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

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Lee, Shin-Da, Hitoshi Nakano, and Gaspar A. Farkas. GABAergic modulation of ventilation and peak oxygen consumption in obese Zucker rats. J Appl Physiol 90: 1707–1713, 2001.—Obesity is often associated with a reduced ventilatory response and a decreased maximal exercise capacity. GABA is a major inhibitory neurotransmitter in the mammalian central nervous system. Altered GABAergic mechanisms have been detected in obese Zucker rats and implicated in their hyperphagic response. Whether altered GABAergic mechanisms also contribute to regulate ventilation and influence exercise capacity in obese Zucker rats is unknown and formed the basis of the present study. Eight lean [317 ± 18 (SD) g] and eight obese [450 ± 27 g] Zucker rats were studied at 12 wk of age. Ventilation at rest and ventilation during hypoxic (10% O2) and hypercapnic (4% CO2) challenges were measured by the barometric method. Peak O2 consumption (\(\dot{V}_{O_2\text{peak}}\)) in response to a progressive treadmill test to exhaustion was measured in a metabolic treadmill. Ventilation and \(\dot{V}_{O_2\text{peak}}\) were assessed after administration of equal volumes of DMSO (vehicle) and the GABA\(_A\) receptor antagonist bicuculline (1 mg/kg). In lean animals, bicuculline administration had no effect on ventilation and \(\dot{V}_{O_2\text{peak}}\). In obese rats, bicuculline administration significantly (\(P < 0.05\)) increased resting ventilation (465 ± 53 and 542 ± 72 ml·kg\(^{-1}\)·min\(^{-1}\) for control and bicuculline, respectively), ventilation during exposure to hypoxia (899 ± 148 and 1,038 ± 83 ml·kg\(^{-1}\)·min\(^{-1}\) for control and bicuculline, respectively), and \(\dot{V}_{O_2\text{peak}}\) (62 ± 3.7 and 67 ± 3.5 ml·kg\(^{-1}\)·min\(^{-1}\) for control and bicuculline, respectively). However, in obese Zucker rats, ventilation in response to hypercapnia did not change after bicuculline administration (608 ± 96 vs. 580 ± 69 ml·kg\(^{-1}\)·min\(^{-1}\)). Our findings indicate that endogenous GABA depresses ventilation and limits exercise performance in obese Zucker rats.

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ing hypercapnic exposure, and peak O2 consumption (\(V\dot{O}_2\) 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 \(V\dot{O}_2\) 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 (\(Fa\)/\(fa\)) 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 light 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 sensitive pressure transducer (model P55, Grass Instruments, Quincy, MA). The signal was received and amplified by a Grass DC driver (model 7PCPA) 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 \(\geq\)12 times during the recording, for calibration purposes. Barometric pressure to the nearest 1 h was obtained from the Internet posting of the US Weather Bureau located at the Buffalo International Airport.

From the pressure oscillations due to breathing, tidal volume (\(V_T\)) was computed using the formula of Drorbaugh and Penn (8), with incorporation of the analytic modification suggested by Jacky (17). For each condition, the average \(V_T\) and breathing frequency (f) were calculated over a period corresponding to \(\geq30\) successive breaths. Pulmonary ventilation (\(V_E\) and \(V\dot{E}\)) was also calculated (\(V_E = V_T \times f\)) and expressed at body temperature and water-saturated conditions (\(V_E\) in ml/min STPD and \(V\dot{E}\) in ml/kg \(\times\) min \(\times\) STPD). Colonic temperature was measured continuously from a rectal probe (Tele-thermometer, Yellow Springs Instruments, Yellow Springs, OH) and taken as representative of body temperature (\(T_b\)). Chamber temperature and humidity were monitored by means of a flow-through probe (Fisher Scientific, Pittsburgh, PA) mounted within the chamber. The rat was placed into the chamber and exposed to room air (21% O2-balance N2) for 30 min, hypoxia (10% O2, balance N2) for 20 min, room air for 15 min, and hypercapnia (4% CO2-23% O2-balance N2) for 10 min. Ventilatory patterns were recorded at the end of 30 min in room air, at 10 and 20 min during the hypoxic exposure, and at the end of the hypercapnic exposure.

\(V\dot{O}_2\) peak. The exercise test to elicit peak aerobic activity (\(V\dot{O}_2\) peak) was performed in a metabolic treadmill (Columbus Instruments, Columbus, OH). To maintain a constant flow rate, airflow through the metabolic treadmill was provided from pressurized air tanks (BOC Gases). Flow was controlled by a flowmeter (Dwyer Instruments) and maintained steady at 5 l/min throughout the exercise test.

Because of differences in exercise capacity between lean and obese animals (22), the exercise protocols used to elicit \(V\dot{O}_2\) peak were slightly different for lean and obese rats. The treadmill slope was set at 20% for lean animals and 10% for obese animals and remained constant throughout the exercise test. After injection, each rat was placed into the metabolic treadmill for 30 min before initiation of the exercise test. The protocol for lean animals consisted of an initial speed of 10 m/min followed by a 3 m/min increase in speed every 2 min until the animal could no longer continue to run. Obese rats began at 10 m/min followed by a 3 m/min increase every 3 min.

\(O_2\) uptake and \(CO_2\) output. \(O_2\) uptake (\(V\dot{O}_2\)) and \(CO_2\) output (\(V\dot{CO}_2\)) 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-3A/1, respectively, Ametek Applied Electrochemistry, Sunnyvale, CA) arranged in series. The calibrations and lineairities of the gas analyzers were checked twice daily using certified calibration gases (BOC gases). \(V\dot{O}_2\) and \(V\dot{CO}_2\) 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 O2-kg\(^{-0.75}\) 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. \(V\dot{O}_2\) peak was expressed in absolute terms (ml O2/min STPD) and in relative terms, corrected for total body mass (ml O2-kg\(^{-1}\)min\(^{-1}\) STPD) and for EBM (ml O2-kg\(^{-0.75}\)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 ≥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) before the actual
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 groups. Because of interactions among the three factors, the effects of bicuculline on V˙E, V˙E/kg, V T, lean and obese groups. Because of interactions among the experimental period and tested by unpaired design were conducted to analyze all parameters. Body between (lean and obese) and two within (gases and drugs) ed-measures ANOVA under general linear model in a one treated with vehicle or bicuculline.

Table 1. Resting ventilatory parameters in lean and obese Zucker rats treated with vehicle or bicuculline

<table>
<thead>
<tr>
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<th>Lean Rats</th>
<th>Obese Rats</th>
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<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Bicuculline</td>
</tr>
<tr>
<td>Tb, °C</td>
<td>38.5 ± 0.2</td>
<td>38.3 ± 0.2*</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>134 ± 17</td>
<td>136 ± 10</td>
</tr>
<tr>
<td>VT, ml</td>
<td>1.35 ± 0.11</td>
<td>1.34 ± 0.29</td>
</tr>
<tr>
<td>V˙E/kg, ml/kg</td>
<td>4.27 ± 0.43</td>
<td>4.24 ± 0.71</td>
</tr>
<tr>
<td>Ve, ml/min</td>
<td>180 ± 27</td>
<td>183 ± 41</td>
</tr>
<tr>
<td>V˙E/kg, ml·kg⁻¹·min⁻¹</td>
<td>570 ± 71</td>
<td>577 ± 113</td>
</tr>
<tr>
<td>V˙O₂, ml·kg⁻¹·min⁻¹</td>
<td>17.8 ± 3.1</td>
<td>17.3 ± 2.6</td>
</tr>
<tr>
<td>V˙CO₂, ml·kg⁻⁰.⁷⁵·min⁻¹</td>
<td>13.7 ± 0.9</td>
<td>14.1 ± 1.4</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 8. Tb, body temperature; f, breathing frequency; VT, tidal volume; V˙E/kg, VT normalized by body weight; V˙E, minute ventilation; Ve/kg, Ve normalized by body weight; V˙O₂, O₂ consumption normalized by effective body mass; V˙CO₂, CO₂ production normalized by effective body mass. *Significant difference between vehicle and bicuculline, P < 0.05.

Ventilatory parameters. In lean animals compared with their control values (vehicle), all ventilatory parameters (V˙E, V˙E/kg, f, VT, and V˙E/kg) during room air breathing, hypoxic challenges, and hypercapnic challenges were unaltered after administration of bicuculline (Tables 1 and 2). Ve/kg, f, and VT/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˙E and V˙E/kg) and tidal volume (VT and VT/kg) after bicuculline administration. Bicuculline administration significantly increased resting ventilation by 17% compared with control values and was attributed to an increase in VT (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). Ve/kg, f, and VT/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

<table>
<thead>
<tr>
<th></th>
<th>Lean Rats</th>
<th>Obese Rats</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Bicuculline</td>
</tr>
<tr>
<td>Tb, °C</td>
<td>38.0 ± 0.1</td>
<td>37.8 ± 0.3*</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>188 ± 15</td>
<td>176 ± 13</td>
</tr>
<tr>
<td>VT, ml</td>
<td>2.05 ± 0.20</td>
<td>2.03 ± 0.38</td>
</tr>
<tr>
<td>V˙E/kg, ml/kg</td>
<td>6.49 ± 0.62</td>
<td>6.42 ± 1.16</td>
</tr>
<tr>
<td>Ve, ml/min</td>
<td>385 ± 39</td>
<td>356 ± 64</td>
</tr>
<tr>
<td>V˙E/kg, ml·kg⁻¹·min⁻¹</td>
<td>1,216 ± 91</td>
<td>1,123 ± 179</td>
</tr>
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</table>

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

Hypoxia

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>Vehicle</td>
<td>Bicuculline</td>
</tr>
<tr>
<td>Tb, °C</td>
<td>38.1 ± 0.1</td>
<td>37.7 ± 0.3*</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>141 ± 14</td>
<td>146 ± 17</td>
</tr>
<tr>
<td>VT, ml</td>
<td>1.80 ± 0.21</td>
<td>1.84 ± 0.35</td>
</tr>
<tr>
<td>V˙E/kg, ml/kg</td>
<td>5.68 ± 0.43</td>
<td>5.80 ± 1.10</td>
</tr>
<tr>
<td>Ve, ml/min</td>
<td>254 ± 47</td>
<td>271 ± 75</td>
</tr>
<tr>
<td>V˙E/kg, ml·kg⁻¹·min⁻¹</td>
<td>798 ± 103</td>
<td>855 ± 215</td>
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Hypercapnia

Ventilatory parameters.
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 (VO₂ peak).** Consistent with the ventilatory data, VO₂ peak was unaltered after bicuculline administration in lean animals compared with control values (Table 3, Fig. 2). In obese Zucker rats, however, bicuculline administration increased VO₂ peak. The av-

Table 3. VO₂ peak in lean and obese Zucker rats treated with vehicle or bicuculline

<table>
<thead>
<tr>
<th></th>
<th>Lean Rats</th>
<th>Bicuculline</th>
<th>Obese Rats</th>
<th>Bicuculline</th>
</tr>
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<tbody>
<tr>
<td>VO₂ peak</td>
<td></td>
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<tr>
<td>ml/min</td>
<td>31.2 ± 2.5</td>
<td>31.5 ± 3.1</td>
<td>32.1 ± 1.85</td>
<td>34.5 ± 1.9*</td>
</tr>
<tr>
<td>ml·kg⁻¹·min⁻¹</td>
<td>90.2 ± 7.5</td>
<td>89.5 ± 8.4</td>
<td>64.4 ± 4.4</td>
<td>68.2 ± 4.1*</td>
</tr>
<tr>
<td>ml·kg⁻⁰·⁷⁵·min⁻¹</td>
<td>69.1 ± 5.2</td>
<td>68.9 ± 6.3</td>
<td>62.2 ± 3.7</td>
<td>66.8 ± 3.5*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 8. VO₂ peak (ml/min), peak VO₂ absolute value; VO₂ peak (ml·kg⁻¹·min⁻¹), peak VO₂ normalized by total body mass; VO₂ peak (ml·kg⁻⁰·⁷⁵·min⁻¹), peak VO₂ normalized by effective body mass. *Significant difference between vehicle and bicuculline, P < 0.05.
erage increase in \( \dot{V}_2 \) for all eight obese animals after bicuculline administration was \(-8\%\) compared with control (62.2 \pm 3.7 vs. 66.8 \pm 3.5 mlkg\(^{-0.75}\)min\(^{-1}\); \( P < 0.05\), single-group repeated measures). The effect of bicuculline administration on \( \dot{V}_2 \) is shown graphically for individual lean and obese animals in Fig. 2.

**DISCUSSION**

Our major findings can be summarized as follows. 1) Antagonism of GABA\(_A\) receptors does not change ventilation at rest or during ventilatory challenges in lean Zucker rats. 2) Breathing at rest in obese Zucker rats is modulated by endogenous GABA acting on GABA\(_A\) receptors. 3) Ventilation during hypoxic, but not hypercapnic, exposure is modulated by endogenous GABA acting on GABA\(_A\) receptors in obese Zucker rats. 4) Antagonism of GABA\(_A\) receptors in obese, but not in lean, Zucker rats leads to increased \( \dot{V}_2 \).

GABA is the major inhibitory neurotransmitter in the mammalian CNS and acts at \(-25-40\%\) of the synapses within the CNS (4). GABA can exert its effect via ionotropic (GABA\(_A\) and GABA\(_C\)) receptors to produce fast synaptic inhibition or metabotropic (GABA\(_B\)) 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 \( \dot{V}_2 \). Indeed, in normal human subjects, increasing brain GABA concentration by administration of vigabatrin, 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 \( T_b \) (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 \( \dot{V}_2 \) 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 \( V_l \) and not \( f \). The selective effect on \( V_l \) is consistent with previous reports indicat-
ing that direct exogenous central administration of GABA or GABA\textsubscript{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\textsubscript{2} level, metabolic rate (V\textsubscript{O}\textsubscript{2}), or T\textsubscript{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\textsubscript{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\textsuperscript{+} 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\textsubscript{2} exposure (13), indicating that the preexisting GABAergic modulation at rest was not directly mediated by GABA\textsubscript{A} receptors but compensated by central chemical drive or neutralized by increased CO\textsubscript{2}/H\textsuperscript{+} (15). The ventilation during hypercapnic exposure in lean and obese Zucker rats is not modulated by GABA\textsubscript{A} receptors.

Relative V\textsubscript{O}\textsubscript{2,peak} (ml\textmiddot kg\textsuperscript{-0.75}\textmiddot min\textsuperscript{-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\textsubscript{O}\textsubscript{2,peak} in obese animals and lessened the difference between lean and obese animals. Thus endogenous GABA, which tonically inhibits V\textsubscript{O}\textsubscript{2,peak} in obese animals, may partially account for their poor exercise capacity. The underlying mechanism of GABAergic inhibition on V\textsubscript{O}\textsubscript{2,peak} is unknown. To our knowledge, there has been no study specifically on the role of GABA in V\textsubscript{O}\textsubscript{2,peak}, but the effect of GABA on running time to exhaustion in normal-weight rats was investigated in two studies: muscimol, a GABA\textsubscript{A} receptor agonist, injected directly into the posterior hypothalamus, significantly decreased treadmill run time to exhaustion (29), whereas baclofen, a GABA\textsubscript{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\textsubscript{O}\textsubscript{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\textsubscript{O}\textsubscript{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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REFERENCES
GABAergic modulation of $V_\dot{E}$ and exercise in obesity


