Dopaminergic modulation of ventilation in obese Zucker rats

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Dopaminergic modulation of ventilation in obese Zucker rats. J Appl Physiol 92: 25–32, 2002.—To investigate the hypothesis that the impaired respiratory drive noted in morbid obesity was attributable to altered dopaminergic mechanisms acting on peripheral and/or central chemoreflex sensitivity, seven obese and seven lean Zucker rats were studied at 11 wk of age. Ventilation (V˙E) was measured by the barometric technique during hyperoxic (100% O2), normoxic (21% O2), hypoxic (10% O2), and hypercapnic (7% CO2) exposures after the administration of vehicle (control), haloperidol (Hal, 1 mg/kg, a central and peripheral dopamine (Da) receptor antagonist), or domperidone (Dom, 0.5 mg/kg, a peripheral Da receptor antagonist). In both lean and obese rats, Hal increased tidal volume and decreased respiratory frequency during hyperoxia or normoxia, resulting in an unchanged V˙E. In contrast, Dom did not affect tidal volume, frequency, or V˙E during hyperoxia or normoxia. During hypoxia, however, V˙E significantly increased from 1,132 ± 136 to 1,348 ± 98 ml·kg−1·min−1 (P < 0.01) after the administration of Dom in obese rats, whereas no change was observed in lean rats. Hal significantly decreased V˙E during hypoxia compared with control in lean but not obese rats. In both lean and obese rats, Hal decreased V˙E in response to hypercapnia, whereas Dom had no effect. Our major findings suggest that peripheral chemosensitivity to hypoxia in obese Zucker rats is reduced as a result of an increased dopaminergic receptor modulation in the carotid body.

haloperidol; domperidone; peripheral chemosensitivity; hypoxia

MOREBID OBESITY IS OFTEN ASSOCIATED with respiratory deficits, including alveolar hypoventilation. It has been demonstrated that severely obese patients with obesity hypoventilation syndrome exhibited blunted ventilatory responses to hypoxia and/or hypercapnia (21, 39), suggesting that the pathogenesis in the alveolar hypoventilation may be linked to altered chemoreflex mechanisms (39).

The control of breathing is modified by inputs that originate from central and peripheral chemoreceptors. Dopamine (Da), a monoamine neurotransmitter, is the most abundant catecholamine in the brain and in ca-

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METHODS

Animals

Seven pairs of the lean (Fa?) and obese (fa/fa) male Z rats were studied at ~11–12 wk of age. Animals were purchased at 4 wk of age from Vassar College, Poughkeepsie, NY. One lean and one obese rat were housed per cage. Ambient temperature was maintained at 24°C with a 12:12-h light-dark cycle. All animals were provided with standard laboratory chow (Purina) and water ad libitum. The Institutional Animal Care and Use Committee, University at Buffalo, approved all experimental protocols.

Techniques and Measurements

Ventilation was measured by using the barometric technique, which has been previously described (17–19, 23). A cylindrical Plexiglas chamber with a volume of 4 liters was used for the measurements of V̇e. The rat was placed in the chamber within a restrainer that did not permit backward rotation. The animal chamber had an inlet tube that was connected to pressurized air tanks (BOC Gases). Inlet flow was regulated at 2 l/min by a flowmeter (Dwyer Instruments, Michigan City, IN). An Ametek S-3A/I O2 analyzer and an Ametek CD-3A CO2 analyzer measured the concentrations of inflowing or outflowing O2 and CO2, respectively. The calibrations of the gas analyzers were checked routinely, using certified calibration gases (BOC Gases). To measure V̇e, 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 (Statham Laboratories, model 236). The signal was received, amplified (Grass Instruments), and displayed on an oscillographic strip chart recorder (Grass polygraph). An average of 50 breaths was recorded on paper at a speed of 10 mm/s. Injection and withdrawal of 0.3 ml of air with a 1-ml syringe were performed several times during the recording, for calibration purposes. Body temperature (Tb) was measured continuously by a thermometer probe (Yellow Springs Instruments) placed at least 5 cm into the rectum. The thermometer was calibrated with a mercury thermometer over the range from 35 to 40°C of temperature. Chamber temperature and relative humidity were monitored by a recording thermometer (Yellow Springs Instruments) placed at least 5 cm into the rectum. A thermometer probe (Yellow Springs Instruments) placed at least 5 cm into the rectum.

Pulmonary V̇E was calculated (V̇E = VT × f) and expressed in either absolute value (ml/min) or corrected value for body weight (ml.kg⁻¹.min⁻¹). O2 consumption (V̇O2) and CO2 production (V̇CO2) were calculated from the inflow-outflow O2 and CO2 differences multiplied by the gas flow, neglecting the small error introduced by a respiratory quotient less than unity. All V̇O2 and V̇CO2 values (presented at standard temperature and pressure dry) are expressed either in raw data (ml/min) or per unit of effective body mass because lean and obese rats of the same size have different body compositions (28). Effective body mass for lean and obese Z rats was calculated as 1.00 × M0.75 and 0.86 × M0.75, respectively, where M is the body weight (kg) of the animal.

Experimental Protocol

To reduce the stress level during the experiment, all animals were habituated to an intraperitoneal injection of 0.4 ml of saline, the insertion of the thermoprobe, and the restraining device within the chamber for 60 min on 2 successive days before the first experimental study.

Study 1. To rule out the possible stress effects due to handling, insertion of the thermoprobe, and restraint, a preliminary study was performed in lean (n = 6) and obese (n = 6) Z rats at 8 wk of age. After an intraperitoneal injection of dimethyl sulfoxide (DMSO; 1 ml/kg) and the insertion of a colonic thermoprobe, the rat was placed into the barometric chamber within the restrainer, and it breathed room air for 60 min. Tb and V̇e were measured at 5- and 10-min intervals, respectively.

Study 2. Each animal was tested at 3-day intervals after an intraperitoneal injection of equal volumes of vehicle (DMSO, 1 ml/kg), Hal (1 mg/kg, central and peripheral DA receptor antagonist), or Dom (0.5 mg/kg, peripheral DA receptor antagonist). The solutions were prepared daily and placed in vials labeled as I, II, or III. The three agents were given in a randomized design on days 1, 4, and 7. The investigator involved in the actual testing remained blinded to the contents of the vials until the entire study was completed and analyzed. To minimize any potential differences due to circadian rhythms, experiments were begun in each animal at the exact same time between 0800 and 1500.

After the administration of the agent, the rat was placed into the barometric chamber within the restrainer and exposed to normoxia (21% O2, balance N2) for 30 min followed by hyperoxia (100% O2) for 3 min, normoxia for 10 min, and hypoxia (10% O2, balance N2) for 3 min. Thereafter, the rat was exposed to hyperoxia (100% O2) for 5 min again followed by hypercapnia (7% CO2, balance O2) for 5 min. Ventilatory data were collected during the last minute of each gas exposure. The total experimental period was 60 min.

Statistical Analysis

Body weights of individual rats were averaged over the experimental period, and differences between lean and obese rats were tested by unpaired Student’s t-test. In study 1, analysis of variance (ANOVA) with repeated measure was used. In study 2, the differences in V̇e responses to hyperoxia/ hypoxia or hypercapnia between lean and obese Z rats were analyzed by factorial ANOVA concerning phenotype and gas exposure. The differences between data among the responses after each agent administration within a single group were analyzed by one-way ANOVA. When significance was indicated (P < 0.05), a Bonferroni’s correction for multiple comparisons was used. A P value of <0.05 was considered statistically significant. All data presented in the text, tables, and figures are means ± SD.

RESULTS

Study 1

As shown in Fig. 1, the mean Tb at 5 min after DMSO injection was 38.1 ± 0.1°C in lean and 37.9 ± 0.1°C in obese Z rats, respectively, and these values did not change significantly during the entire 60-min observation period. Although V̇e was increased at 10 min after DMSO injection in the two groups, no difference in V̇e was detected from 20 to 60 min after injection (Fig. 1).

Study 2

Comparisons between control lean and obese rats. The obese Z rats weighed more than age-matched lean animals (438 ± 42 vs. 283 ± 18 g, P < 0.01). Obese Z
obese rats adopted a breathing strategy with a higher f and a lower VT (ml/kg) than lean rats during room air breathing (Table 1). Resting VO₂ and V̇CO₂ during room air were not different between lean and obese rats. Figure 2 illustrates different ventilatory responses to hypoxia (Fig. 2A) and hypercapnia (Fig. 2B) between lean and obese Z rats. Although V̇E values during hyperoxia (100% O₂) and normoxia (21% O₂) breathing were not different between lean and obese rats, ventilatory response to 3-min hypoxia (10% O₂) was significantly reduced in obese rats compared with lean rats (P < 0.01). In addition, ventilatory response to 5-min hypercapnia (7% CO₂) was also significantly reduced in obese rats compared with lean rats (P < 0.01).

**Normoxia.** As shown in Table 1, in both lean and obese Z rats, neither Hal nor Dom administration changed Th, VO₂, and V̇CO₂ during room air breathing. However, Hal significantly decreased f and increased V̇E, resulting in no changes in V̇E compared with the vehicle control in both lean and obese Z rats. On the other hand, Dom had no effects on f, VT, and V̇E in both lean and obese Z rats during normoxic breathing (Table 1).

**Hyperoxia and hypoxia.** The changes in V̇E, f, and VT during hyperoxia, normoxia, and hypoxia exposure after vehicle or Hal injection are summarized in Fig. 3. In lean Z rats during hyperoxia as well as normoxia, the administration of Hal did not change V̇E, although f decreased and VT increased. During hypoxic exposure, the administration of Hal in lean rats elicited a significant depression in V̇E (P < 0.05) due to a decrease in f and little change in VT. In contrast to lean rats, obese rats displayed no change in V̇E in response to Hal during hypoxia, because of a decrease in f and an increase in VT (6.31 ± 0.85 to 7.28 ± 0.61 ml/kg, P < 0.05).

In four of the seven lean rats, Dom elicited an increase in VT without changes in f during hypoxia, resulting in an increase in V̇E. However, the remaining three lean rats exhibited no changes in VT, f, and V̇E during hypoxia. Dom did not significantly change f, VT, and V̇E during hypoxia compared with vehicle control in lean rats as a group (Fig. 4). In contrast, all obese rats increased VT during hypoxia after administration of Dom compared with vehicle control (7.57 ± 0.88 vs. 6.31 ± 0.85 ml/kg, P < 0.01) without changes in f, resulting in a pronounced rise in V̇E compared with control (1,348 ± 98 vs. 1,132 ± 136 ml·kg⁻¹·min⁻¹, P < 0.01). On the other hand, Dom did not change any parameters during hyperoxia in both lean and obese rats (Fig. 4).

**Hypercapnia.** In both lean and obese rats, Hal decreased V̇E responses to hypercapnia mainly because of a decreased response in VT (Fig. 5). The patterns of

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**Table 1. Effects of haloperidol and domperidone on respiratory and metabolic parameters during room air breathing**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Haloperidol</th>
<th>Domperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean Zucker rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Th, °C</td>
<td>38.3 ± 0.1</td>
<td>38.2 ± 0.2</td>
<td>38.2 ± 0.2</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>127 ± 17</td>
<td>99 ± 18*</td>
<td>137 ± 15</td>
</tr>
<tr>
<td>VT, ml</td>
<td>1.44 ± 0.13</td>
<td>1.73 ± 0.22*</td>
<td>1.43 ± 0.13</td>
</tr>
<tr>
<td>VT, ml/kg</td>
<td>5.15 ± 0.53</td>
<td>6.11 ± 0.67*</td>
<td>5.06 ± 0.54</td>
</tr>
<tr>
<td>V̇E, ml/min</td>
<td>182 ± 28</td>
<td>170 ± 36</td>
<td>198 ± 39</td>
</tr>
<tr>
<td>V̇E, ml/kg</td>
<td>648 ± 87</td>
<td>599 ± 114</td>
<td>702 ± 123</td>
</tr>
<tr>
<td>V̇O₂, ml/kg/min</td>
<td>19.7 ± 2.2</td>
<td>16.9 ± 3.3</td>
<td>18.3 ± 2.1</td>
</tr>
<tr>
<td>V̇O₂, ml/kg²/75/min</td>
<td>16.5 ± 1.9</td>
<td>14.1 ± 2.3</td>
<td>15.2 ± 2.4</td>
</tr>
<tr>
<td>Obese Zucker rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Th, °C</td>
<td>38.0 ± 0.2</td>
<td>37.9 ± 0.2</td>
<td>38.0 ± 0.2</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>151 ± 15§</td>
<td>114 ± 10?</td>
<td>148 ± 13</td>
</tr>
<tr>
<td>VT, ml</td>
<td>1.80 ± 0.38†</td>
<td>2.29 ± 0.32*</td>
<td>1.89 ± 0.26</td>
</tr>
<tr>
<td>VT, ml/kg</td>
<td>4.06 ± 0.61†</td>
<td>5.14 ± 0.66*</td>
<td>4.31 ± 0.39</td>
</tr>
<tr>
<td>V̇E, ml/min</td>
<td>270 ± 63§</td>
<td>262 ± 44</td>
<td>280 ± 43</td>
</tr>
<tr>
<td>V̇E, ml/kg</td>
<td>608 ± 90</td>
<td>588 ± 84</td>
<td>639 ± 62</td>
</tr>
<tr>
<td>V̇O₂, ml/kg²/75/min</td>
<td>18.3 ± 3.0</td>
<td>16.6 ± 2.0</td>
<td>18.0 ± 2.2</td>
</tr>
<tr>
<td>V̇O₂, ml/kg²/75/min</td>
<td>15.9 ± 2.4</td>
<td>14.3 ± 1.2</td>
<td>15.7 ± 2.2</td>
</tr>
</tbody>
</table>

Values are means ± SD. Th, body temperature; f, respiratory frequency; VT, tidal volume; V̇E, ventilation; V̇O₂, O₂ uptake; V̇CO₂, CO₂ production. *P < 0.05, †P < 0.01; significantly different from corresponding control value. §P < 0.05, ¶P < 0.01; significantly different from corresponding control value in lean rats.
alterations in $V_e$, $f$, and $V_t$ with Hal were not different between lean and obese rats. On the other hand, Dom did not affect $V_e$, $f$, or $V_t$ in response to hypercapnia compared with control in both lean and obese rats (data are not shown).

**DISCUSSION**

**Critique of Experimental Design**

Before discussing our results, we need to address several limitations of the experimental design. First, restraint may have influenced $V_e$, and our vehicle, DMSO, may have stimulated $V_e$ (8) and depressed body temperature (25). However, as demonstrated in study 1, $V_e$ and $T_b$ were constant (Fig. 1) at least during the experimental period tested in study 2, and therefore we do not believe that either restraint or DMSO affected our findings. In addition, a potential neurotoxicity has been reported when DMSO is administered daily for 10 successive days (5). However, because we injected each animal with DMSO at 3-day intervals and only on three occasions, it is unlikely that neurophysiological alterations would have resulted.

Second, although we did not examine dose-response relationship and time course of drug activity, the doses of Hal and Dom selected in the present study and the timing of the ventilatory parameters after drug administration were determined carefully according to previous reports. Hal, a neuroleptic agent that crosses the BBB, has been widely used in conscious rats ranging in doses up to 2 mg/kg (ip) to examine its effect on seizures and behavior (22, 29). Hal is known to progressively increase $V_e$ at low doses (0.1–100 $\mu$g/kg) and to

![Fig. 3. Changes in $V_e$, respiratory frequency ($f$), and tidal volume ($V_t$) during hyperoxia, normoxia, and hypoxia with vehicle control or haloperidol. Haloperidol decreased $f$ under the 3 conditions in both lean (A) and obese (B) rats. In lean rats, haloperidol did not change $V_t$ during hypoxia compared with control, leading to a reduction in $V_e$ during hypoxia. In contrast, haloperidol increased $V_t$ in response to hypoxia compared with control, resulting in minimal changes in $V_e$ in obese rats. *$P$, 0.05, **$P$, 0.01, significantly different from corresponding control value. Values are means ± SD.](http://jap.physiology.org/)
decrease V˙E at intermediate doses (1 mg/kg) (6). This dual action of Hal on V˙E is considered to reflect either peripheral chemoreceptor stimulation or central dopaminergic neuron inhibition. Thus, to block both peripheral and central Da receptors, we chose an intermediate dose (1 mg/kg) of Hal to investigate the difference in ventilatory response to chemical stimuli between lean and obese rats. The changing patterns in V˙E, f, and VT with haloperidol were not different between lean and obese rats. *P < 0.05, **P < 0.01, significantly different from corresponding control value. Values are means ± SD.

Therefore, to achieve a sufficient inhibition of peripheral Da receptors, we selected 0.5 mg/kg of Dom in the present study. In all rats tested, behavioral effects such as hypoactivity or sedation were never observed after the administration of either agent.

Two major families of Da receptors, referred to as D1 and D2, have been identified (10). Because two selective D2 antagonists, Hal and Dom, have been widely utilized for the investigation of dopaminergic mechanism, we selected them to examine our hypothesis in the present experimental design. Any effects we observed should be ascribed predominantly to D2 receptors because we limited the scope of our study to the effects of Da acting on central and/or peripheral D2 receptors. Because Hal and Dom were injected systematically to produce a widespread antagonistic action, we have to add a cautionary note that any effects we observed cannot be isolated either to any specific system or to any neural structure. Nevertheless, the goal of the present study was to differentiate the ventilatory effects of endogenous Da acting on central and/or peripheral D2 receptors and potential difference in ventilatory response between lean and obese Z rats.

**Normoxia and Hyperoxia**

Da is widely accepted as an inhibitory neurotransmitter in the carotid body (2). In mammals, Da and Da receptor agonists injected into the central nervous system consistently produced ventilatory augmentation during either normoxia or hypoxia (13), whereas peripheral Da receptor antagonism consistently enhanced V˙E and carotid chemoreceptor discharge (2). Thus Da appears to exert a dual effect on respiratory modulation: central ventilatory stimulation and peripheral ventilatory depression.

Because Hal crosses the BBB, it produces effects that are a combination of peripheral chemoreceptor stimulation and central dopaminergic neuron inhibition. In the present study, both lean and obese Hal-treated rats decreased f and increased VT, resulting in an unchanged V˙E during hyperoxic and normoxic breathing. These results are in agreement with a previous study in rats showing that the intracerebroventricular injection of Hal elicited a depression in f and an increase in VT, suggesting a tonic influence on Da receptors involved in central respiratory regulation (13). Dom, on the other hand, does not cross the BBB; thus its effects are limited to peripheral chemoreceptors. Because Dom administration did not affect f, VT, and V˙E in both lean and obese Z rats during hyperoxic and normoxic breathing, endogenous Da acting on D2 receptors does not modulate V˙E under these conditions without hypoxia. Our findings are consistent with a report in healthy humans reporting that Dom administration produced no significant change in V˙E during normoxic breathing (9).

**Hypoxia**

As stated earlier, Hal crossing the BBB antagonizes both central and peripheral D2 receptors, which con-
sists of reversing Da-mediated peripheral ventilatory stimulation and central ventilatory depression. Indeed, it has been demonstrated that Hal greatly attenuates the ventilatory response to hypoxia despite an increase in carotid chemoreceptor activity, suggesting that Da acts as an excitatory neurotransmitter in the integrating centers projecting from peripheral chemoreceptor activity (31). In lean Z rats, Hal did not change $V_T$, but $f$ declined during hypoxia, resulting in a significant decrease in $V_E$ compared with vehicle control, suggesting that the role of central D2 modulation of $V_E$ outweigh the role of peripheral D2 receptors in lean Z rats. In contrast, the administration of Hal in obese Z rats significantly increased $V_T$ with a concomitant decline in $f$ during hypoxia, resulting in no (minimal) overall effect on $V_E$. Although the central inhibitory effects by Hal are superimposed on the ventilatory output in obese Z rats, the augmented $V_T$ response to hypoxia by Hal seems to be due to an increased D2 contribution to the peripheral chemoreceptors in obese Z rats. However, from our results with Hal, we cannot exclude a possibility that central D2-mediated hypoxic ventilatory stimulation may be blunted in obese Z rats.

It is known that the peripheral Da receptor antagonist Dom stimulates $V_E$ and carotid body chemoreceptor afferent neural activity (16, 38). Moreover, in normal awake cats and goats, Dom increases $V_E$ in response to hypoxia by removing tonic inhibition from endogenous carotid body Da receptors (16, 35). We noted that, in lean Z rats, $V_E$ in response to acute hypoxia did not significantly increase after treatment with Dom (Fig. 4), suggesting no tonic peripheral inhibitory ventilatory modulation by Da in lean rats. Walsh et al. (37) showed that, in humans, half of the population did not augment their hypoxic ventilatory response when pretreated with Dom, suggesting a wide variability in individual hypoxic sensitivities in response to Dom. Tatsumi et al. (35) also demonstrated in cats that peripheral chemoreceptor responsiveness to hypoxia was highly variable among individual cats as well as the ventilatory response to Dom. In the present study, four of the seven lean (Fa/Fa or Fafaf) rats, but all the obese (fafa) rats, exhibited increased $V_T$ and $V_E$ responses to hypoxia after the administration of Dom, indicating that a genetic factor may account for the variable responsiveness to Dom during hypoxia. Nevertheless, in comparison between the two groups, we found that the administration of Dom in obese Z rats restored the ventilatory response to hypoxia compared with vehicle control, such that it became indistinguishable from that of control lean rats (Fig. 4). These results suggest that in the carotid body Da could have a pivotal role in modulating the depressed ventilatory responses to hypoxia observed in obese Z rats compared with lean Z rats.

Our findings from both the Hal and Dom studies suggest that the sensitivity to hypoxia in the peripheral chemoreceptors in obese Z rats may be blunted as a result of an abnormality originating from dopaminergic mechanisms. Further studies, including measurement of the carotid sinus nerve activity, however, will be necessary to substantiate our perspectives.

**Hypercapnia**

In contrast to the role of Da on ventilatory sensitivity to hypoxia, controversy remains over its role in mediating the response to hypercapnia. In the present study, Hal decreased ventilatory response to hypercapnia mainly as a result a decreased response in $V_T$, whereas Dom had no the effect on them in both lean and obese rats. These results are consistent with the findings of Berkenbosch et al. (1), who reported that Hal diminished both the peripheral and central ventilatory sensitivity to CO2 whereas Dom had no effect on peripheral CO2 sensitivity in anesthetized cats. Donnelly et al. (7) further demonstrated that Hal had no effect on carotid sinus nerve discharge in response to hypercapnia in cats. From our results, we suggest that D2 receptors in the central pathways play an important role in ventilatory response to hypercapnia in both lean and obese Z rats. In contrast to the above findings, it has been reported that Dom enhanced the ventilatory response to hypercapnia via an effect on the carotid bodies in awake goats (16), and also Dom augments that peripheral chemosensory discharge in response to hypercapnia in anesthetized cats (14). These conflicting findings could be ascribed, at least in part, to species differences, to the state of consciousness, or to differences in dosages of drugs or levels of hypercapnia.

In comparison with lean rats, obese Z rats did not differ in the effects of both Hal and Dom on their hypercapnic ventilatory response, suggesting that the dopaminergic mechanisms for CO2 sensitivity in the brain stem integrating centers or the peripheral chemoreceptors may not be different between obese and lean Z rats. We, therefore, suggest that the mechanism underlying the decreased hypercapnic ventilatory response in obese Z rats may not be dopaminergic D2 modulation in origin.

**Obesity and Hypoxic Chemosensitivity**

Previous studies have shown that severely obese subjects with alveolar hypoventilation have depressed ventilatory responses to hypoxia (21, 39). In the present study, obese Z rats were much heavier than lean rats and displayed blunted ventilatory response to hypoxia. In our previous studies, we have suggested that several neuromodulators including the opioids, GABA, nitric oxide, and glutamate may partially account for the depressed ventilatory response in obese Z rats (17–19, 23). The novel finding reported herein is that the blunted ventilatory response to hypoxia could be linked to a depression of the peripheral chemoreflex response of dopaminergic origin. The genetically obese Z rat has a mutation in the gene expressing leptin receptors (27), which have been found to be widely distributed in many organs. Leptin is known to inhibit Da release from neuronal endings of hypothalamic synaptosomes (3). Thus, in obese Z rats, abnormal leptin receptors lead to a disrupted leptin transport
into the carotid body, resulting in an enhancement of Da release, which may be contributing to the blunted ventilatory response to hypoxia. Although little is known about whether obesity per se affects the peripheral dopaminergic metabolism, we suggest that an inhibitory action of Da in the carotid body may in part contribute to the development of obesity hypventilation. Future studies evaluating the effects of Da receptor antagonists on obese Z rats of various ages may be used to test this hypothesis.

In conclusion, the present results suggest that peripheral chemosensitivity to hypoxia in obbe Z rats may be blunted as a result of a altered dopaminergic mechanisms. Recent evidences, however, support a genetic predisposition for a reduced ventilatory response to hypoxia (32, 34). Thus, beside a mutation in leptin receptor, the altered dopaminergic modulation observed in obbe Z rats may be genetic in origin. Furthermore, either synergistic or additive interaction of obesity with a preexisting genetic predisposition may exacerbate the blunted ventilatory response to hypoxia in obbe Z rats. Further studies are needed to investigate the interactions between genetic and environmental factors on the drive to breathe in obesity.

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