solitarius (62 %) and hypothalamus (64 %) than occur in the parabrachial nucleus (29 %) and nucleus accumbens (17 %).

As shown above, a higher percentage of single spike responses and shorter response durations were recorded in the nucleus accumbens than in the three other structures. The nucleus accumbens is a forebrain region located rostral to the hypothalamus, hence, it is possible that the nucleus accumbens receives gastric vagal inputs after they have been processed in the hypothalamus. Signals from the hypothalamus project to different forebrain areas, including the accumbens. The nucleus accumbens, therefore, may only receive part of diversified gastric vagal signals via the hypothalamus. Our results suggest that the accumbens receives less excitatory gastric vagal inputs than the other three structures studied. Due to polysynaptic connections and/or divergence of gastric inputs, the synaptic drive from the gastric vagal inputs to the nucleus accumbens is less powerful than in the other nuclei.

Several different neurotransmitter systems have been identified in the nucleus accumbens and their role in food-related activities has been investigated. Hernandez and Hoebel observed, by microdialysis, that a rat food reward increased extracellular dopamine in the nucleus accumbens[12], and depletion of dopamine in the nucleus accumbens was shown to decrease drinking and wheel running induced by periodic food presentation[13,15]. A study by McCullough and Salamone indicated that dopamine in the nucleus accumbens was important for the stimulation of locomotor activity induced by periodic food presentation[15]. It has been shown that cocaine alters μ opioid receptor-mediated G-protein activity in several brain areas, including nucleus accumbens[16]. Opioids in the nucleus accumbens also play a role in feeding behavior. For example, Fletcher demonstrated that opioid antagonists inhibited feeding induced by 8-OH-DPAT[17]. Interaction between dopamine and opioid systems has also been identified[18,19] which could be important to the feeding related actions of these accumbal systems. Autoradio-

graphic localization of cholecystokinin receptors was shown in the nucleus accumbens[20], and the link between cholecystokinin, CNS, and food intake was well documented[21,22]. The above studies suggest that the nucleus accumbens may contribute to central autonomic regulation. The present study offers evidence that the nucleus accumbens has the potential for processing gastric vagal information originating from the proximal stomach. Gastric vagal inputs may modulate accumbal functioning, which then manifests influence over autonomic activities through efferent pathways to autonomic nuclei in the brainstem and spinal cord.

In summary, the present study localized and characterized gastric vagally evoked responses in the nucleus accumbens. Our data suggest that the nucleus accumbens may play a role in the processing of gastric vagal signals concerned with the ingestive process.

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