Gastric leptin: a novel role in cardiovascular regulation

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Sartor DM, Verberne AJ. Gastric leptin: a novel role in cardiovascular regulation. Am J Physiol Heart Circ Physiol 298: H406–H414, 2010. First published November 25, 2009; doi:10.1152/ajpheart.00997.2009.—Gastric-derived leptin affects satiety and gastrointestinal function via vagal mechanisms and has been shown to interact with the gut hormone cholecystokinin (CCK). CCK selectively inhibits splanchnic sympathetic nerve discharge (SND) and the activity of a subset of presympathetic vasomotor neurons in the rostroventrolateral medulla (RVLM). The present study sought to examine the effects of gastric leptin on arterial pressure (AP), heart rate (HR), SND, and RVLM neuronal activity to determine whether its effects on cardiovascular regulation are dependent on CCK1 receptors and vagal afferent transmission. To mimic gastric leptin, leptin (15–30 μg/kg) was administered close to the coeliac artery in anesthetized, artificially ventilated Sprague-Dawley rats. Within 5 min, leptin selectively decreased the activity of RVLM neurons also inhibited by CCK (−27 ± 4%; P < 0.001; n = 15); these inhibitory effects were abolished following administration of the CCK1 receptor antagonist lorglumide. Leptin significantly decreased AP and HR (−10 ± 2 mmHg, P < 0.001; and −8 ± 2 beats/min, P < 0.01; n = 35) compared with saline (−1 ± 2 mmHg, 3 ± 2 beats/min; n = 30). In separate experiments, leptin inhibited splanchnic SND compared with saline (−9 ± 2% vs. 2 ± 3%; P < 0.01; n = 8). Bilateral cervical vagotomy abolished the sympathoinhibitory, hypotensive, and bradycardic effects of leptin (P < 0.05; n = 6). Our results suggest that gastric leptin may exert acute sympathoinhibitory and cardiovascular effects via vagal transmission and CCK1 receptor activation and may play a separate role to adipose leptin in short-term cardiovascular regulation.

rostral ventrolateral medulla; sympathetic nerve; cholecystokinin; reflex; rat

Several studies have linked increases in sympathetic nerve discharge (SND) associated with obesity to high levels of circulating adipose-derived leptin, although this correlation is not particularly strong in humans (for reviews see Refs. 9, 10, 14, and 16). Leptin administration increases SND to brown adipose tissue (involved in thermogenesis in rodents), hindlimb, kidney, and adrenal gland and is believed to be due to the central actions of leptin (16, 17). Although increased levels of circulating leptin in obesity are linked to leptin resistance, this is not uniform and in rodent models is selective for metabolic function while sparing the pressor and renal sympathoexcitatory components (16).

Bado et al. (1) discovered that gastric epithelial cells also synthesize and secrete leptin, and although relatively little is known about this distinct pool of leptin, it has been suggested that it may subserve different functions to those of adipose leptin (1, 11). Vagal afferent terminals and nodose ganglion neurons express leptin receptor (Ob-R) mRNA (3), and in vivo and in vitro studies have demonstrated activation of vagal afferent neurons by leptin (24, 25, 40). Relative to adipose-derived leptin, the gastric pool of leptin is small and unlikely to significantly alter circulating levels (1), suggesting that its actions may be confined to the gut. This source of leptin is mobilized in response to food intake and may act in a paracrine fashion on subdiaphragmatic vagal afferents, different to the mode of action for adipose leptin (1, 4, 19, 25). Leptin applied within the gut acutely activates a subpopulation of neurons in the nucleus of the solitary tract that are also responsive to gastric vagal stimulation (42). It is feasible that the gastric source of leptin may subserve separate physiological functions to those of adipose leptin in which endocrine effects are predominantly due to actions in the brain (16). Paracrine release of this hormone close to the terminals of vagal afferents would result in much higher local concentrations than would be attained by circulating leptin (16). The fact that leptin levels do not increase postprandially in humans (37) and are only marginally elevated after feeding in rats (1) directly supports a paracrine mode of action for the gastric-derived source of leptin.

Peptides that influence feeding behavior such as cholecystokinin (CCK), leptin, neuropeptide Y, and orexin may all participate in an integrated response to regulate cardiovascular and sympathetic activity (20). In particular, CCK subserves many important functions relating to digestion including augmentation of gastrointestinal blood flow (34), and both feeding and CCK administration precipitate the release of gastric leptin in the rat (1). Evidence is emerging for an interactive relationship between leptin and CCK at the level of vagal afferents (2): CCK and leptin activate some vagal afferents in a cooperative manner (24), and activation of vagal afferent neurons by CCK is potentiated by leptin in vitro (40). Furthermore, leptin receptors are expressed on CCK-releasing cells in the duodenum, and luminal leptin increases CCK release (12). There appears to be a positive feedback loop involving leptin and CCK, suggesting that these peptides are codependent on their secretion and may potentiate their own effects by cross-stimulating the secretion of one another (11, 12). Mutations in the leptin receptor result in reduced levels of plasma CCK in response to a meal (12), and given that CCK plays such a major role in feeding behavior, this association may be of pathological significance in obesity (28).

We have previously demonstrated that CCK has differential effects on sympathetic vasomotor outflow and on subsets of presynaptic vasomotor neurons in the rostroventrolateral medulla (RVLM) that are critically important for cardiovascular regulation and the maintenance of sympathetic vasomotor tone (29–31, 34, 35, 38). To date, no study has examined vagally mediated interactions of CCK and leptin on the activity of presynaptic vasomotor neurons in the RVLM or on vasomotor SND. Therefore, the aim of this study was to...
examine the acute effects of leptin administered within the gastrointestinal circulation (termed close arterial; to mimic the effects of gastric leptin) on cardiovascular regulation. We examined the effects of leptin administration on arterial pressure and heart rate (HR), splanchic and lumbar SND, and the activity of different subpopulations of RVLM presympathetic vasomotor neurons discriminated by their sensitivity to CCK (30, 34, 35, 38). Since leptin in the gastrointestinal tract may promote CCK release (11, 12), an additional aim was to determine the involvement of CCK₁ receptors in the cardiovascular response to leptin and to determine whether this was dependent on vagal afferent transmission. Adipose leptin is actively and unidirectionally transported into the central nervous system and is thought to regulate appetite, thermogenesis, and sympathetic outflow by inducing transcriptional changes in the hypothalamus (16, 22). On the other hand, many of the effects of gastric leptin have, to date, been shown to be acute and dependent on vagal afferent transmission (1, 4, 19, 25). To identify a difference between the cardiovascular effects of gastric versus adipose sources of leptin, a comparison of the effects of intravenous (mimicking adipose-derived leptin that is released into the general circulation) versus close arterial leptin administration was also made. We hypothesized that leptin administration within the gastrointestinal circulation would have similar, acute effects on cardiovascular function to those reported for CCK and may play a separate role to adipose leptin in short-term regulation of blood pressure.

METHODS

Animals. All experiments were performed using male Sprague-Dawley rats (270–430 g, n = 41; Animal Resource Center Perth, Western Australia). This study was approved by the Ethical Review Committee of Austin Health (Heidelberg, Victoria, Australia) and complied with the principles outlined in the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Materials. The following reagents were used: rat leptin (Peprotech, Rocky Hill, NJ), CCK-octapeptide (CCK-8, sulfated form: American Peptide, Sunnyvale, CA), and phenylephrine (PE) and lorglumide (from Sigma-Aldrich Chemical, Castle-Hill, New South Wales, Australia).

Animal preparation. All animals were anesthetized with isoflurane, tracheostomized, and artificially ventilated with 100% O₂ containing 1.3–1.5% isoflurane (50–60 breaths/min; 1 ml/100 g). Adequacy of anesthetic depth was verified by absence of an eyeblink response following corneal probing and of a withdrawal response to firm toe pinch. Catheters were placed into the right brachial artery and left jugular vein for measurement of arterial blood pressure (AP) and HR and for intravenous drug administration, respectively. For elevation of AP and baroreflex activation, an inflatable occlusive cuff was placed around the abdominal aorta, below the level of the coeliac artery. The isolated nerve trunks were placed onto the bared tips of a pair of Teflon-coated silver wires (bare diameter, 250 μm; A-M Systems, Everett, WA), embedded in silicone sealant (Kwik-Cast; Coherent Life Sciences, Hilton, South Australia), and externalized through the sutured wound. In experiments in which vagotomy was performed, a ligature was placed loosely around each vagus nerve at the medivial level and, once all of the preliminary tests were performed, was pulled through a piece of plastic tubing to sever the nerve. Care was taken to ensure that the aortic depressor nerve was left intact. SND was quantified as arbitrary units of activity and calculated as described previously (33, 34).

Extracellular single-unit recording of RVLM presympathetic neurons. Extracellular single-unit recording of RVLM presympathetic neurons was performed as described previously (30, 34, 35). Only neurons that were barosensitive and spatially projecting were studied further. Spinally projecting neurons were identified using antidromic activation and the collision test (30, 34, 35). AP, HR, and sympathetic nerve and single-unit responses to baroreflex activation (octic occlusion or PE; 5–10 μg/kg iv) and/or unloading [sodium nitroprusside (SNP), 5 μg/kg], and the CCK-induced gastrointestinal circulatory reflex (CCK: 1–4 μg/kg iv) were tested just prior to close arterial saline administration and/or close arterial leptin administration (15–30 μg/kg). Doses of CCK, SNP, and PE used in this study were submaximal, as determined previously (30, 34, 35, 39). Arterial conduction velocities (CV) were calculated by dividing the straight line distance (in meters) between the recording and spinal stimulating electrodes by the antidromic latency (in seconds).

Data analysis and statistics. AP, HR, SND, and extracellular unit discharge were recorded using a computerized data acquisition system (Cambridge Electronic Design, Cambridge, UK) and Spike2 software and analyzed as described previously (30, 34, 35).

Data are expressed as means ± SE. The one-way ANOVA was used for comparisons in the neuronal studies and overall AP and HR effects. In instances in which the normality test failed, the Kruskal-Wallis test was used for comparisons in the neuronal studies and overall AP and HR effects. In instances in which the normality test failed, the Kruskal-Wallis test was used for comparisons in the neuronal studies and overall AP and HR effects. In instances in which the normality test failed, the Kruskal-Wallis test was used for comparisons in the neuronal studies and overall AP and HR effects.

Table 1. Effect of close arterial/intravenous leptin/saline infusion on AP and HR

<table>
<thead>
<tr>
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<th>n</th>
<th>ΔAP, mmHg</th>
<th>ΔHR, beats/min</th>
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<tr>
<td>Intravenous</td>
<td></td>
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<tr>
<td>Leptin, 15–30 μg/kg</td>
<td>7</td>
<td>2±2</td>
<td>1±4</td>
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<tr>
<td>Close arterial</td>
<td></td>
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<tr>
<td>Leptin, 15–30 μg/kg</td>
<td>35</td>
<td>−10±2†</td>
<td>−8±2*</td>
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<tr>
<td>Saline</td>
<td>30</td>
<td>−1±2</td>
<td>3±2</td>
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Values are means ± SE. AP, arterial pressure; HR, heart rate. *P < 0.01; †P < 0.001, significant difference between close arterial leptin and intravenous leptin; †P < 0.001, significant difference between close arterial leptin and close arterial saline.
Wallis test was used to determine significance. The paired t-test was used to compare AP, HR, and SND pre-/postintervention. In all other analyses, the unpaired t-test was used to calculate the level of significance between means, and normality of the data was tested using the method of Kolmogorov and Smirnov. In instances in which the normality test failed, the nonparametric Mann-Whitney test was used to test for significant differences between means (GraphPad Instat version 3.05 for Windows 95; GraphPad Software, San Diego, CA).

RESULTS

Effect of close arterial leptin, intravenous leptin, or close arterial saline on AP and HR.

For simplicity, the AP and HR responses to leptin/saline from the SSND, LSND, and RVLM neuronal studies below were grouped together. Before saline or leptin infusions, baseline AP and HR did not differ between the groups (P > 0.05 for all). Physiological doses (15–30 μg/kg) of leptin administered close arterial produced a significant hypotensive and bradycardic response when compared with close arterial saline or intravenous leptin (Table 1).

SSND and LSND responses to close arterial leptin infusion.

The effects of close arterial saline and close arterial leptin infusion on AP, HR, and SND were examined in 14 animals (SSND, 8 animals; and LSND, 6 animals). Within 5 min of close arterial leptin infusion, SSND decreased significantly from baseline compared with close arterial saline infusion (P < 0.01; see Table 2 and Fig. 1), and this sympathoinhibitory response coincided with the depressor and bradycardic phase of the response. In contrast, close arterial leptin did not inhibit LSND, and this response was not significantly different to close arterial saline infusion (P > 0.05; Table 2).

Effect of bilateral cervical vagotomy on leptin-induced SSND sympathoinhibitory response.

In six separate experiments, the effects of leptin were examined before and after bilateral cervical vagotomy. Bilateral vagotomy did not significantly alter baseline SSND (pre, 128 ± 16 U; and post, 143 ± 16 U), AP (pre, 104 ± 10 mmHg; and post, 109 ± 3 mmHg), and HR (pre, 361 ± 11 beats/min; and post, 364 ± 6 beats/min; P > 0.05 for all). Loss of the sympathoinhibitory response to CCK was used to confirm the effectiveness of bilateral vagotomy, as described previously (34). Leptin (15 μg/kg close arterial) induced a sympathoinhibitory response (−10 ± 3%)

### Table 2. Effect of close arterial saline/leptin on SSND and LSND

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<tr>
<th></th>
<th>%ΔSSND</th>
<th>%ΔLSND</th>
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<tr>
<td>Leptin, 15–30 μg/kg</td>
<td>−9±2*</td>
<td>3±5</td>
</tr>
<tr>
<td>Saline</td>
<td>2±3</td>
<td>9±3</td>
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Values are means ± SE; n = 8 for splanchnic sympathetic nerve discharge (SSND) group and 6 for lumbar sympathetic nerve discharge (LSND) group. *P < 0.01, significant difference between close arterial leptin and close arterial saline.

![Fig. 1. Arterial blood pressure (AP), heart rate (HR), and splanchnic sympathetic nerve discharge (SSND) responses to close arterial administration of saline (A) or leptin (15 μg/kg; B). Directly following a 5-min infusion period, leptin induced a sympathoinhibitory response that was accompanied by bradycardia and a depressor response. Saline infusion did not induce sympathoinhibition, bradycardia, or a depressor response. Bpm, beats/min.](http://ajpheart.physiology.org/)

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that was converted to a sympathoexcitatory response (14 ± 4%) following bilateral vagotomy (Fig. 2; \(P < 0.01\)). The hypotensive and bradycardic responses to leptin were also reversed following bilateral cervical vagotomy (AP: pre, -8 ± 4 mmHg and post, 2 ± 1 mmHg; \(P < 0.05\); HR: pre, -9 ± 3 beats/min and post, 23 ± 6 beats/min; \(P < 0.05\)).

**Effects of close arterial leptin on RVLM presympathetic vasomotor neurons.** The effects of close arterial leptin on RVLM presympathetic vasomotor neurons was tested in 21 animals. Upon identification of a barosensitive, spinaly projecting RVLM neuron, sensitivity to intravenous administration of CCK was tested (Figs. 3A and 4A). Neurons were designated as CCK sensitive if they were inhibited by CCK (Fig. 3A). Those that were not inhibited or activated by CCK were classified as CCK-insensitive neurons (Fig. 4A). Only one neuron was studied per experiment (15 CCK-sensitive neurons + 6 CCK-insensitive neurons were studied in total). To determine whether the effects of leptin were localized to the gastrointestinal region, the effects of both close arterial and intravenous leptin administration on the firing rate of presympathetic vasomotor RVLM neurons were examined. The effects of close arterial saline (\(n = 16\)) and intravenous leptin (\(n = 7\)) were only examined in a subgroup of experiments in which close arterial leptin was tested (total, \(n = 21\)), and these were administered before close arterial leptin. When the response to leptin was tested more than once, the average of the two responses was used. Within 5 min of administration, close arterial leptin infusion significantly decreased the firing rate of CCK-sensitive RVLM neurons (average latency, 4.3 ± 0.3 min; Figs. 3C and 5) but not of CCK-insensitive neurons (Figs. 4C and 5), compared with saline controls (tested on both CCK-sensitive/-insensitive neurons; Fig. 5); in contrast, intravenous leptin had no significant effect on the firing rate of CCK-inhibited neurons (Fig. 5). The inhibitory response to close arterial leptin occurred in conjunction with depressor and bradycardic responses (Fig. 3C). The CV of CCK-sensitive RVLM neurons inhibited by leptin (from 1.2 to 7.0 m/s; mean, 4.0 ± 0.5 m/s; \(n = 15\)) was significantly greater than those insensitive to CCK or leptin (from 0.5 to 3.3 m/s; mean, 1.4 ± 0.5 m/s; \(n = 6\); \(P < 0.005\)), but the firing rate of both groups was similar (17 ± 3 and 17 ± 7 spikes/s, respectively; \(P > 0.05\)).

**Effects of lorglumide on close arterial leptin on RVLM presympathetic vasomotor neurons.** In five of the experiments above, subsequent to the examination of the effects of close arterial saline and leptin on CCK-sensitive RVLM neurons, the CCK\(_1\) receptor antagonist lorglumide (5–10 mg/kg iv) was administered. Lorglumide administration increased AP from 93 ± 6 mmHg to 111 ± 5 mmHg (\(P < 0.05\)) but did not significantly increase HR (356 ± 22 beats/min to 356 ± 18 beats/min; \(P > 0.05\)) or firing rate of RVLM neurons (12 ± 1 spikes/s to 12 ± 1 spikes/s; \(P > 0.05\)). Following lorglumide administration, CCK (4 \(\mu g/kg\) iv) was administered to ensure the effectiveness of CCK\(_1\) receptor blockade. The inhibitory response to CCK was abolished in all cases. Subsequent to lorglumide administration, ~10 min elapsed before readministration of close arterial leptin. Before CCK\(_1\) receptor blockade, close arterial leptin produced an inhibitory effect on the firing rate of all CCK-sensitive RVLM neurons (~24 ± 2%) that was totally reversed following lorglumide administration (17 ± 9%; \(P < 0.01\); Fig. 6). The average CV for these neurons was 4.9 ± 0.7 m/s. The inhibitory effect of close arterial leptin on AP was slightly greater after lorglumide (~4 ± 1 mmHg before and ~9 ± 2 after; \(P < 0.01\)), and although there was a tendency for reversal of the bradycardic
effect, this was not significant (−13 ± 4 beats/min before and 4 ± 9 beats/min after; \( P > 0.05 \)).

**DISCUSSION**

This study has for the first time demonstrated that administration of physiological doses of leptin within the gastrointestinal circulation induces acute and specific cardiovascular responses that are not reproduced by intravenous administration of the hormone, suggesting a localized action within the gut. It is also the first demonstration of the inhibitory effects of leptin on SSND. Furthermore, it has demonstrated that the inhibitory effects of close arterial leptin administration on SSND and on a subset of presympathetic vasomotor neurons of the RVLM are dependent on vagal afferent transmission and on CCK₁ receptor activation. These observations suggest that gastrointestinal leptin may subserve a distinct role to that of adipose-derived circulating leptin. Leptin administered close to the gastric circulation specifically inhibits gastrointestinal vasomotor function and induces modest hypotensive and bradycardic effects that are abolished following bilateral cervical vagotomy, suggesting that gastric leptin may contribute to reflexly mediated gastrointestinal vasodilation.

Intravenous CCK administration induces differential effects on LSND and SSND (31, 33, 34), whereby it inhibits SSND and activates LSND. In this study, close arterial leptin administration also selectively inhibited SSND. Although leptin-induced inhibition of SSND was modest, it should be noted that this response occurred despite a concomitant depressor response to leptin that would be expected to induce an increase in SND due to unloading of baroreceptors.

The inhibitory effect of close arterial leptin administration on CCK-sensitive RVLM presympathetic neurons was more striking than its effects on SSND and is particularly notable due to the accompanying depressor effect of leptin. There is mounting evidence to suggest that RVLM presympathetic neurons that are inhibited by CCK may specifically drive the sympathetic vasomotor drive to the gastrointestinal vasculature. Their inhibition results in withdrawal of vasomotor tone and vasodilation in the gut (30, 31, 33–35), a reflex that is dependent on subdiaphragmatic vagal afferents (38).
Others have suggested that the effects of gastric leptin may be due to CCK release or leptin/CCK interactions (2, 11–13, 19, 23–27, 41) and leptin receptors are located on CCK-releasing enteroendocrine cells of the gastrointestinal mucosa (12). In support of this notion, we demonstrated that RVLM presympathetic vasomotor neurons that were inhibited by CCK were also inhibited by close arterial leptin and that CCK1 receptor blockade totally abolished the inhibitory effects of leptin on RVLM presympathetic neurons.

However, neither the modest hypotensive nor bradycardic responses to leptin were significantly abolished subsequent to loroglumide administration. This suggests that although the sympathoinhibitory effects of close arterial leptin may be due to CCK release and subsequent activation of the CCK sympathoinhibitory reflex (see Refs. 30–35), the modest hypotensive/bradycardic effects may be due to other effects of leptin. Gastric vagal afferents can be divided into two types with respect to leptin responsiveness: 1) those responsive to leptin alone and 2) those responsive to leptin only following CCK-8 pretreatment (40), or alternatively with respect to capsaicin sensitivity/insensitivity (27). It is possible that leptin induces CCK release, which then acts on one population of neurons to induce sympathetic responses while also activating a separate population of vagal afferents to induce its modest bradycardic and hypotensive effects, perhaps via a vago-vagal reflex. This is supported by the observation that, unlike the loroglumide experiments, vagotomy abolished not only the splanchic sympa-thoinhibitory response to leptin but also the hypotensive and bradycardic effects.

Intraduodenal administration of leptin in similar doses to those used in our study stimulates CCK release (23). It is not surprising then that many of the actions of leptin reported here are similar to those previously reported for CCK (for review see Ref. 31). Leptin, released from the gut in response to a meal, may induce indirect vasodilator effects (via CCK-induced sympathetic withdrawal) on the gut circulation to aid in digestive processes while simultaneously activating reflex compensatory mechanisms to induce vasoconstriction in other vascular beds. This latter point is supported by the results of the current study in which close arterial leptin infusion modestly activated CCK-insensitive presympathetic vasomotor RVLM neurons, consistent with sympathoexcitatory effects. The differential effect of leptin on RVLM neurons is mirrored by the differential effects of leptin on SSND and LSND.

In accordance with our previous studies, the mean CV of CCK-inhibited (and leptin-inhibited) neurons was signifi-
cantly higher than those of neurons not inhibited by CCK (or leptin). This observation is consistent with the idea that neurons inhibited by CCK and leptin are predominantly non-C1 neurons that have lightly myelinated spinal axons (34, 35).

Vagal afferent neurons that are sensitive to both CCK and leptin have been identified (3, 27), and structures that are accessed by close arterial leptin administration, including the stomach and upper gastrointestinal tract, pancreas, and liver (confirmed in preliminary studies in our laboratory using close arterial dye injections), are innervated by vagal afferents. Relative to adipose-derived leptin, the gastric pool of leptin is small and unlikely to significantly alter circulating levels, suggesting that its actions may be confined to the gut (1, 25). It is feasible that the gastric source of leptin may subserve separate physiological functions to those of adipose leptin in which effects are predominantly due to actions in the brain (16). The sympathoexcitatory and hypotensive actions of leptin administered intravenously or intracerebroventricularly require hours/days/weeks to take effect (5–8, 15, 17, 18, 21, 36) and are thought to be due to active leptin transport into the brain and subsequent induction of transcriptional changes in the hypothalamus. Furthermore, these effects of leptin occur with much higher

Fig. 5. Group data from neuronal studies (total, n = 21 RVLM presympathetic vasomotor neurons) demonstrating that close arterial leptin infusion selectively inhibits CCK-sensitive (n = 15) but not CCK-insensitive (n = 6) neurons; close arterial saline (n = 16) and intravenous leptin (n = 7) were tested in addition to close arterial leptin in a subset of neurons. Close arterial saline infusion was tested on both CCK-sensitive and -insensitive neurons with no significant effect. Similarly, intravenous leptin did not significantly inhibit CCK-sensitive RVLM neurons. Data are shown as means ± SE. Asterisks indicate statistically significant differences between groups (**p < 0.01 and ***p < 0.001).

Fig. 6. Effect of close arterial leptin infusion on a CCK-sensitive RVLM presympathetic vasomotor neuron before and after intravenous administration of the CCK1 receptor antagonist lorglumide (5 mg/kg). A: close arterial leptin infusion inhibits the FR of this neuron by ~20% within 5 min of administration, and this is accompanied by a small decrease in AP. B: following intravenous lorglumide, the neuronal inhibitory response to leptin was totally abolished but the hypotensive effect was not. This neuron had a baseline FR of 18 spikes/s, a latency of 7.5 ms, and a conduction velocity of 4.3 m/s.
does than those used in the present study (5, 7, 8, 15, 17, 18, 21, 36). In contrast, the results of the present study are in agreement with those of others, who demonstrated that the effects of physiological doses of leptin administered into the gastrointestinal circulation occurred within 5 min (25). The selective effects of close arterial but not intravenous leptin on RVLM presynaptic neurons, AP, and HR are consistent with a vagal afferent mode of action, since close arterial administration is likely to achieve higher local concentrations of leptin in the vicinity of gastrointestinal vagal afferent terminals compared with intravenous administration. This suggests that in the physiological setting, gastric-derived leptin may act in a paracrine fashion on gastrointestinal vagal afferents to induce reflex cardiovascular effects.

In conclusion, the results of this study suggest that close arterial leptin selectively and acutely inhibits a subset of RVLM neurons via a CCK1 receptor-dependent mechanism. Furthermore, leptin has a modest but selective sympathoinhibitory effect on SSND and induces modest hypotensive and bradycardic responses that are mediated by vagal afferents. In the physiological setting, leptin released from the stomach in response to a meal may participate in gastrointestinal vasodilation that occurs during digestion via a vagally mediated, CCK1 receptor-dependent mechanism.

GRANTS
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DISCLOSURES
No conflicts of interest are declared by the author(s).

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