GABAergic modulation of ventilation and peak oxygen consumption in obese Zucker rats

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RECENT INVESTIGATORS have established important links between altered central neural pathways and regulation of obesity. There is, however, a lack of studies investigating whether altered neural mechanisms also influence control of breathing in obesity. The obese Zucker rat, a model of morbid obesity, presents many of the same deficits noted in obese humans, including reduced lung function, increased chest wall limitations, blunted ventilatory responses, and reduced exercise capacity (2, 9, 22, 34). Reduced ventilation in response to hypoxic or hypercapnic exposures is observed in some obese humans and in obese Zucker rats (22, 33, 34, 39). The underlying mechanisms responsible for the depressed ventilatory responses in obesity are unknown but are thought to represent part of the pathogenesis of obesity hypoventilation syndrome (OHS) (33, 39).

GABA, a major inhibitory neurotransmitter in the mammalian central nervous system (CNS) (4), is known to reduce resting ventilation, ventilation during hypoxic exposure, and metabolic function (13, 18, 20, 27). During hypoxic challenges, brain GABA levels increase (19, 37) and have been shown to exert an inhibitory modulatory effect during the late hypoxic ventilatory response (16, 27, 37). Despite elevations in brain GABA levels during hypercapnic challenges (15), the role of GABA as a neuromodulator of the hypercapnic ventilatory response is less well established, although a study did note that hypothalamic GABAergic mechanisms are involved (30).

The obese Zucker rat presents accelerated synthesis of GABA in the hypothalamus and brain stem (28) and possesses altered brain GABAergic mechanisms that contribute to their overeating (7, 28). The role of GABA in mediating breathing control or exercise regulation in obesity has, to our knowledge, not been previously investigated. Whether altered GABAergic mechanisms modulate ventilation and exercise capacity in obese Zucker rats is unknown and formed the basis of our study.

Because obese Zucker rats are known to possess altered brain GABAergic mechanisms, we hypothesized that ventilation and maximal exercise capacity in obese Zucker rats would also be modulated by a GABAergic mechanism. Because GABA is known to inhibit respiratory activity predominantly via GABA$_A$ ionic receptors (12), bicuculline, a selective GABA$_A$ receptor antagonist, was used to investigate whether endogenous GABA modulates ventilation at rest, ventilation during hypoxic exposure, ventilation dur-
ing hypercapnic exposure, and peak \(O_2\) consumption (\(V_{O_2} \text{peak}\)) in obese Zucker rats. Studies were conducted after administration of equal volumes of vehicle (DMSO) or bicuculline. The agents were given in a blinded-randomized design with 72 h of recovery between successive ventilatory or \(V_{O_2} \text{peak}\) tests. A parallel study design was used, with lean age-matched Zucker rats serving as controls.

**METHODS**

**Animals.** The studies were performed on eight lean (\(Fa\/?\)) and eight obese (\(fa/fa\) age-matched male Zucker rats. Animals were purchased from Vassar College (Poughkeepsie, NY) at 4 wk of age. One lean and one obese rat were housed per cage. Ambient temperature was maintained at 21°C, and an artificial 12:12-h light-dark cycle was set. The lighting period began at 7 AM. Standard laboratory chow (Ralston Purina, St. Louis, MO) and water were provided ad libitum. All protocols were approved by the Institutional Animal Care and Use Committee of the State University of New York at Buffalo. Animals underwent testing at 12 wk of age.

**Pulmonary ventilation.** Breathing pattern was recorded by the barometric technique of plethysmography (22, 24, 34). A cylindrical Plexiglas chamber with a volume of 4 liters was used for the measurement of breathing pattern. The rat was placed in the chamber within a restrainer that did not allow backward rotation. A flow of gas through the chamber was provided by a wall-mounted compressed air source (during the preliminary habituation period and for washout; see **Experimental protocol** or from pressurized gas tanks (BOC Gases). Inlet flow was regulated by a flowmeter (Dwyer Instruments, Michigan City, IN) and maintained steady at 1.5 l/min during measurement of gas exchange but raised to 4 l/min for a few minutes to aid washin at the time of changeover of the gas mixture. The chamber was completely sealed after momentary interruption of the flow through it, and the oscillations in pressure caused by breathing were recorded by a pressure transducer (model PT5, Grass Instruments, Quincy, MA). The signal was received and amplified by a Grass DC driver (model T7CPA) and displayed on an oscillographic strip-chart recorder (model 7 polygraph, Grass Instruments). An average of 80 breaths was recorded on chart paper at a speed of 10 mm/s. Injection and withdrawal of 0.3-ml volumes were performed at 12 times per minute until the animal could no longer continue to run. Obese rats began at 10 min followed by a 3 min increase every 3 min.

\[ V_{O_2} \text{ uptake and } CO_2 \text{ output.} \] \(O_2\) uptake (\(V_{O_2}\)) and \(CO_2\) output (\(V_{CO_2}\)) were measured in the barometric chamber or during the exercise test. The concentrations of the chamber (barometric or treadmill) inflowing or outflowing \(CO_2\) and \(O_2\) were monitored by \(CO_2\) and \(O_2\) gas analyzers (models CD-3A and S-3A1, respectively. Ametek Applied Electrochemistry, Sunnyvale, CA) arranged in series. The calibrations and linearities of the gas analyzers were checked twice daily using certified calibration gases (BOC gases). \(V_{O_2}\) and \(V_{CO_2}\) were calculated from the inflow-outflow \(O_2\) and \(CO_2\) differences multiplied by the gas flow; the small error introduced by the respiratory quotient less than unity was neglected (11). Data are presented at STPD, corrected for the effective mass exponent according to Refinetti (32), and expressed in kilograms to the power of 0.75 (\(ml\ O_2\cdot kg^{-0.75}\cdot min^{-1}\ STPD\)). Effective body mass (EBM) was calculated as 1.00 \(M^{0.75}\) and 0.86 \(M^{0.75}\) for lean and obese animals, respectively (32). EBM was used to minimize differences in adipose tissues between lean and obese rats. \(V_{O_2} \text{peak}\) was expressed in absolute terms (\(ml\ O_2/min\ STPD\)) and in relative terms, corrected for total body mass (\(ml\ O_2/kg^{-1}\cdot min^{-1}\ STPD\)) and for EBM (\(ml\ O_2/kg^{-0.75}\cdot min^{-1}\ STPD\)).

**Experimental protocol.** Animals were tested 30 min after a subcutaneous injection of equal volumes (1 ml/kg) of DMSO (vehicle) or bicuculline (1 mg/kg). Bicuculline effects are noted within 10 min of injection and last for >2 h in rodents (27, 38). The present studies were carried out 30 min after injection and completed within 75 min of injection. The solutions were prepared daily and placed in vials labeled **solutions I and II**. The agents were given in a blinded design and randomized order. The investigators involved in the actual testing remained blinded to the contents of the vials until the ventilatory and exercise tests were completed and analyzed. Ventilation and exercise tests were performed on four separate occasions with a \(\geq 72\)-h recovery period between successive tests. Four lean and four obese Zucker rats underwent ventilatory test on **days 1 and 4** and exercise test on **days 7 and 10**; the remaining four pairs underwent ventilatory test on **days 2 and 5** and exercise test on **days 8 and 11**. Thus ventilatory and exercise tests were completed within a 2-wk period. In an attempt to minimize any stress during the study, all animals were habituated on five separate occasions to the restraint device (80 min) and twice to treadmill walking (10 m/min for 10 min).
testing period. To minimize any potential differences due to circadian rhythms, each rat was injected and tested at exactly the same time on each testing day.

Statistical analysis. The planned comparisons with repeated-measures ANOVA under general linear model in a one between (lean and obese) and two within (gases and drugs) design were conducted to analyze all parameters. Body weights of individual animals were averaged over the 2-wk experimental period and tested by unpaired t-test between (lean and obese) and two within (gases and drugs) measures ANOVA under general linear model in a one factor with their control values (vehicle), all ventilatory parameters (V<sub>E</sub>, V<sub>E</sub>/kg, V<sub>t</sub>, VT/kg, VT normalized by body weight; V<sub>E</sub>, minute ventilation; V<sub>E</sub>/kg, V<sub>E</sub> normalized by body weight; VO<sub>2</sub>, O<sub>2</sub> consumption normalized by effective body mass; V<sub>CO</sub><sub>2</sub>, CO<sub>2</sub> production normalized by effective body mass. *Significant difference between vehicle and bicuculline, P < 0.05.

RESULTS

At 12 wk of age, male obese Zucker rats weighed ~40% more than age-matched lean animals (450 ± 27 vs. 317 ± 18 g, P < 0.01, unpaired t-test).

| Table 1. Resting ventilatory parameters in lean and obese Zucker rats treated with vehicle or bicuculline |
|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Lean Rats                                           | Bicuculline                                         | Lean Rats                                           | Bicuculline                                         |
| T<sub>b</sub>, °C                                    | 38.5 ± 0.2                                         | 38.3 ± 0.2*                                         | 38.4 ± 0.3                                         |
| f, breaths/min                                      | 134 ± 17                                          | 136 ± 10                                           | 154 ± 16                                           |
| V<sub>T</sub>, ml                                    | 1.35 ± 0.11                                        | 1.34 ± 0.26                                        | 1.38 ± 0.26                                        |
| V<sub>E</sub>/kg, ml/kg                              | 4.27 ± 0.43                                        | 4.24 ± 0.71                                        | 3.06 ± 0.49                                        |
| V<sub>E</sub>, ml/min                               | 180 ± 27                                          | 183 ± 41                                           | 209 ± 32                                           |
| V<sub>E</sub>/kg, ml·kg·min<sup>−1</sup>             | 570 ± 71                                          | 577 ± 113                                          | 465 ± 53                                           |
| VO<sub>2</sub>/kg, ml·kg·min<sup>−1</sup>             | 17.8 ± 3.1                                        | 17.3 ± 2.6                                        | 17.5 ± 2.0                                        |
| V<sub>CO</sub><sub>2</sub>/kg·ml·min<sup>−1</sup>      | 13.7 ± 0.9                                         | 14.1 ± 1.4                                        | 16.1 ± 1.4                                        |

Values are means ± SD; n = 8. T<sub>b</sub>, body temperature; f, breathing frequency; V<sub>T</sub>, tidal volume; V<sub>E</sub>/kg, V<sub>T</sub> normalized by body weight; V<sub>E</sub>, minute ventilation; V<sub>E</sub>/kg, V<sub>E</sub> normalized by body weight; VO<sub>2</sub>, O<sub>2</sub> consumption normalized by effective body mass; V<sub>CO</sub><sub>2</sub>, CO<sub>2</sub> production normalized by effective body mass.

Ventilatory parameters. In lean animals compared with their control values (vehicle), all ventilatory parameters (V<sub>E</sub>, V<sub>E</sub>/kg, f, V<sub>T</sub>, and V<sub>E</sub>/kg) during room air breathing, hypoxic challenges, and hypercapnic challenges were unaltered after administration of bicuculline (Tables 1 and 2). V<sub>E</sub>/kg, f, and V<sub>T</sub>/kg during room air breathing, 10% hypoxic exposure, or 4% hypercapnic exposure are shown for individual animals in Fig. 1.

In contrast, obese Zucker rats exhibited an increased ventilation (V<sub>E</sub> and V<sub>E</sub>/kg) and tidal volume (V<sub>T</sub> and V<sub>T</sub>/kg) after bicuculline administration. Bicuculline administration significantly increased resting ventilation by 17% compared with control values and was attributed to an increase in V<sub>T</sub> (Table 1). Similarly, the ventilation during hypoxic exposures also increased in obese rats after bicuculline administration. Bicuculline administration significantly increased ventilation during hypoxic exposures by 15% and was also attributed to an increase in tidal volume (Table 2). V<sub>E</sub>/kg, f, and V<sub>T</sub>/kg are shown for individual animals in Fig. 1. These changes in ventilation after bicuculline administration were not related to changes in metabolic rates (Table 1). Ventilatory parameters measured

| Table 2. Ventilatory parameters during hypoxic or hypercapnic exposures in lean and obese Zucker rats treated with vehicle or bicuculline |
|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Lean Rats                                           | Bicuculline                                         | Lean Rats                                           | Bicuculline                                         |
| Hypoxia                                             |                                                     | Hypoxia                                             |                                                     |
| T<sub>b</sub>, °C                                    | 38.0 ± 0.1                                         | 37.8 ± 0.3*                                         | 38.0 ± 0.2                                         |
| f, breaths/min                                      | 188 ± 15                                          | 176 ± 13                                           | 176 ± 24                                          |
| V<sub>T</sub>, ml                                    | 2.05 ± 0.20                                        | 2.03 ± 0.38                                        | 2.31 ± 0.41                                        |
| V<sub>E</sub>/kg, ml/kg                              | 6.49 ± 0.62                                        | 6.42 ± 1.16                                        | 5.13 ± 0.71                                        |
| V<sub>E</sub>, ml/min                               | 395 ± 39                                          | 356 ± 64                                           | 405 ± 79                                           |
| V<sub>E</sub>/kg, ml·kg·min<sup>−1</sup>             | 1,216 ± 91                                        | 1,123 ± 179                                        | 899 ± 147                                          |

Values are means ± SD; n = 8. *Significant difference between vehicle and bicuculline, P < 0.05.

Hypercapnia                                          |                                                     | Hypercapnia                                         |                                                     |
| T<sub>b</sub>, °C                                    | 38.1 ± 0.1                                         | 37.7 ± 0.3*                                         | 38.0 ± 0.3                                         |
| f, breaths/min                                      | 141 ± 14                                          | 146 ± 17                                           | 154 ± 14                                          |
| V<sub>T</sub>, ml                                    | 1.80 ± 0.21                                        | 1.84 ± 0.35                                        | 1.77 ± 0.23                                        |
| V<sub>E</sub>/kg, ml/kg                              | 5.68 ± 0.43                                        | 5.80 ± 1.10                                        | 3.93 ± 0.39                                        |
| V<sub>E</sub>, ml/min                               | 254 ± 47                                          | 271 ± 75                                           | 274 ± 51                                           |
| V<sub>E</sub>/kg, ml·kg·min<sup>−1</sup>             | 788 ± 103                                         | 855 ± 215                                          | 608 ± 96                                           |

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in response to the hypercapnic gas challenge were unaffected in the obese Zucker rats after administration of bicuculline (Table 2, Fig. 1).

Tb was measured continuously throughout the ventilatory measurements. After administration of bicuculline, lean Zucker rats revealed a small, but significant, drop (−0.2°C, P < 0.01) in Tb. In lean rats, decreased Tb after bicuculline administration was noted in eight of eight paired measurements during room air breathing, seven of eight observations during hypoxia, and eight of eight observations during hypercapnia. In contrast, Tb was not altered in obese Zucker rats by bicuculline administration (Tables 1 and 2).

Exercise test (V̇O₂peak). Consistent with the ventilatory data, V̇O₂peak was unaltered after bicuculline administration in lean animals compared with control values (Table 3, Fig. 2). In obese Zucker rats, however, bicuculline administration increased V̇O₂peak. The av-

Table 3. V̇O₂peak in lean and obese Zucker rats treated with vehicle or bicuculline

<table>
<thead>
<tr>
<th></th>
<th>Lean Rats</th>
<th>Obese Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Bicuculline</td>
</tr>
<tr>
<td>V̇O₂peak (ml/min)</td>
<td>31.2 ± 2.5</td>
<td>31.5 ± 3.1</td>
</tr>
<tr>
<td>ml·kg⁻¹·min⁻¹</td>
<td>90.2 ± 7.5</td>
<td>89.5 ± 8.4</td>
</tr>
<tr>
<td>ml·kg⁻⁰·⁷⁵·min⁻¹</td>
<td>69.1 ± 5.2</td>
<td>68.9 ± 6.3</td>
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</table>

Values are means ± SD; n = 8. V̇O₂peak (ml/min), peak V̇O₂ absolute value; V̇O₂peak (ml·kg⁻¹·min⁻¹), peak V̇O₂ normalized by total body mass; V̇O₂peak (ml·kg⁻⁰·⁷⁵·min⁻¹), peak V̇O₂ normalized by effective body mass. *Significant difference between vehicle and bicuculline, P < 0.05.
mainly via GABAA receptors (12). In GABAergic neurons, administration has shown that GABA inhibits respiratory activity via ionotropic (GABAA and GABAC) receptors to produce fast synaptic inhibition or metabotropic (GABAB) receptors to produce slow, prolonged inhibitory signals (6). GABA may be involved as a neurotransmitter in the generation, transmission, and modulation of respiratory-related neural activities (12–14, 18, 20). In the present study, bicuculline, a selective antagonist of GABA_A receptors, was chosen, because previous studies have shown that GABA inhibits respiratory activity mainly via GABA_A receptors (12). In GABAergic neurons, GABA_A receptors facilitate Cl⁻ flux into neurons, resulting in hyperpolarization, whereas antagonism of GABA_A receptors by bicuculline will decrease Cl⁻ flux, resulting in depolarization and increased excitation (6, 18). Thus any effect noted in the present study is restricted to a modulatory role exerted by endogenous GABA acting specifically on GABA_A receptors. GABA_A receptors are located throughout the neural axis and modulate numerous systems. In the present study, bicuculline was injected systemically, which consequently produced a widespread antagonistic action. Thus any effect noted here cannot be localized to any specific system or brain region. The goal of the present study, however, was to determine whether GABAergic mechanisms regulate ventilation and exercise capacity in obese Zucker rats. Clearly, additional experiments using a reductionist approach are required to specifically identify those brain areas that are directly responsible.

In the present study, baseline (DMSO) ventilatory and metabolic values (Table 1) for lean and obese rats are within the range of previously published values (22, 24). In the present study, comparisons of ventilation between lean and obese animals are complicated by the large differences in body weight and body composition. However, in the present study, our primary purpose was to assess the role of GABA in modulating ventilation. Thus lean and obese rats were used as their own control, such that weight differences between both groups are inconsequential.

In lean rats, bicuculline administration did not alter resting ventilation, ventilation during hypoxic exposure, ventilation during hypercapnic exposure, or VO₂peak. Indeed, in normal human subjects, increasing brain GABA concentration by administration of vigratrin, an agent that prevents the breakdown of GABA, had no effects on resting ventilation or on chemical ventilatory drive (10). Thus, consistent with the human literature, GABA does not exert a significant effect on control of respiration in normal-weight rats. In lean Zucker rats, however, bicuculline administration did induce a small, but long-lasting, decrease in T₅0 (Table 1), providing indirect evidence that bicuculline's effect persisted during the entire testing period. At the dose selected, no other side effect, such as bicuculline-induced seizures or increased mortality (38), was noted.

In contrast, bicuculline administration elevated resting ventilation, ventilation during hypoxic exposure, and VO₂peak in age-matched obese Zucker rats. The obese Zucker rat presents accelerated synthesis of GABA in the brain stem (28) and possesses altered brain GABAergic mechanisms (7, 28). After 8 wk of chronic artificial respiratory loading in rats, brain GABA levels are increased and responsible for depressing ventilation (31). Thus the increased chest wall loading or airway narrowing that is present in obesity (2, 9) may represent a possible stimulus responsible for the altered GABAergic mechanisms. In the present study, bicuculline administration significantly increased resting ventilation in obese rats, which was attributed to an increase in VT and not f. The selective effect on VT is consistent with previous reports indicat-

![Graph showing effects of bicuculline administration on relative peak O₂ consumption (VO₂peak) in individual lean (○) and obese (●) Zucker rats. Solid line, line of identity. Symbols above line of identity represent animals whose VO₂peak increased after bicuculline administration; symbols below line of identity represent animals whose VO₂peak decreased after bicuculline administration.](http://jap.physiology.org/)

**Fig. 2.** Effects of bicuculline administration on relative peak O₂ consumption (VO₂peak) in individual lean (○) and obese (●) Zucker rats. Solid line, line of identity. Symbols above line of identity represent animals whose VO₂peak increased after bicuculline administration; symbols below line of identity represent animals whose VO₂peak decreased after bicuculline administration.
ing that direct exogenous central administration of GABA or GABA_A receptor agonist produces a dose-dependent depression in respiratory amplitude with only minor effects on f (14, 20). In obese Zucker rats, systemic administration of bicuculline increased ventilation without any observed changes in surrounding CO_2 level, metabolic rate (V_O_2), or T_b. In anesthetized dogs, Kneussl and colleagues (20) reported that centrally administered GABA decreased ventilation and metabolic rate. In a second study, Kneussl and colleagues (21) further showed, however, that the reduction in metabolic rate was independent of the central effects of GABA on respiration. Our results also support the concept that GABAergic modulation of ventilation is independent of metabolic rate or T_b.

During hypoxia, the respiratory drive is determined by a balance between the stimulation of peripheral chemoreceptors and the central depression of hypoxia on respiration (35). It has been postulated that the late phase of the ventilatory response to hypoxia is modulated by a variety of neurotransmitters, including GABA (18, 35). Brain GABA content is elevated during hypoxic (37) and hypercapnic exposures (15, 19). The rise in ventilation after treatment with bicuculline during hypoxia is consistent with previous studies in anesthetized cats (27), sedated newborn piglets (16), or anesthetized rats (35).

During hypercapnia, the respiratory drive is primarily determined by central chemoreceptors, which respond to changes in H^+ concentration. In the present study, bicuculline administration had no effect on ventilation during 4% hypercapnia in lean and obese animals. It has been previously reported that intracerebroventricular administration of GABA did depress an increased ventilation during 10% CO_2 exposure (13), indicating that the preexisting GABAergic modulation at rest was not directly mediated by GABA_A receptors but compensated by central chemical drive or neutralized by increased CO_2/H^+ (15). The ventilation during hypercapnic exposure in lean and obese Zucker rats is not modulated by GABA_A receptors.

Relative V_O_2_peak (ml·kg^{-0.75}·min^{-1}) was reduced in the obese animals compared with the lean animals (Table 2), mirroring findings in obese humans (2). Bicuculline administration led to an increase in V_O_2_peak in obese animals and lessened the difference between lean and obese animals. Thus endogenous GABA, which tonically inhibits V_O_2_peak in obese animals, may partially account for their poor exercise capacity. The underlying mechanism of GABAergic inhibition on V_O_2_peak is unknown. To our knowledge, there has been no study specifically on the role of GABA in V_O_2_peak, but the effect of GABA on running time to exhaustion in normal-weight rats was investigated in two studies: muscimol, a GABA_A receptor agonist, injected directly into the posterior hypothalamus, significantly decreased treadmill run time to exhaustion (29), whereas baclofen, a GABA_B receptor agonist, enhanced endurance time to exhaustion (1). Does exercise contribute to an increase in brain GABA content? Striatal GABA levels remain unchanged after short-term exercise in rats (25), whereas whole brain GABA content is reduced after prolonged exercise in rats (5). Whether GABA levels during exercise in obese rats are different from those in lean rats is unknown, and additional studies using microdialysis in free-running rats are required to provide an answer. The increase in V_O_2_peak after bicuculline administration may, however, be secondary to improved ventilatory function. Although the respiratory system is not normally considered a limiting factor to peak exercise, this may not be so in certain pathological situations that affect the respiratory system, such as aging, lung disease, and obesity (2, 36). The mass loading due to fat deposition in and around the chest, coupled with the reduced ventilatory drive, may restrict ventilation during exercise. Thus we can speculate that, after bicuculline administration, the increased respiratory drive resulted in the obese rats attaining a higher ventilation and a concomitant higher V_O_2_peak. At present, however, we have no means of measuring ventilation during maximal exercise in obese rats. Nevertheless, we conclude that reduced exercise capacity in obese Zucker rats may be attributed to altered GABAergic mechanisms.

Significance. OHS is the combination of extreme obesity, somnolence, hypoventilation, arterial desaturation and hypercapnia, and pulmonary hypertension (33). The precise underlying pathophysiology of OHS is unclear and involves multiple factors, including impaired respiratory control, respiratory muscle weakness, abnormal respiratory load compensation, and chest wall limitations (3, 33, 39). The depressed chemical ventilatory drive is one recognized theory to explain the pathogenesis of OHS (33, 39). Although a role of GABA in OHS has not, to our knowledge, been previously proposed, the present results suggest that GABAergic tonic inhibition may be potentially responsible. In addition to GABA, complex interactions among the various neurotransmitters and neuromodulators involved in the etiology of obesity, such as leptin, neuropeptide Y, dopamine, opioids, adenosine, and several hormones (23), may directly or indirectly be involved in GABAergic regulation. Additional studies are required to address the role of GABAergic mechanisms in morbidly obese humans.

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