Effect of Chlormadinone Acetate, a Synthetic Progesterone, on Hypoxic Ventilatory Response in Men

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Abstract Ten healthy young males were studied with a double-blind, cross-over trial to determine whether or not chlormadinone acetate (CMA), a potent synthetic progesterone, augments hypoxic chemosensitivity. Seven days after CMA administration, inspiratory minute volume ($\dot{V}t$) and tidal volume ($Vt$) significantly increased. $P_{aCO_2}$ decreased by 3.0 ± 2.6 (S.D.) Torr ($p < 0.05$) and plasma bicarbonate decreased by 2.9 ± 1.1 mM ($p < 0.01$). During CMA administration, the atmospheric hypoxic ventilatory response (HVR), assessed by minute ventilatory ($\Delta \dot{V}t/\Delta SaO_2$), and occlusion pressure responses ($\Delta P_{CO_2}/\Delta SaO_2$), significantly increased about 1.9 ($p < 0.05$) and 1.6 times ($p < 0.01$) compared to the placebo response, respectively. The calculated normocapnic HVR ($\Delta \dot{V}t/\Delta SaO_2$) increased about 2.3 times the placebo run. Hypoxic response evaluated by the withdrawal test, which represents the peripheral chemosensitivity without involving the influence due to secondary hypoxic depression, was about 1.7 times the placebo response ($p < 0.05$). We conclude that CMA augments hypoxic respiratory chemosensitivity.

Key words: synthetic progesterone, hypoxic ventilatory response, progressive hypoxia test, withdrawal test.

Progesterone augments alveolar ventilation during pregnancy (Magnus-Levy, 1904), and during the luteal phase of the menstrual cycle (Hasselbalch and Gammeltoft, 1915). A similar effect was found to occur after the administration of synthetic progesterone (Sutton et al., 1975; Kryger et al., 1978). Enhancement of both hypercapnic ventilatory response (HCVR) and hypoxic ventilatory response...
(HVR) during the luteal phase have also been reported (Schoene et al., 1981; White et al., 1983). However, the effects of the commonly used synthetic progesterone, medroxyprogesterone acetate (MPA) on HCVR and HVR are controversial. Some investigators have observed an increased ventilatory response slope, whereas others have observed merely a shift in the response curve (Skatrud et al., 1978; Zwillich et al., 1978; Schoene et al., 1980). One particular difficulty in assessing HVR is its dependency on the end-tidal $P_{CO_2}$ ($PET_{CO_2}$) level. A decrease in $PET_{CO_2}$ due to increased alveolar ventilation effectively attenuates the hypoxic ventilatory drive, so that real HVR may be underestimated.

Using chlormadinone acetate (CMA), which has 10 times the luteinizing activity of MPA (Brennan and Kraay, 1963), we have shown enhanced HCVR in normal men (Kimura et al., 1984) and in patients with chronic obstructive pulmonary disease (COPD) (Tatsumi et al., 1986). Seven days' administration of CMA in COPD patients revealed that HVR significantly increased only when $PET_{CO_2}$ was restored to the normocapnic level (Tatsumi et al., 1986). However, restoring $PET_{CO_2}$ after sustained hypocapnia may have resulted in overcompensating for arterial $[H^+]$, thus overestimating HVR.

In the present study, the effect of CMA on healthy male subjects was investigated. The HVR was determined by both progressive isocapnic hypoxia and withdrawal tests, and an attempt was made to resolve the difficulties in assessing an accurate response.

SUBJECTS AND METHODS

Studies were performed on 10 healthy young males in the medical school. Their age, height, and weight were $23.1 \pm 1.7$ year (mean ± S.D.), $172.2 \pm 5.8$ cm, and $65.3 \pm 7.5$ kg, respectively.

Using a double blind, randomized cross-over selection method, the subjects were given either CMA or a placebo orally at a dose of 25 mg twice a day for 7 days. Then, after a 2-week washout period, they again participated by taking the alternate ingestion for 7 days.

All tests were performed on the day before each administration period and on the last day of each administration period. Arterial blood gases were measured at rest for pH, arterial $P_{O_2}$ ($P_{O_2}$), and arterial $P_{CO_2}$ ($P_{CO_2}$) (Instrumentation Laboratory model 1303). Plasma bicarbonate concentration ($[HCO_3^-]$) was calculated using the Henderson-Hasselbalch equation. Pulmonary function tests were performed on vital capacity (VC), forced expiratory volume in 1 s (FEV$_{1.0}$) measured by hot wire flowmeter (Minato AS 4500), and functional residual capacity (FRC) measured by the He-gas dilution method (CHESTAC-30). The subjects rested for about 10 min, and then inspiratory minute ventilation ($V_t$), tidal volume ($VT$), breathing frequency ($f$), inspiratory time ($T_i$), expiratory time ($T_e$), duty cycle ($T_i/T_{TOT}$), mean inspiratory flow ($VT/T_i$), and mouth occlusion pressure at 0.2 s after beginning of inspiration ($P_{oc}$) were determined as the subjects breathed.
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through a mouthpiece with a respiratory valve and a nose clip. Respiratory flow was
detected by a hot wire flowmeter (Minato RF-2), and \( V_T \), \( T_I \), and \( T_E \) were
electrically displayed by an analog calculator from the flow signal. The \( O_2 \)
consumption (\( \dot{V}_{O_2} \)), \( CO_2 \) production (\( \dot{V}_{CO_2} \)), and the respiratory gas exchange ratio
(\( R \)) were determined from the volume of expired gas and its \( O_2 \) and \( CO_2 \) contents,
measured by a rapid response analyzer (Sanei 1H-21).

The HVR was assessed by an isocapnic progressive hypoxia test and by a
withdrawal test. The details of the experimental set-up have already been reported
(REBUCK and CAMPBELL, 1974; HONDA et al., 1979). Briefly, in the isocapnic
progressive hypoxia test, the subjects were seated, rebreathing in a closed-circuit
connected to a bag containing 6–8 l of room air. Beginning with the end-tidal \( P_{O_2} \)
(\( P_{ET_{O_2}} \)) at rest, the \( P_{ET_{O_2}} \) was gradually decreased at a rate of about 10 Torr per min,
maintaining the end-tidal \( P_{CO_2} \) (\( P_{ET_{CO_2}} \)) constant. Oxygen saturation (\( S_{AO_2} \)) was also
continuously measured by an ear oximeter (BIOX II A). The subjects discontinued
rebreathing when \( S_{AO_2} \) dropped below 70%. The isocapnic progressive hypoxia test
was measured at two \( P_{ET_{CO_2}} \) levels. The first measurement, conducted at a resting
\( P_{ET_{CO_2}} \) level, was the atmospheric HVR, and the second run, conducted at \( P_{ET_{O_2}} \),
about 5 Torr higher than at rest, was the hypercapnic HVR.

![Figure 1](image)

**Fig. 1.** An example of the withdrawal test. \( \dot{V}_C \) is defined as the averaged minute
ventilation volumes of ten breaths before the \( O_2 \) inhalation. \( \dot{V}_W \) is defined as the
averaged breath-by-breath minute ventilation volume between the 5th and the 20th
s after the first \( O_2 \) breath. The difference between \( \dot{V}_C \) and \( \dot{V}_W \) is expressed in
absolute magnitude (\( \Delta \dot{V} \)) or in relative change, \( \Delta \dot{V} \% \), which is calculated by
(\( \Delta \dot{V}/\dot{V}_C \) \times 100. \( \Delta \dot{V} \) and \( \Delta \dot{V} \% \) are taken as the parameters for peripheral ventilatory
chemosensitivity.
The withdrawal test to evaluate independent peripheral chemosensitivity used in the present study was developed by Honda et al. (1979), and is a modification of Dejours' single breath test (Dejours, 1962). The subjects rebreathed in a closed circuit consisting of a mouthpiece connected to a respiratory valve, respiratory tubing, a rubber bag with a capacity of about 8 l, and a CO₂ absorber placed in a bypass. A 100-l-capacity Douglas bag filled with O₂ was placed in front of the inspiratory valve. As shown in Fig. 1, \( P_{\text{ETO}_2} \) was adjusted to 55 Torr by introducing the proper amount of O₂ into the circuit. The \( P_{\text{ETCO}_2} \) was maintained at 5 Torr higher than the resting level by adjusting the bypass flow to the CO₂ absorber. After keeping \( P_{\text{ETO}_2} \) and \( P_{\text{ETCO}_2} \) at the above-mentioned levels for 3 min, two breaths of pure oxygen were given by turning the three-way stopcock. As much as possible, this maneuver was done so that it would not be noticed by the subject. Thus a drop in ventilation \( (\Delta V) \) up to 20 s after breathing O₂ was seen as the peripheral chemosensitivity. This O₂ administration was repeated three times for each subject.

The statistical significance of the data was assessed using the Student's paired t-test. Because there was no difference between the data from the pre-drug day and the data during placebo administration, we worked with the difference in data between CMA and placebo administration.

RESULTS

The data for arterial blood gases, pulmonary functions, metabolic rates, and breathing parameters during placebo and CMA administration are shown in Table 1. During CMA administration, \( P_{\text{aCO}_2} \) decreased by 3.0 ± 2.6 (S.D.) Torr \((p < 0.05)\) and plasma \([HCO_3^-]\) decreased by 2.9 ± 1.1 mm \((p < 0.01)\). However no significant change occurred in either pH or \( P_{\text{aO}_2} \). Pulmonary functions and metabolic rates were not changed by CMA administration. The \( \dot{V}l \) increased by 1.1 ± 3.5 l/min \((p < 0.05)\) with a considerable increase in \( V_T \), 0.06 ± 0.31 l \((p < 0.05)\). But there was no significant change in \( f, T_i, T_e, V_T/T_i, T_i/T_TOT, \) and \( P_2 \).

The ventilatory and occlusion pressure response to hypoxia are shown in Table 2. They are evaluated as the slopes of response lines expressed by \( \Delta \dot{V}_l/\Delta S_{\text{aO}_2} \) and \( \Delta P_2/\Delta S_{\text{aO}_2} \), and the magnitude of \( \dot{V}_l \) and \( P_2 \) at \( S_{\text{aO}_2} = 80\% \). In atmospheric HVR (Fig. 2), the ventilatory response \( (\Delta \dot{V}_l/S_{\text{aO}_2}) \) during CMA administration significantly increased about 1.9 times the placebo response \((p < 0.05)\). The atmospheric occlusion pressure response \( (\Delta P_2/\Delta S_{\text{aO}_2}) \) increased in all subjects and the mean \( \Delta P_2/\Delta S_{\text{aO}_2} \) was about 1.6 times the placebo run. At \( S_{\text{aO}_2} = 80\% \), on the other hand, \( P_2 \) significantly increased \((p < 0.05)\) while \( \dot{V}_l \) did not, although the magnitude of both parameters was about 1.4 times higher with CMA than with the placebo. In the hypercapnic HVR, \( \Delta \dot{V}_l/\Delta S_{\text{aO}_2} \), and \( \Delta P_2/\Delta S_{\text{aO}_2} \) with CMA significantly increased about 1.3 \((p < 0.05)\) and 1.4 times \((p < 0.01)\), respectively. The elevations of both minute ventilation and occlusion pressure at \( S_{\text{aO}_2} = 80\% \) were highly significant.

During CMA administration, resting \( P_{\text{ETCO}_2} \) was 2.0 ± 0.7 (S.D.) Torr lower.
Table 1. Changes in arterial blood gases, pulmonary functions, breathing parameters, and metabolic rate during administration of placebo and CMA.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.39 ± 0.03</td>
<td>7.37 ± 0.01</td>
</tr>
<tr>
<td>$P_{A}O_2$ (Torr)</td>
<td>98.2 ± 8.9</td>
<td>97.1 ± 6.1</td>
</tr>
<tr>
<td>$P_{A}CO_2$ (Torr)</td>
<td>37.7 ± 4.2</td>
<td>34.6 ± 2.1*</td>
</tr>
<tr>
<td>[HCO$_3^-$] (nm)</td>
<td>23.1 ± 1.6</td>
<td>20.2 ± 1.3**</td>
</tr>
<tr>
<td>%VC</td>
<td>118.0 ± 17.1</td>
<td>117.9 ± 14.6</td>
</tr>
<tr>
<td>FEV$_{1.0}$ % (%)</td>
<td>84.8 ± 9.7</td>
<td>84.5 ± 8.7</td>
</tr>
<tr>
<td>%FRC</td>
<td>100.2 ± 20.3</td>
<td>106.5 ± 22.0</td>
</tr>
<tr>
<td>$\dot{V}_{O_2}$ (ml/min)</td>
<td>277 ± 29.8</td>
<td>284 ± 31.7</td>
</tr>
<tr>
<td>$\dot{V}_{CO_2}$ (ml/min)</td>
<td>247 ± 49.7</td>
<td>247 ± 30.8</td>
</tr>
<tr>
<td>$R$</td>
<td>0.89 ± 0.12</td>
<td>0.90 ± 0.09</td>
</tr>
<tr>
<td>$f$ (cpm)</td>
<td>14.4 ± 2.9</td>
<td>16.1 ± 3.5</td>
</tr>
<tr>
<td>$\dot{V}_I$ (l/min)</td>
<td>8.6 ± 2.0</td>
<td>10.0 ± 1.7*</td>
</tr>
<tr>
<td>$V_T$ (l)</td>
<td>0.56 ± 0.15</td>
<td>0.62 ± 0.12*</td>
</tr>
<tr>
<td>$T_I$ (s)</td>
<td>1.58 ± 0.35</td>
<td>1.61 ± 0.39</td>
</tr>
<tr>
<td>$T_E$ (s)</td>
<td>2.34 ± 0.51</td>
<td>2.29 ± 0.67</td>
</tr>
<tr>
<td>$T_I/T_{TOT}$</td>
<td>0.40 ± 0.06</td>
<td>0.42 ± 0.06</td>
</tr>
<tr>
<td>$V_T/T_I$ (l/s)</td>
<td>0.36 ± 0.06</td>
<td>0.40 ± 0.08</td>
</tr>
<tr>
<td>$P_{2}$ (cmH$_2$O)</td>
<td>2.4 ± 0.8</td>
<td>2.6 ± 1.4</td>
</tr>
</tbody>
</table>

Values are mean ± S.D.; $n = 10$. *$p < 0.05$, **$p < 0.01$; difference between placebo and CMA.

Table 2. Comparison of hypoxic ventilatory response (HVR) between placebo and CMA.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atmospheric HVR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta \dot{V}<em>I/\Delta S</em>{A,O_2}$ ($l \cdot min^{-1} \cdot %^{-1}$)</td>
<td>0.45 ± 0.28</td>
<td>0.87 ± 0.68*$</td>
</tr>
<tr>
<td>$\dot{V}<em>I$ at $S</em>{A,O_2}$ 80% ($l \cdot min^{-1}$)</td>
<td>17.0 ± 4.6</td>
<td>24.9 ± 13.3</td>
</tr>
<tr>
<td>$\Delta P_{2}/\Delta S_{A,O_2}$ (cmH$_2$O $\cdot$ %$^{-1}$)</td>
<td>0.18 ± 0.17</td>
<td>0.28 ± 0.21**</td>
</tr>
<tr>
<td>$P_{2}$ at $S_{A,O_2}$ 80% (cmH$_2$O)</td>
<td>5.6 ± 2.8</td>
<td>7.8 ± 3.7*</td>
</tr>
<tr>
<td><strong>Hypercapnic HVR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta \dot{V}<em>I/\Delta S</em>{A,O_2}$ ($l \cdot min^{-1} \cdot %^{-1}$)</td>
<td>1.08 ± 0.47</td>
<td>1.42 ± 0.69*$</td>
</tr>
<tr>
<td>$\dot{V}<em>I$ at $S</em>{A,O_2}$ 80% ($l \cdot min^{-1}$)</td>
<td>35.8 ± 10.1</td>
<td>49.7 ± 18.7**</td>
</tr>
<tr>
<td>$\Delta P_{2}/\Delta S_{A,O_2}$ (cmH$_2$O $\cdot$ %$^{-1}$)</td>
<td>0.44 ± 0.26</td>
<td>0.61 ± 0.23**</td>
</tr>
<tr>
<td>$P_{2}$ at $S_{A,O_2}$ 80% (cmH$_2$O)</td>
<td>11.7 ± 5.3</td>
<td>18.2 ± 7.6***</td>
</tr>
<tr>
<td><strong>Normocapnic HVR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta \dot{V}<em>I/\Delta S</em>{A,O_2}$ ($l \cdot min^{-1} \cdot %^{-1}$)</td>
<td>0.45 ± 0.28</td>
<td>1.03 ± 0.70*</td>
</tr>
</tbody>
</table>

Values are mean ± S.D., $n = 10$. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; difference between placebo and CMA.

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Because hypocapnia is known to attenuate HVR, we attempted to obtain a normocapnic HVR during CMA administration, with PETCO$_2$ restored to the same level as the placebo. REBUCK et al. (1977) demonstrated that minute ventilation can be expressed as a function of SaO$_2$ and P$_{CO_2}$:

$$\dot{V} = a_1 \cdot SaO_2 \cdot P_{CO_2} + a_2 \cdot SaO_2 + a_3 \cdot P_{CO_2} + a_4$$ (1)

By partial differentiation of Eq. (1) with respect to SaO$_2$, hypoxic ventilatory response can be expressed as

$$\frac{\partial \dot{V}}{\partial SaO_2} = a_1 \cdot P_{CO_2} + a_2$$ (2)

Fig. 2. A comparison of atmospheric HVR between placebo and CMA. Upper half, the ventilatory response to SaO$_2$; lower half, the occlusion pressure response. The dotted and solid lines represent the HVR during CMA and placebo administration, respectively. The vertical lines show the magnitude of ventilation or occlusion pressure at SaO$_2$ 80% (mean ± S.D.).
We have plotted the individual slopes of the ventilatory responses vs. PETCO₂ at both atmospheric and hypercapnic levels during CMA administration (Fig. 3). Equation (2) can be expressed as the PETCO₂ vs. d V/dSao₂ response line drawn by connecting the two plots as in the graph on the left. Then, the normocapnic HVR can be derived from the PETCO₂ level corresponding to the placebo run. The graph on the right in Fig. 3 demonstrates the individual normocapnic hypoxic sensitivity during CMA administration, calculated by the above procedure, is compared with that of the placebo. The vertical bar represents the magnitude of slope of the ventilatory response (mean ± S.D.). A significant difference was found (p < 0.01).

Fig. 3. A comparison of normocapnic HVR slope between CMA and placebo administration. On the left side, the method of obtaining normocapnic HVR in CMA administration is shown. Hypoxic sensitivity, \( \Delta V/\Delta S_{O_2} \), experimentally obtained at atmospheric and hypercapnic (PETCO₂ elevated by 5 Torr) conditions are plotted against PETCO₂. Using the line connecting these two points, normocapnic hypoxic sensitivity can be read from the PETCO₂ value obtained in the placebo run. On the right side, the individual normocapnic hypoxic sensitivity during CMA administration, calculated by the above procedure, is compared with that of the placebo. The vertical bar represents the magnitude of slope of the ventilatory response (mean ± S.D.). A significant difference was found (p < 0.01).

We have plotted the individual slopes of the ventilatory responses vs. PETCO₂ at both atmospheric and hypercapnic levels during CMA administration (Fig. 3). Equation (2) can be expressed as the PETCO₂ vs. \( \Delta V/\Delta S_{O_2} \) response line drawn by connecting the two plots as in the graph on the left. Then, the normocapnic HVR can be derived from the PETCO₂ level corresponding to the placebo run. The graph on the right in Fig. 3 demonstrates the individual normocapnic HVR slope compared with the atmospheric HVR's obtained in the placebo run. The normocapnic HVR with CMA increased about 2.3 times what it was with the placebo. In two subjects, however, the atmospheric PETCO₂ after CMA was higher than the placebo run. Accordingly, the calculated magnitude of the normocapnic HVR slope of these subjects became smaller than the placebo slope, although the atmospheric HVR slope actually measured was demonstrated to be higher than the placebo run. The reason why PETCO₂ of these subjects increased by CMA is obscure, but individual susceptibilities to the drug as well as test procedures may be accounted for these variability.

Figure 4 shows the results of the withdrawal test in which individual values are
represented by the average of the three repeated trials. With CMA, both the absolute and relative magnitudes of the hypoxic peripheral chemosensitivities ($\Delta V$ and $\Delta V\%$, respectively) significantly increased to about 1.7 times what they were with the placebo.

Two subjects experienced breathlessness on exertion and one subject experienced depression in libido during CMA administration, but no other side effects were observed among the subjects.

**DISCUSSION**

This study demonstrated that CMA augmented hypoxic ventilatory response (HVR) not only in the progressive hypoxia test but also in the withdrawal test.

The effect of synthetic progesterone (medroxyprogesterone acetate, MPA) on HVR in normal man is controversial. SCHÖNE et al. (1980), using a hyperbola analysis in the progressive hypoxia test, observed no significant change in atmospheric hypoxic ventilatory chemosensitivity (parameter $A$) but saw occlusion pressure sensitivity (parameter $A_p$) increase significantly after MPA administration. On the other hand, ZWILLICH et al. (1978) found no significant elevation in either atmospheric ventilatory response or occlusion pressure response after 36 h of MPA administration. However, when $P_{ET CO_2}$ was restored to the normocapnic level, they
did find a significant increase.

Sustained hypocapnia because of a respiratory stimulant such as MPA, may result in decreased plasma \([\text{HCO}_3^-]\). Therefore, restoring \(P_{\text{ETCO}_2}\) to the normocapnic level induces overcompensation in arterial \([\text{H}^+]\), as can be seen by Henderson’s equation,

\[
[\text{H}^+] = K' \cdot \frac{S \cdot P_{\text{CO}_2}}{[\text{HCO}_3^-]} \tag{3}
\]

where \(K'\) is the apparent dissociation constant for the bicarbonate buffer system, and \(S\) is the solubility coefficient for \(P_{\text{CO}_2}\). Since \([\text{H}^+]\) is known to stimulate ventilation, the observation by Zwillich et al. (1978) does not necessarily mean that HVR is truly augmented.

In this study, using CMA, we found a significant increase in the atmospheric hypoxic ventilatory slope as well as in the hypoxic occlusion pressure drive at \(S_{\text{aO}_2} 80\%\). As seen in Table 1, both \(P_{\text{aCO}_2}\) and plasma \([\text{HCO}_3^-]\) are significantly less with CMA than with the placebo, and no significant change in arterial pH was observed. The fact that an enhanced HVR was obtained with CMA, even with lower \(P_{\text{aCO}_2}\) than with the placebo, may signify that HVR is truly augmented by CMA. Augmentation of the hypercapnic HVR with CMA was more significant than the atmospheric HVR, indicating the hypoxia-hypercapnia interaction.

We further observed enhanced ventilatory and occlusion pressure response with the normocapnic progressive HVR test. This does, however, include some additional hypoxic response due to overcompensation in arterial \([\text{H}^+]\).

The reason why the HVR was stronger with CMA than with MPA is not clear at present. However, Morikawa et al. (personal communication) found in a double-blind cross-over study comparing CMA, MPA, and placebo that CMA was slightly stronger in producing respiratory alkalosis than MPA. This may mean that CMA is also a stronger respiratory stimulant than MPA.

Enhanced hypoxic chemosensitivity was also confirmed by the withdrawal test, which evaluated HVR without involving hypoxic depression due to sustained hypoxia. Therefore, an increase in reflex hypoxic chemoreceptor activity due to CMA was confirmed.

It is still unclear what mechanisms play roles in respiratory stimulation by progesterone. In this study, HVR, as assessed by progressive hypoxia and withdrawal tests, was augmented by CMA. Possible organizations responsible for the CMA stimulation cannot directly be estimated from our study. However, Skatrud et al. (1978) have proposed that the stimulant effect of progesterone on respiration is produced by stimulation of the CNS, and in COPD patients, CMA restored the impaired load compensation which was most likely mediated by the higher CNS function (Kimura et al., 1986). On the other hand, Mei et al. (1977) have suggested, based on their studies using cross-circulation techniques on dogs, that progesterone does not act on the peripheral chemoreceptors. However, the results we obtained in the withdrawal test suggest that peripheral chemoreflex loop is also involved in
augmentation of ventilatory activities. Considering the previous investigations mentioned above, CMA may have activated somewhere the brain-stem neuronal mechanism which receives the afferent signal from the peripheral chemoreceptors.

In normal women, both atmospheric HVR (SCHOENE et al., 1981; WHITE et al., 1983) and reflex hypoxic response (TAKANO, 1984) significantly increased in the luteal phase of the menstrual cycle as compared with the follicular phase. Why do women during the menstrual cycle clearly show augmented HVR with much less progestational activity than men given a strong synthetic progesterone? MPA has 15 and CMA has 150 times the activity of progesterone alone. BRODEUR et al. (1986) recently demonstrated in rats that the number of progesterone receptors increase when estradiol is given in combination with MPA. Thus, ventilation is more effectively stimulated. The differences in HVR between men and women may be explained by this mechanism.

In COPD patients, CMA did not significantly augment the hypocapnic HVR, as measured by TATSUMI et al. (1986), whose methods and procedures were about the same as in this study. This difference can be explained by the fact that the decrement of PETCO2 in the COPD patients was more than 2 times that in the present subjects by CMA administration. Accordingly, hypocapnic HVR in the COPD patients may have effectively attenuated. In fact, normocapnic HVR in these patients was significantly augmented by CMA.

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REFERENCES


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