OBESITY IS REACHING epidemic proportions and is commonly associated with elevated arterial pressure (AP), which can lead to serious cardiovascular complications. While the pathogenesis of obesity-related hypertension has been partly attributed to heightened sympathetic nerve activity, the precise pathophysiology remains uncertain (19–21). The hormones leptin and cholecystokinin (CCK) play a key role in controlling food intake and body weight (16, 18), and under normal physiological conditions, leptin is involved in the maintenance of cardiovascular homeostasis, having both pressor and depressor effects (24). However, serum leptin concentrations are elevated in obesity, suggesting a resistance to its beneficial actions including augmentation of thermogenic metabolism and suppression of appetite that act to maintain normal body weight (30). On the other hand, animal studies have indicated that leptin acts in the brain to induce sympathoexcitatory effects that are preserved in obesity, and these may contribute to elevated AP (24, 30, 35–38). Others have suggested that high-leptin levels may be associated with an impairment of the depressor effects of leptin and/or augmentation of the nonsympathetic pressor effects (such as oxidative stress), further implicating this peptide in obesity-related hypertension (5–7).

To date, adipose-derived leptin has received the most attention, but leptin is also released from the stomach in response to feeding (22, 47) and is thought to act in a paracrine fashion on sensory nerves within the gut at higher concentrations than can be achieved by circulating adipose leptin (22). This has prompted suggestions that gastric leptin may subserve different physiological functions to those of adipose leptin (3, 22, 24, 33, 41). Although gastric leptin acts synergistically with CCK at vagal afferents to regulate food intake (3, 4, 23, 32, 33), this relationship may also be important in cardiovascular regulation (41). Leptin infusion close to the coeliac artery inhibits a subset of cardiovascular-controlling neurons in the rostroventrolateral medulla that are also inhibited by CCK and are thought to be responsible for supplying sympathetic vasomotor outflow to the gastrointestinal tract (40–42, 44, 45, 49). Furthermore, leptin and CCK specifically inhibit splanchnic sympathetic nerve discharge (SSND) and induce a modest bradycardia and hypotension, effects that are dependent on intact vagal afferents and CCK1 receptors (40, 41). These effects in response to physiological doses of leptin administered close arterially were not observed when the same doses were administered intravenously, nor with close arterial saline infusion (41), suggestive of a localized action within the gastrointestinal region. It has been suggested that gastric leptin may trigger the release of CCK to induce vagally mediated effects on sympathetic vasomotor function (41). These studies demonstrated for the first time that gastrointestinal hormones are able to influence cardiovascular parameters via central mechanisms and may play a role in gastrointestinal vasodilation. Given that the gastrointestinal tract receives up to 30% of the total blood volume, alterations in gastrointestinal circulatory control mechanisms may have adverse consequences on cardiovascular homeostasis.

Sprague-Dawley rats exhibit a polygenic mode of inheritance in response to a medium high-fat diet (MHFD); whereas some display the obesity-prone (OP) phenotype, others are obesity resistant (OR) (9, 17). OP animals display similar characteristics to those seen in obese humans including the elevation of AP, sympathetic nerve activity, and the renin-angiotensin system, as well as the development of hyperleptinemia, hyperinsulinemia, and abnormal lipid profiles (9, 17, 28).
DIET ALTERS SYMPATHETIC RESPONSES TO GASTRIC HORMONES

28, 29), making this model ideal for examining the pathogenesis of obesity-related hypertension. The association between CCK and leptin may be significant in obesity in which leptin resistance may occur at both the receptor and the signaling level (1) to induce changes in afferent signal transmission that may be crucial in the pathophysiology of obesity-related hypertension. Therefore, in the present study we sought to determine whether the sympathoinhibitory effects of leptin and CCK are altered in animals fed a MHFD and/or specifically in OP animals with elevated AP and leptin levels. We hypothesize that OP animals will have reduced sympathoinhibitory responses to gastric leptin and CCK and that these may be associated with elevated AP in these animals.

METHODS

Animals. All experiments were carried out using male Sprague-Dawley rats (152–252 g; n = 32; Animal Resource Centre, Perth, Western Australia). This study was approved by the Austin Health Animal Ethics Committee (Heidelberg, Victoria, Australia). All experimental procedures performed abide by the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. Animals were housed in pairs in a temperature-controlled animal facility with a 12-h:12-h light-dark cycle. Six-week-old animals were acclimatized for 4 days before being placed on specified diets that were purchased from Speciality Feeds (Glen Forrest, WA, Australia). Seventy-five percent of the rats were fed a MHFD (15.5% total fat and 31% kcal calculated energy from fat; SF04-037; n = 24), and the remaining 25% were fed the low-fat diet (LFD; 4% total fat and 4% kcal calculated energy from fat; AIN93M; n = 8) and served as controls. To accommodate the maximum of eight electrophysiological experiments that could be carried out per week (at 2 per day), the rats were staggered so that each week only eight rats were placed on their respective diets (2 on LFD; and 6 on MHFD). All rats remained on the designated diets for 13 wk and were housed in pairs with free access to unlimited food and water. Weight and food intake were recorded daily, and food was changed twice a week.

Materials. The following reagents were used: CCK octapeptide (CCK-8 sulfated form; American Peptide, Sunnyvale, CA), rat leptin (Peptotech, Rocky Hill, NJ), and phenylephrine and clonidine (Sigma-Aldrich, Castle Hill, NSW, Australia).

General surgical procedures. At the end of the 13-wk feeding period, rats were anesthetized in a chamber saturated with isoflurane vapor (VM Supplies, Chelsea Heights, Victoria, Australia). Control and MHFD animals were chosen in random order for nerve recording experiments to avoid bias. The rats were tracheotomized and artificially ventilated with 100% O2 (1 ml/100 g body wt, and 50–60 breaths/min) containing 1.5–1.7% isoflurane. The adequacy of anesthesia was assessed by noting the absence of withdrawal to firm toe pinch and the absence of an eye blink to gentle corneal probing. These tests were repeated every 15 min throughout the duration of the surgery. Core temperature was maintained between 36–38°C with a servo-controlled heating pad linked to a rectal probe (Coherent Scientific, Hilton, SA, Australia). AP and heart rate (HR) were recorded by inserting a Teflon cannula (0.76 mm OD; and 0.30 mm ID) into the right brachial artery. The left jugular vein was also cannulated using a polyethylene cannula (0.96 mm OD; and 0.58 mm ID) for intravenous administration. A micro-stat analyzer (Helena, Victoria, Australia). Baseline AP was determined using a Beckman Coulter DXC800 autoanalyzer. A rat radioimmunoassay kit was used to measure leptin (Linco Research, St. Charles, MO), and CCK levels were measured as previously described (10). Insulin was measured using a double-antibody radioimmunoassay kit (Pharmacia, Upssala, Sweden), and glucose levels were determined using an Analox GM7 Micro-stat analyzer (Helena, Victoria, Australia). Baseline AP was monitored for at least 5 min at the end of all surgery and before drug administration.

Excision of fat pads. At the end of the experiment, animals were euthanized using an overdose of isoflurane (4% in inspired air). The abdominal area was opened for excision of fat pads. Subcutaneous and infrarenal fat pads from the right side were excised, weighed, and doubled to give an estimate of each respective fat mass. Total epididymal fat was also collected and weighed. The combined fat content was the sum of all three individual fat pads (subcutaneous + infrarenal + epididymal). The adiposity index was calculated as follows: combined fat content/(final weight – combined fat content)·100.

Data analysis and statistics. At the completion of surgery, at least 10–15 min were allowed for stabilization before the experimental protocols were initiated. The SSND response to CCK administration was measured immediately following CCK administration and during the nadir of the depressor response to CCK, as previously described (44). Leptin administration usually induced a modest depressor response within 2–5 min of administration, and the SSND response was measured in the period coinciding with this response as previously described (41). In the absence of a depressor response, AP and SSND were averaged over the 2.5–min period following leptin administration.

Just before the animals being euthanized at the end of the experiment, clonidine (200 μg/kg iv) was administered to establish the zero level of nerve discharge as previously described (43). Recordings of AP, HR, and SSND were stored and analyzed using a Cambridge Electronic Design, computer-assisted data acquisition system and Spike2 software (version 5.13, Cambridge, UK). SSND was analyzed off-line, full-wave rectified, and averaged over 1-s intervals. The residual nerve discharge signal remaining after clonidine administration was regarded as noise, which upon subsequent computer analysis was systematically subtracted from the full-wave rectified signal and...
so established the zero level of nerve discharge. The level of resting sympathetic nerve discharge recorded at the beginning of the experiment was used as the 100% level of nerve discharge and was derived by averaging the signal over a 30-s period. Sympathetic nerve discharge was therefore quantified as arbitrary units of activity. Data are expressed as means ± SE.

To determine significant differences and trends that were due to genetic factors or due to diet consumption alone, the results obtained from the experiments were analyzed in two ways. First, the rats on the MHFD were stratified according to weight gain. The upper tertile of rats fed the MHFD were allocated to the OP (n = 8) group and the lower tertile to the OR (n = 8) group, and χ² analysis was used as confirmation as previously described (10, 27). The remainder of the rats fed the MHFD not falling into either the OP or OR groups (i.e., middle tertile; n = 8) were excluded from weight gain analyses. LFD animals served as controls. Second, animals were also grouped and analyzed according to their respective diets: MHFD (consisting of OP, OR, and middle tertile group) versus LFD, thus including all 32 animals. Student’s t-test was used to analyze the data from the diet grouping. One-way analysis of variance followed by the Tukey-Kramer multiple comparison test was used to analyze the data from animals grouped according to weight gain. When the normality test failed, the Kruskal-Wallis test or the nonparametric Mann-Whitney test was used to determine significance (GraphPad Instat, version 3.05 for Windows 95, GraphPad Software, San Diego, CA). The Grubbs outlier test (GraphPad Instat; http://www.graphpad.com/quickcalcs/) was used to exclude any outliers.

RESULTS

Body weight, fat pad mass, and food intake in control, OP, OR, and MHFD rats. The weight gain and initial and final weight of rats receiving a MHFD or LFD are presented in Table 1. The initial body weight of OP, OR, and control animals was taken just before initializing the feeding regime so established the zero level of nerve discharge. The level of resting sympathetic nerve discharge recorded at the beginning of the experiment was used as the 100% level of nerve discharge and was derived by averaging the signal over a 30-s period. Sympathetic nerve discharge was therefore quantified as arbitrary units of activity. Data are expressed as means ± SE.

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Table 1. Characteristics of animals grouped according to weight gain (OP, OR) or diet (MHFD) compared with control animals on a LFD

<table>
<thead>
<tr>
<th></th>
<th>Control (LFD)</th>
<th>OP</th>
<th>OR</th>
<th>MHFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline AP, mmHg</td>
<td>105 ± 3.0</td>
<td>115 ± 2.7*</td>
<td>104 ± 3.2†</td>
<td>109 ± 1.8</td>
</tr>
<tr>
<td>Baseline HR, beats/min</td>
<td>371 ± 16</td>
<td>378 ± 8</td>
<td>385 ± 15</td>
<td>394 ± 7</td>
</tr>
<tr>
<td>Initial weight, g</td>
<td>239 ± 10.8</td>
<td>227 ± 9.7</td>
<td>206 ± 12.3</td>
<td>214 ± 6.3</td>
</tr>
<tr>
<td>Final weight, g</td>
<td>558 ± 15.5*</td>
<td>654 ± 15.4**</td>
<td>493 ± 16.9††</td>
<td>572 ± 16</td>
</tr>
<tr>
<td>Weight gain, g</td>
<td>319 ± 11.8</td>
<td>427 ± 12.5***</td>
<td>287 ± 9.0†††</td>
<td>359 ± 13.1</td>
</tr>
<tr>
<td>Subcutaneous fat, g</td>
<td>14.6 ± 1.2</td>
<td>25.3 ± 3.1**</td>
<td>15.9 ± 1.9†</td>
<td>20.6 ± 1.5*</td>
</tr>
<tr>
<td>Epididymal fat, g</td>
<td>9.6 ± 3.6</td>
<td>15.8 ± 5.0*</td>
<td>8.9 ± 2.9††</td>
<td>12.3 ± 4.9</td>
</tr>
<tr>
<td>Infrarenal fat, g</td>
<td>14.9 ± 2.2</td>
<td>23.2 ± 1.9*</td>
<td>13 ± 1.5††</td>
<td>18.7 ± 1.2</td>
</tr>
<tr>
<td>Total fat, g</td>
<td>39.1 ± 4.1</td>
<td>64.3 ± 6.2**</td>
<td>37.8 ± 3.9†††</td>
<td>49.5 ± 2.8</td>
</tr>
<tr>
<td>Adiposity index, %</td>
<td>7.4 ± 0.7</td>
<td>10.9 ± 0.9*</td>
<td>8.1 ± 0.7†</td>
<td>9.8 ± 0.5*</td>
</tr>
<tr>
<td>Plasma leptin, ng/ml</td>
<td>12.2 ± 2.4</td>
<td>25.2 ± 3.6*</td>
<td>14.3 ± 2.7†</td>
<td>19.8 ± 2.0*</td>
</tr>
<tr>
<td>Plasma CCK, fmol/ml</td>
<td>5.5 ± 1.1</td>
<td>2.1 ± 0.4**</td>
<td>2.8 ± 0.4*</td>
<td>2.9 ± 0.3**</td>
</tr>
<tr>
<td>Plasma triglycerides, mmol/l</td>
<td>2.2 ± 0.4</td>
<td>2.2 ± 0.4</td>
<td>2.6 ± 0.4</td>
<td>2.7 ± 0.2</td>
</tr>
<tr>
<td>Plasma cholesterol, mmol/l</td>
<td>1.3 ± 0.1</td>
<td>1.4 ± 0.04</td>
<td>1.2 ± 0.08</td>
<td>1.3 ± 0.04</td>
</tr>
<tr>
<td>Plasma insulin, ng/ml</td>
<td>2.5 ± 0.5</td>
<td>3.1 ± 0.4</td>
<td>2 ± 0.5</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>Plasma glucose, mmol/l</td>
<td>14.3 ± 0.7</td>
<td>13.5 ± 0.7</td>
<td>13.4 ± 1.0</td>
<td>13.8 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE for control low-fat diet (LFD), obesity-prone (OP), or obesity-resistant (OR) rats (n = 7 to 8 rats/group) and moderate high-fat diet (MHFD) rats (n = 23 to 24 rats). AP, arterial pressure; HR, heart rate; CCK, cholecystokinin. *P < 0.05, control vs. OP or OR or MHFD; **P < 0.01, control vs. OP or MHFD; ***P < 0.001, control vs. OP, OR. †P < 0.05, OP vs. OR; ††P < 0.01, OP vs. OR; †††P < 0.001, OP vs. OR; αP < 0.05, control vs. OR.
DIET ALTERS SYMPATHETIC RESPONSES TO GASTRIC HORMONES

The present study is the first to demonstrate that diet is capable of altering sympathetic vasomotor reflex function. High-fat diets may decrease vagal afferent sensitivity to specific gastrointestinal hormones and indirectly lead to increased vascular resistance in the splanchnic bed. This has possible implications in obesity in which the heightened sympathoexcitatory effects of adipose leptin (34), together with the reduced/reversed sympathoinhibitory effects of gastric leptin and CCK, may predispose obese animals to elevated pressor responses, possibly impacting on AP.

Plasma leptin levels and adiposity were significantly elevated in OP rats compared with OR and control rats, and collectively, MHFD rats had significantly elevated plasma leptin levels and adiposity compared with control rats. This is in agreement with other studies demonstrating an association between high-leptin levels and adiposity (12, 13). CCK released in response to a meal is impaired in obese Zucker rats with leptin receptor deficiency (23), and morbidly obese women have less circulating CCK compared with their lean counterparts (51). Interestingly, in our study, OP, OR, and MHFD animals collectively had significantly lower circulating CCK levels compared with control animals, suggesting that the diet is altering the release of this hormone. Low CCK levels could not be directly attributed to higher circulating leptin.

Arterial CCK were not significantly different among any of the groups (control, \(-19 \pm 4\) beats/min, \(-5 \pm 1\) mmHg; OP, \(-16 \pm 3\) beats/min, \(-4 \pm 1\) mmHg; OR, \(-18 \pm 3\) beats/min, \(-6 \pm 1\) mmHg; and MHFD, \(-17 \pm 3\) beats/min, \(-6 \pm 1\) mmHg; \(P > 0.05\) for all). Close arterial leptin infusion induced modest but significant sympathoinhibitory effects within 5 min of administration in control animals that were reversed in OP and OR groups (Figs. 3 and 4). Similarly, the sympathoinhibitory responses to close arterial leptin were also reversed in MHFD animals compared with control animals (Fig. 3). The HR and AP responses to close arterial leptin were not significantly different among any of the groups (control, \(-4 \pm 2\) beats/min, \(-4 \pm 2\) mmHg; OP, \(-4 \pm 3\) beats/min, \(0 \pm 1\) mmHg; OR, \(-4 \pm 2\) beats/min, \(-2 \pm 2\) mmHg; and MHFD, \(-1 \pm 1\) beats/min, \(-1 \pm 2\) mmHg; \(P > 0.05\) for all). It should be noted that two of the OP animals died under anesthesia before meaningful SSND data were able to be collected. Furthermore, we have previously reported that leptin induces a decrease in AP accompanied by a decrease in SSND (41). We therefore excluded SSND data from two animals (1 OP animal and 1 animal in the midgroup belonging to the MHFD grouping) in which leptin induced an increase in AP accompanied by a small decrease in SSND, since the latter may have been the result of baroreflex activation.

**DISCUSSION**

The present study has used a rat model of obesity that reflects many of the characteristics found in obese humans including elevated AP, hyperleptinemia, and increased adiposity. We hypothesized that in obesity, a disruption in the neural sympathoinhibitory signals elicited by gastric leptin and CCK would be associated with elevated AP. In our study, when compared with control animals, OP animals displayed blunted/reversed splanchnic sympathoinhibitory responses to CCK and gastric leptin, respectively. In analyzing the data according to diet, we were able to determine that, collectively, MHFD animals also displayed blunted or reversed responses, suggesting that diet may be altering the signaling of these hormones.

**Fig. 1.** The effects of close arterial (CA) cholecystokinin (CCK) administration (2 \(\mu\)g/kg) on splanchnic sympathetic nerve discharge (SSND) of animals grouped according to weight gain [obesity prone (OP) or obesity resistant (OR)] or diet [medium high-fat diet (MHFD)]. Data are shown as means ± SE; \(n\), number of rats. For weight gain groupings: *\(P < 0.05\), **\(P < 0.001\); ANOVA. For diet analysis control vs. MHFD: ††\(P < 0.01\); Student’s \(t\)-test.

**Fig. 2.** The effects of CA CCK administration (2 \(\mu\)g/kg) on SSND, heart rate [HR; in beats/min (bpm)], and arterial pressure (AP) in a control animal (A) vs. an OP animal (B). Note that the inhibitory response (–20%) in the control animal was blunted (–10%) in the OP animal.
(often associated with leptin resistance) or a loss in the leptin-CCK feedback loop (23), since OR animals also had lower CCK levels. Nevertheless, further studies are required to determine specifically whether gastric leptin stores (3), rather than circulating leptin, may be affected in obese Sprague-Dawley rats. In the present study, plasma levels of insulin, glucose, triglycerides, and cholesterol did not differ significantly between animals grouped according to weight gain or diet. One possibility for this is that blood samples were collected subsequent to the induction of anesthesia, which has been shown to alter the levels of circulating substances (2, 8). Furthermore, we did not fast our animals, and this may have affected our results (26). The glucose levels were elevated in all of our animals, and this is likely to be anesthetic dependent (25, 39).

Baseline AP was significantly elevated in OP rats compared with OR and control animals, although when grouped according to diet (MHFD vs. LFD), these differences were no longer apparent. Others have also shown elevated AP in OP rats compared with OR animals, suggesting that diet does not play a predominant role (17, 48). Consistent with that reported by others (48), the MHFD did not induce any significant differences in baseline HR among the groups. Our results reflect that increased body weight and adiposity, rather than diet, correlate with elevated AP since OP rats but not OR rats (also fed a MHFD) developed elevated AP. Nevertheless, the blunted sympathoinhibitory responses to CCK and leptin (in OP, OR, and MHFD animals in general) do not appear to directly impact resting AP, which was only elevated in OP animals. Increased circulating leptin in OP animals has been linked to hypertension in obesity (see Ref. 24 for review) and may be partially responsible for the elevated AP in our OP animals. The AP responses to CCK and leptin were relatively small and not significantly different among the groups, although there was a tendency for a blunted response to leptin in MHFD animals. Perhaps this is because AP is influenced by several factors other than sympathetic drive.

Rats maintained on a high-fat diet demonstrate reduced sensitivity to the satiating effects of CCK (14, 15, 46). Others have also shown that high-fat diets reduce the short-term sensitivity to CCK as determined by decreased Fos expression in the nucleus of the solitary tract, elevated food intake, and reduced CCK1 receptor expression in vagal afferent neurons in mice (31). Leptin and CCK are thought to have an interactive relationship, stimulating one another’s release and thereby potentiating one another’s effects (4, 23). Mice on a high-fat diet have reduced leptin receptor expression in vagal afferents of the nodose ganglion, and this may lead to a blunted CCK-mediated signaling (31). In agreement with these studies, we demonstrated that close arterial CCK administration induced greater responses in control animals compared with animals fed a MHFD (both OP and OR animals). Nevertheless, because the animals were not fasted, it is possible that they were in the postabsorptive state during the experiments and that the MHFD itself may have acutely altered gastric afferent responses.

**Fig. 3.** The effects of CA leptin administration (15 μg/kg) on SSND of animals grouped according to weight gain (OP, OR) and diet (MHFD). Data are shown as means ± SE; n, number of animals. For weight gain groupings: *P < 0.05, **P < 0.01; ANOVA. For diet analysis control vs. MHFD: †††P < 0.001; Student’s t-test.

**Fig. 4.** The effects of CA leptin administration (15 μg/kg) on SSND, HR, and AP in a control animal (A) vs. an OP animal (B). Note that the modest inhibitory response (−10%) in the control animal was reversed (13%) in the OP animal.
Either way, our observations are consistent with the concept that diet may alter vagal afferent signaling in response to CCK.

In the current study, the sympathoinhibitory response to close arterial leptin infusion in control animals was totally abolished or reversed in animals fed a MHFD, with both OP and OR animals being affected, suggesting that diet alters the response to this peptide. Both the current and previous studies from our laboratory have demonstrated that the sympatheoinhibitory effects of close arterial leptin administration are modest compared with the acute effects induced by a 2 μg/kg dose of CCK (41, 44). Furthermore, we have suggested that the effects of leptin are due to CCK release (41). In view of the blunted sympatheoinhibitory effects of CCK in MHFD animals, it was not surprising then that the more modest inhibitory response to close arterial leptin was reversed in these animals, perhaps due to an unmasking of sympatheoexcitatory mechanisms.

While the aetiology of obesity-related hypertension remains to be determined, it is generally accepted that both long-term and short-term mechanisms are likely to play a role. Circulating adipose leptin is transported into the central nervous system where it induces transcriptional changes that are likely to be involved in long-term signaling mechanisms (24). Conversely, the acute effects of gastric leptin (and CCK) are associated with local release within the gastrointestinal tract and subsequent paracrine activation of vagal afferents and are likely to be involved in short-term signaling mechanisms (33, 41). Increased vascular resistance due to sympathetically mediated vasoconstriction is thought to contribute to elevated AP in obesity (48). There is also evidence to suggest that high levels of circulating leptin may contribute specifically to sympathoexcitatory mechanisms associated with elevated AP in obesity (24, 34). On the other hand, others have demonstrated that a reduction in nonsympathetic vasodilator mechanisms may also be important (5–7). Although the results failed to support our original hypothesis that elevated AP in obesity would be directly associated with reduced sympathoinhibitory responses to gastric leptin and CCK, to our knowledge, ours is the first study demonstrating that a MHFD is associated with a reduction or reversal in acute sympathoinhibitory responses likely to be involved in short-term signaling mechanisms. While speculative, it remains a possibility that in OP animals, this phenomenon may be additive to the sympathetic pressor effects associated with high-circulating leptin levels that are linked to long-term signaling (24).

In conclusion, we have demonstrated that feeding animals a high-fat diet is associated with blunted or reversed splanchic sympathoinhibitory responses to the gastrointestinal hormones CCK and leptin, respectively. Therefore, diet may alter vagal afferent sensitivity to gastrointestinal hormones, thereby influencing sympathetic vasmotor mechanisms involved in gastrointestinal circulatory control. A disruption to the fine balance of sympathoinhibitory/sympatheoexcitatory mechanisms may, in turn, have some impact on the maintenance of elevated AP, particularly after prolonged obesity.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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