Role of endogenous female hormones in hypoxic chemosensitivity

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[1]*Cardiovascular Pulmonary Research Laboratory, University of Colorado Health Sciences Center, Denver 80262;* [2]*Department of Chest Medicine, School of Medicine, Chiba University, Chiba 260, Japan; and* [3]*Department of Anthropology, University of Colorado at Denver, Denver, Colorado 80217*

Tatsumi, Koichiro, Cheryl K. Pickett, Christopher R. Jacoby, John V. Weil, and Lorna G. Moore. Role of endogenous female hormones in hypoxic chemosensitivity. *J. Appl. Physiol.* 83(5): 1706–1710, 1997.—Effective alveolar ventilation and hypoxic ventilatory response (HVR) are higher in females than in males and after endogenous or exogenous elevation of progesterone and estrogen. The contribution of normal physiological levels of ovarian hormones to resting ventilation and ventilatory control and whether their site(s) of action is central and/or peripheral are unclear. Accordingly, we examined resting ventilation, HVR, and hypercapnic ventilatory responses (HCVR) before and 3 wk after ovariectomy in five female cats. We also compared carotid sinus nerve (CSN) and central nervous system translation responses to hypoxia in 6 ovariectomized and 24 intact female animals. Ovariectomy decreased serum progesterone but did not change resting ventilation, end-tidal P_{CO_2}, or HCVR (all P = NS). Ovariectomy reduced the HVR shape parameter A in the awake (38.9 ± 5.5 and 21.2 ± 3.0 before and after ovariectomy, respectively, $P < 0.05$) and anesthetized conditions. The CSN response to hypoxia was lower in ovariectomized than in intact animals (shape parameter A = 22.6 ± 2.5 and 54.3 ± 3.5 in ovariectomized and intact animals, respectively, $P < 0.05$), but central nervous system translation of CSN activity into ventilation was similar in ovariectomized and intact animals. We concluded that ovariectomy decreased ventilatory and CSN responsiveness to hypoxia, suggesting that the presence of physiological levels of ovarian hormones influences hypoxic chemosensitivity by acting primarily at peripheral sites.

progesterone; estrogen; carotid body; ovariectomy; hypercapnic ventilatory response

EFFECTIVE ALVEOLAR ventilation and hypoxic ventilatory response (HVR) are higher in females than in males when controlled for differences in body size (1, 16). Such gender differences are likely due to actions of ovarian hormones. The administration of progesterone combined with estrogen raises alveolar ventilation, HVR, and hypercapnic ventilatory response (HCVR) via receptor-mediated mechanisms of action involving central as well as peripheral sites (5, 8, 9, 12). In support of central nervous system sites is evidence of progesterone receptors in the hypothalamus and increased integrated phrenic neural activity after the acute administration of progesterone to estrogen-pretreated animals (3, 4). In support of the involvement of peripheral as well as central sites is the finding that chronic administration of these hormones or their sustained elevation during pregnancy increases HVR as the result of stimulatory effects of progesterone on the carotid body and of estrogen on the central nervous system translation of carotid sinus nerve (CSN) activity into ventilation (8, 9).

Normal, physiological levels of ovarian hormones may also raise HVR, as suggested by previous, separate studies, in which we found lower HVR shape parameter A values in postmenopausal than in premenopausal women (77 ± 12 and 107 ± 11, respectively, $P < 0.05$) and in ovariectomized than in intact female cats (25 ± 6 and 41 ± 5, respectively, $P < 0.05$) (12, 16, 23). However, in each case, different groups were compared; this complicates the assessment of the influence of endogenous ovarian hormones by introducing variation in age, body size, and other interindividual characteristics. The site at which normal, physiological levels of ovarian hormones influence ventilation and ventilatory control is unknown. Therefore, the present studies were undertaken to compare resting ventilation and ventilatory responses to hypoxia and hypercapnia within the same awake animals before and after ovariectomy. To determine whether differences were due to peripheral or central chemoreflex actions, we measured the CSN response to hypoxia and the central nervous system translation of CSN activity into ventilation in separate groups of anesthetized intact and ovariectomized female cats.

METHODS

Animals. Resting ventilation, HVR, and HCVR were measured in five awake and anesthetized female cats before and 3 wk after ovariectomy. Ventilatory and CSN responses to hypoxia were measured in these same animals and in one additional ovariectomized animal under anesthesia. Because these measurements can be made only once in a given animal, the ventilatory and CSN responses to hypoxia in the six ovariectomized animals were compared with values obtained in an additional 24 intact female cats. Ovariectomy was carried out under sterile conditions in animals anesthetized with intramuscular injection of acetylpromazine (0.1 mg/kg) and ketamine (10 mg/kg).

Awake animal preparation. A small Teflon button with an indwelling cannula for respiratory gas sampling was permanently implanted in the trachea during isoflurane anesthesia. Two days later, the awake animal was placed in a ventilated 21-liter body plethysmograph equipped with inlet and outlet ports, thermometer, and calibration syringe (2, 7). The temperature of the chamber was maintained at 21–25°C by circulating cold water through copper tubing lining the circumference of the chamber. After an acclimatization period

to stabilize the animal, the chamber's inlet and outlet ports were occluded and the pressure changes (model CD 15, Validyne, Northridge, CA) within the chamber were recorded for 20–40 s for measurement of tidal volume. A known volume of air was withdrawn and injected at the end of an inspiration for calibration purposes, and the air temperature in the chamber was read at the time of each measurement. Respiratory gases were measured by O_2 fuel cell (Applied Technical Products, Denver, CO) and CO_2 infrared analyzer (model LB-2, Sensor Medics, Anaheim, CA), which had been calibrated with gases analyzed by the Scholander technique. Signals were recorded on a four-channel strip chart recorder (model 2400, Gould, Cleveland, OH).

Anesthetized animal preparation. Cats were anesthetized with a mixture of 40 mg of chloralose and 200 mg of urethan per kilogram of body weight administered intravenously. Measurements were made under conditions in which the level of anesthesia was sufficient to suppress the pain-withdrawal reflex but low enough to preserve the corneal reflex and minimize ventilatory depression. Core temperature was maintained at 38.2–38.8°C with a heating pad servo-controlled by a rectal temperature probe. For the measurements before ovariectomy, cats were intubated and their ventilatory responses were obtained as described below. For the final measurements, a catheter was inserted into the femoral vein for supplemental administration of anesthetic and into the femoral artery for sampling arterial blood. After tracheostomy, a tracheal cannula was inserted into the distal trachea and connected to a low-resistance, low-dead space (2 ml) respiratory valve. Inspiratory flow was measured by pneumotachograph (model CD 15, Validyne), and respiratory gases were analyzed. The flowmeter was calibrated against a Tissot spirometer, with flow rate to the gas analyzer (100 ml/min) taken into account. Signals from the monitoring instruments were connected to a digital computer (Nova 1200, Data General, Southboro, MA), and values were averaged over 30-s intervals.

CSN recording. After the proximal trachea and esophagus were ligated and reflected to expose the carotid sinus region, the CSN was carefully stripped of surrounding tissue. Carotid body neural output was recorded by platinum bipolar electrodes from the whole desheathed nerve bundle (6). The amplified signal was filtered (100–3,000 Hz), sampled at a rate of 1 kHz, and processed to produce a measure of amplitude variance of the whole nerve signals, as described previously (14). This approach reflects a summation of action potentials proportional to the activity of independently firing, individual fibers and the number of active fibers. The width of this distribution (amplitude variance) provides a useful index of whole nerve activity (6, 14, 22). Signals were averaged over three respiratory cycles and accumulated by running averages continuously during the measurement period. To minimize baroreceptor contribution in CSN activity, we stripped adventitia from the CSN and also crushed the CSN for ~10 s with a 6-in. needle holder with tips covered by Teflon tape. This technique consistently abolished the clearly audible cardiosynchronous component in CSN activity present before the nerve was crushed. To assess the extent of contamination of our signal by baroreceptor traffic, we previously studied four cats in which pressure was deliberately raised by 32 ± 5 mmHg by phenylephrine infusion and lowered by 38 ± 3 mmHg by nitroprusside (20). Before baroreceptor denervation, these drugs altered neural activity by +19 ± 5% and −10 ± 1%, respectively, whereas hypoxia (40 mmHg) resulted in a rise of 304%. After denervation, the same arterial pressure rise produced no detectable change in CSN activity (0.5 ± 0.5%), and a fall in blood pressure resulted in only a small decrement in neural activity (3 ± 1%). These findings indicate that baroreceptor activity contributes only a minor component of total CSN activity and is nearly abolished by the denervation procedure we employed.

Measurements. During room air breathing, minute ventilation ($\dot{V}_I$), end-tidal P_{O_2} ($P_{ET_{O_2}}$), and end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) were monitored until values became stable in awake and anesthetized animals. Hyperoxic ventilation was measured while the animals were breathing 55% O_2 at the start of the HVR test. Arterial blood was sampled in anesthetized intact or ovariectomized animals for the measurement of blood gases and serum progesterone and estradiol levels by radioimmunoassay.

HVR was determined in duplicate in awake cats by measuring $\dot{V}_I$ at each of 12–15 $P_{ET_{O_2}}$ values ranging from >200 to 40 Torr. In anesthetized animals, duplicate HVR tests were conducted by inducing progressive hypoxia over 8–12 min by gradually adding N_2 to an inspiratory bag initially containing 55% O_2 while recording $\dot{V}_I$. $P_{ET_{CO_2}}$ was maintained within 2 Torr of the resting level by addition of CO_2 to the inspired gas. HVR and CSN responses to hypoxia were measured as the shape parameter A (HVR_A for ventilatory and CSN_A for CSN responses) and by the increment in $\dot{V}_I$ or CSN activity produced by a fall of $P_{ET_{O_2}}$ from 200 to 40 Torr [$\Delta\dot{V}_{I(40-200)}$ and $\Delta CSN_{(40-200)}$]. The shape parameter A describes the hyperbolic relationship between $P_{ET_{O_2}}$ and ventilation or CSN activity. This relationship can be described as follows: $\dot{V}_I = \dot{V}_0 + A/(P_{ET_{O_2}} - 26)$, where $\dot{V}_0$ is the horizontal asymptote for ventilation and A is a measure of the curvature of the relationship. $\dot{V}_0$ is generally similar to the hyperoxic ventilation, but since the two values can differ when A is very large, the empirically measured hyperoxic ventilation is reported in Tables 1–3. The constant 26 represents the $P_{ET_{O_2}}$ at which the slope approaches infinity. This constant was determined empirically in previous studies to produce an optimum curve fit for cats (22). The horizontal position of the ventilatory response curve was expressed by the best $P_{ET_{O_2}}$ asymptote, which, in turn, was calculated by using an iterative procedure as the $P_{ET_{O_2}}$ value yielding the smallest mean square error in the calculation of the shape parameter A (9). Reproducibility between duplicate responses did not differ within animals before vs. after ovariectomy ($r = 0.97$ and 0.85, respectively).

Ventilatory and CSN responses to hypoxia are similar in shape. When these two responses are measured simultaneously and plotted in relation to each other, a linear relationship results that can be used to describe the central nervous system translation of peripheral chemoreceptor activity into ventilation. We calculated the central translation index as the increment in ventilation divided by the increase in CSN activity produced by a decrease in $P_{ET_{O_2}}$ from 200 to 40 Torr.

The ventilatory response to hypercapnia (HCVR) was measured while the CO_2 content of the inspired gas was gradually increased to attain a $P_{ET_{CO_2}}$ of 55 Torr over ~5 min in awake and anesthetized animals. $P_{ET_{O_2}}$ was maintained at >200 Torr throughout the study. HCVR was expressed as the slope (S) of the linear relationship between $P_{ET_{CO_2}}$ and $\dot{V}_I$, and the x-intercept (B) was used to indicate curve position.

Statistics. The effects of ovariectomy were determined using paired t-tests. Student's t-tests were used to evaluate between-group differences. Comparisons were considered significant when $P < 0.05$. Values are means ± SE.

RESULTS

Ovariectomy lowered serum progesterone levels from 2.16 ± 0.68 to 0.020 ± 0.002 ng/ml, but estradiol was

Table 1. *Effects of ovariectomy on ventilation and ventilatory responsiveness in awake cats*

	Before	After
Body weight, kg	2.6 ± 0.1	2.8 ± 0.2
Ventilation during room air		
$\dot{V}_I$, l/min BTPS	1.03 ± 0.12	0.94 ± 0.09
V_T, ml BTPS	30 ± 4	28 ± 2
f, breaths/min	36 ± 3	33 ± 1
$P_{ET_{O_2}}$, Torr	87 ± 1	86 ± 1
$P_{ET_{CO_2}}$, Torr	32 ± 1	33 ± 1
HVR		
A, Torr·l·min^{-1} BTPS	38.9 ± 5.5	21.2 ± 3.0*
Hyperoxic $\dot{V}_I$, l/min BTPS	0.86 ± 0.09	0.79 ± 0.06
Best $P_{ET_{O_2}}$ asymptote, Torr	26 ± 3	30 ± 2
$\Delta\dot{V}_{I(40-200)}$	2.49 ± 0.37	1.24 ± 0.13*
HCVR		
S, l·min^{-1}·Torr^{-1} BTPS	0.09 ± 0.01	0.08 ± 0.01
B, Torr	23 ± 2	22 ± 2

Values are means ± SE. $\dot{V}_I$, minute ventilation; V_T, tidal volume; f, respiratory frequency; *A*, shape parameter; $P_{ET_{O_2}}$, end-tidal P_{O_2}; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}; *S*, slope of relationship between $\dot{V}_I$ and $P_{ET_{CO_2}}$; *B*, *x*-intercept; $\Delta\dot{V}_{I(40-200)}$, increment in ventilation produced by a fall of $P_{ET_{O_2}}$ from 200 to 40 Torr. HVR, hypoxic ventilatory response; HCVR, hypercapnic ventilatory response. *Significantly different from before ovariectomy, $P < 0.05$.

not detectable (<1 pg/ml) before or after ovariectomy. Hormone levels in the intact animals were similar to those before ovariectomy: progesterone averaged 2 ± 1 ng/ml, and estradiol was undetectable. Ovariectomy did not change body weight, resting ventilation, $P_{ET_{O_2}}$, $P_{ET_{CO_2}}$, or HCVR in awake or anesthetized animals (Tables 1 and 2). Body weight, arterial pH, and blood gases were also similar in the larger group of intact and ovariectomized animals (Table 3).

The HVR shape parameter *A* and $\Delta\dot{V}_{I(40-200)}$ decreased in each of the five animals after ovariectomy (Fig. 1), declining by 46% in the awake cats and 61% in the anesthetized animals (Tables 1 and 2). The vertical and horizontal positions of the hypoxic response curve, as assessed by the hyperoxic $\dot{V}_I$ and the best P_{O_2} asymptote, respectively, were unchanged by ovariectomy in awake cats, but the vertical position tended to increase after ovariectomy in anesthetized animals. The magnitude of the change in HVR did not correlate with the absolute or the change in serum progesterone levels. We previously showed that repeated measurements of ventilation and chemical drive in control cats produced no significant change over a 3-wk period (19).

Table 2. *Effects of ovariectomy on ventilation and ventilatory responsiveness in anesthetized cats*

	Before	After
Ventilation during room air		
$\dot{V}_I$, l/min BTPS	0.49 ± 0.04	0.62 ± 0.03
V_T, ml BTPS	25 ± 2	35 ± 4
f, breaths/min	20 ± 3	19 ± 1
$P_{ET_{O_2}}$, Torr	86 ± 3	85 ± 2
$P_{ET_{CO_2}}$, Torr	35 ± 1	35 ± 1
HVR		
A, Torr·l·min^{-1} BTPS	27.1 ± 3.0	10.7 ± 2.0*
Hyperoxic $\dot{V}_I$, l/min BTPS	0.46 ± 0.04	0.59 ± 0.04
Best $P_{ET_{O_2}}$ asymptote, Torr	28 ± 2	27 ± 2
$\Delta\dot{V}_{I(40-200)}$	1.82 ± 0.33	0.75 ± 0.12*
HCVR		
S, l·min^{-1}·Torr^{-1} BTPS	0.03 ± 0.01	0.04 ± 0.01
B, Torr	22 ± 4	24 ± 1

Values are means ± SE. See Table 1 footnote for definition of abbreviations. *Significantly different from before ovariectomy, $P < 0.05$.

Table 3. *Arterial blood gases and ventilatory responsiveness in anesthetized intact and ovariectomized female cats*

	Intact ($n = 24$)	Ovariectomized ($n = 6$)
Body weight, kg	3.5 ± 0.1	3.0 ± 0.3
pH_a	7.34 ± 0.01	7.33 ± 0.02
Pa_{O_2}, Torr	83 ± 1	82 ± 4
Pa_{CO_2}, Torr	34 ± 1	34 ± 1
HVR_A, Torr·l·min^{-1} BTPS	20.1 ± 1.3	11.5 ± 1.5*
Central translation index	0.41 ± 0.04	0.55 ± 0.10
HCVR		
S, l·min^{-1}·Torr^{-1} BTPS	0.04 ± 0.01	0.04 ± 0.01
B, Torr	22 ± 1	21 ± 2

Values are means ± SE. pH_a, arterial pH; Pa_{O_2}, arterial P_{O_2}; Pa_{CO_2}, arterial P_{CO_2}; HVR_A, HVR measured as shape parameter *A*; see Table 1 footnote for definition of other abbreviations. *Significantly different from intact, $P < 0.05$.

Arterial pH, P_{O_2}, and P_{CO_2} were similar in intact and ovariectomized animals under anesthesia. The HVR and the CSN responses to hypoxia were 58% and 43% lower, respectively, in the ovariectomized than in the intact cats (Fig. 2, Table 3). The central nervous system translation index in ovariectomized cats did not differ from that in intact animals (Table 3). HCVR was similar in the two groups.

DISCUSSION

We found that ovariectomy decreased hypoxic ventilatory and CSN responsiveness but did not change effective alveolar ventilation ($P_{ET_{CO_2}}$) or HCVR. Lower hypoxic ventilatory and CSN responses to hypoxia in ovariectomized than in intact cats in the absence of differences in central nervous system translation sug-

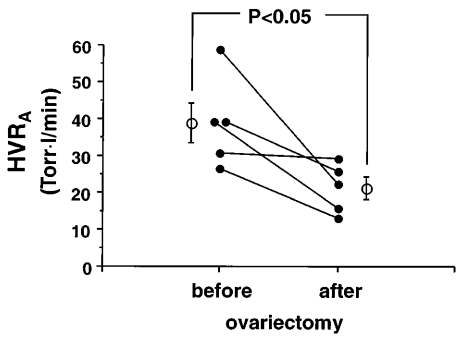

Fig. 1. In awake cats, ventilatory response to hypoxia shape parameter *A* (HVR_A) decreased after ovariectomy. Lines, individual animals; ○ with error bars, means ± SE.

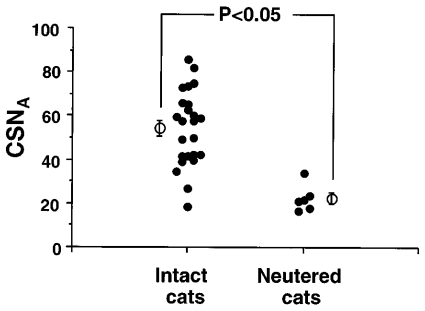

Fig. 2. Carotid sinus nerve response to hypoxia shape parameter *A* (CSN_A) was lower in anesthetized ovariectomized than in anesthetized intact female cats. ●, Individual animals; ○ with error bars, means ± SE.

gested that endogenous female hormones specifically affected the inputs from the carotid body. By extension, these data suggest that normal physiological levels of female hormones act peripherally to raise carotid body hypoxic chemosensitivity.

We used cats as the experimental animal to examine the role of endogenous female hormones in ventilatory control, because our prior studies on the effects of progesterone and gender were done on cats. Limitations of our study were that no measurable change in estradiol occurred, the effects of ovariectomy were examined over a 3-wk period, prior hormone exposure was not controlled, and neural recordings were obtained from the whole CSN. Ovariectomy has previously been shown to reduce progesterone levels from 1.79 ± 0.65 to 0.230 ± 0.005 ng/ml and estradiol from 11.7 ± 4.8 pg/ml in the estrous (follicular) phase to 3.0 ± 0.5 pg/ml in cats (21). As in the present study, the absolute levels and magnitude of decline after ovariectomy were substantially greater for progesterone than for estradiol. The low estradiol levels before ovariectomy and in our intact animals were consistent with our animals not being in the estrous phase, a clearly visible condition marked by distinctive behaviors that usually occur only twice a year. Even if the decline in estradiol levels was not measurable, it may have had physiologically significant effects, since estradiol receptor-mediated events have been detected at levels of estradiol that are too low to be measured by radioimmunoassay (24). We chose to examine the effect of ovariectomy over 3 wk, since this time period proved sufficient to allow observation of an influence of exogenous hormone administration on ventilation and ventilatory control (16). However, whether 3 wk is long enough for the removal of the influences of endogenous ovarian hormones is unknown. All animals were adult at the time of ovariectomy, and thus we were unable to exclude the effects of prior hormonal exposure. We recorded CSN activity from the whole nerve, rather than isolated fibers, to avoid problems of sampling error and insufficient data density (6). We previously showed that stripping the adventitia and crushing the CSN effectively eliminates the cardiosynchronous, baroreceptor response to alterations in blood pressure (20). We were not able to exclude an autonomic component to CSN activity, but since most sympathetic innervation of the carotid body is via the ganglioglomerular nerve, rather than the CSN, and there is a remarkably tight correlation of CSN activity with P_{O_2} (stimulus) and with ventilation (downstream response), we considered it likely that the overwhelming activity was due to chemoreceptor discharge.

The present work indicates that ovariectomy did not change resting ventilation as measured by levels of $\dot{V}_I$ or $P_{ET_{CO_2}}$. Physiological levels of ovarian hormones are often cited as the probable cause of gender differences in ventilation, partly on the basis of the association between alterations in $P_{ET_{CO_2}}$ and hormonal levels seen during the menstrual cycle and the appearance of gender differences in ventilation at the time of menarche and their disappearance after the menopause (15). In cats and other experimental animals the administration of progestin alone does not raise ventilation, but resting ventilation increases after chronic progestin combined with estrogen treatment in a setting where progesterone receptors are elevated (5, 8, 15). However, there is considerable variability in $P_{ET_{CO_2}}$ and $\dot{V}_I$ values, and larger samples may be required to allow observation of differences between ovariectomized and intact animals. Thus the present study and our previous study (16) suggest that sex differences are not due solely to normal, physiological levels of circulating ovarian or testicular hormones but that other factors, including, for example, prior hormonal exposure during development, are likely involved.

Progestin raises HVR in men when $P_{ET_{CO_2}}$ is restored to pretreatment values (18, 25) and in women even under hypocapnic conditions (12). HCVR is unaffected by progestin alone in men but is augmented in women and castrated male cats, particularly when combined with estrogen (8, 12, 13, 18, 25). The 50% diminution in HVR and lack of change in HCVR observed after ovariectomy in the present study occurred in the absence of a change in $P_{ET_{CO_2}}$, suggesting that endogenous ovarian hormones selectively influenced HVR. However, additional experiments that include phrenic neural recordings during hypercapnia and other kinds of respiratory stimuli are required to demonstrate selectivity.

Several lines of evidence suggest that the ventilatory stimulation observed in response to progesterone is due to receptor-mediated actions at central and peripheral sites. We previously showed in rats, cats, and women that the effects of progesterone on ventilation and HVR are augmented in the presence of estrogen (5, 8, 12, 19) and estrogen-induced increased numbers of progesterone receptors (5). Further support is obtained from the observations that the stimulatory effects of progestin require 1 wk to become maximal (13) and the changes in ventilation do not depend closely on the level of circulating hormones or the luteinizing activity of the progestin employed (11), suggesting that alterations in target tissues are required.

Progesterone receptors have been identified in the hypothalamus (3), and progesterone can cross the blood-brain barrier (13). Bayliss et al. (4) showed in

paralyzed, carotid sinus and vagus-denervated cats that acute progesterone treatment raised integrated phrenic nerve activity. This effect was enhanced by prior estradiol administration and blocked by RU-486, a progesterone receptor blocker, as well as by CI-628, an estrogen receptor antagonist. Pretreatment with the transcriptional inhibitor actinomycin D or the translational inhibitor anisomycin attenuated the acute response to progesterone, indicating that these receptor-mediated actions likely induced protein synthesis. We previously showed that progesterone also acts at peripheral sites; the carotid sinus neural output responses to hypoxia increased after chronic exogenous or endogenous elevations in progesterone as the result of stimulatory effects on the carotid body and not descending central stimulatory influences, since the CSN response remained elevated after the CSN was cut while recordings were made from the distal (carotid body) end (8, 9). Estrogen treatment alone had no effect on CSN response to hypoxia but raised the central nervous system translation of CSN activity into ventilation, suggesting that peripheral stimulatory effects of progesterone are further augmented centrally by estrogen (8). The mechanisms by which ovarian hormones stimulate a hypoxic response are unclear, nor is it known whether such influences operate directly on hypoxic sensing or via some other modulator (e.g., dopamine).

In summary, we found in cats that ovariectomy decreased ventilatory and carotid body responses to hypoxia but did not affect effective alveolar ventilation or hypercapnic ventilatory sensitivity. An obvious decrease in progesterone and a possible, but unmeasurable, decrease in estrogen may explain the absence of a change in central nervous system translation with ovariectomy. Alternatively or additionally, chronic reductions in progesterone may have comparatively little central nervous system influence. That the decreased carotid body hypoxic chemosensitivity was able to account for the decreased HVR suggests that the actions of endogenous ovarian hormones on hypoxic ventilatory sensitivity are largely peripheral.

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