Depression of peripheral chemosensitivity by a dopaminergic mechanism in patients with obstructive sleep apnoea syndrome

S. Osanai, Y. Akiba, S. Fujiuchi, H. Nakano, H. Matsumoto, Y. Ohsaki, K. Kikuchi


ABSTRACT: In the present study, respiratory drives to chemical stimuli and peripheral chemosensitivity were evaluated in patients with obstructive sleep apnoea (OSAS). The effects of oral administration of domperidone, a selective dopamine D2-receptor antagonist, were also examined, to study the respiratory effects of endogenous dopamine on peripheral chemoreceptors.

Sixteen patients with OSAS and nine normal control subjects were studied. Respiratory responses to hypercapnia and hypoxia were measured using the rebreathing method and isocapnic progressive hypoxia method, respectively. The hypoxic withdrawal test, which measures the decrease in ventilation caused by two breaths of 100% O2 under mild hypercapnic hypoxic conditions (end-tidal oxygen and carbon dioxide tensions ≅ 8.0 kPa and 5.3–6.7 kPa, respectively), was used to evaluate peripheral chemosensitivity.

In the patients with OSAS, ventilatory responses to hypercapnia and hypoxia were significantly decreased compared with those of control subjects. Hypoxic withdrawal tests showed that peripheral chemosensitivity was significantly lower in patients with OSAS than in normal subjects. Hypercapnic ventilatory response and peripheral chemosensitivity were enhanced by administration of domperidone in the patients with OSAS, although no changes in either of these were observed in the control subjects. The hypoxic ventilatory response and peripheral chemosensitivity in the patients with OSAS were each significantly correlated with severity of hypoxia during sleep.

These findings suggest that peripheral chemosensitivity in patients with obstructive sleep apnoea syndrome may be decreased as a result of abnormality in dopaminergic mechanisms and that the reduced chemosensitivity observed in patients with obstructive sleep apnoea syndrome may affect the severity of hypoxia during sleep.


Obstructive sleep apnoea syndrome (OSAS) is characterized by frequent episodes of upper airway closure during sleep [1]. This airway collapse is due to both a narrow upper airway and a decrease in muscle tone during sleep [2]. It has also been suggested that the critical trigger of apnoea might be instability of breathing during sleep [3] and that the duration of apnoea is influenced by individual respiratory drive [4, 5]. The ventilatory response in patients with OSAS has, therefore, been studied in detail over the last two decades. However, the role of peripheral chemoreception in this syndrome has not been adequately evaluated.

In the present study, the ventilatory response to chemical stimuli and peripheral chemosensitivity was measured in patients with OSAS using the hypoxic withdrawal test [6–8]. The respiratory effect of endogenous dopamine, a major neurotransmitter [9, 10] which might inhibit peripheral chemoreceptors [11, 12], was also assessed by administration of domperidone, a dopamine antagonist [13].

Materials and methods

Study groups

The present experiments were performed with 16 patients with OSAS and nine control subjects (table 1). The diagnosis of OSAS had been reached by standard full-night polysomnography [1, 14]. The patients with OSAS fulfilled the criteria for OSAS proposed by Guilleminault et al. [1]. All of the patients with OSAS snored and

<table>
<thead>
<tr>
<th>Table 1. – Characteristics of subjects</th>
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<tbody>
<tr>
<td>Control subjects</td>
</tr>
<tr>
<td>Sex M/F</td>
</tr>
<tr>
<td>Age yrs</td>
</tr>
<tr>
<td>(24–62)</td>
</tr>
<tr>
<td>BMI kg·m⁻²</td>
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<tr>
<td>(20.9–38.5)</td>
</tr>
<tr>
<td>VC % pred</td>
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<tr>
<td>(78.4–113.1)</td>
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<tr>
<td>FEV₁/FVC %</td>
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<tr>
<td>(79.3–106.4)</td>
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<tr>
<td>PaCO₂ mmHg</td>
</tr>
<tr>
<td>(36.2–42.2)</td>
</tr>
<tr>
<td>PaO₂ mmHg</td>
</tr>
<tr>
<td>(84.8–98.8)</td>
</tr>
</tbody>
</table>

Values are means±SEM with ranges shown in parentheses. OSAS: obstructive sleep apnoea syndrome; M: male; F: female; BMI: body mass index; VC: vital capacity; FEV₁/FVC: forced expiratory volume in one second/final vital capacity; PaCO₂: arterial carbon dioxide tension; PaO₂: arterial oxygen tension. *: p<0.05. (1 mmHg≈0.133 kPa.)
had excessive daytime sleepiness. The clinical characteristics of the patients with OSAS are shown in table 2. At the time of the study, no patient with OSAS had any evidence of hypothyroidism or heart failure. Five patients with OSAS had hypertension treated with calcium channel blockers or angiotensin-converting enzyme inhibitors. All medications were withdrawn under careful observation 1 week before the studies. No patient required administration of these medications during the study period. The control subjects were recruited from among hospital staff members who were naive concerning respiratory physiology. No control subjects had health problems and none were receiving any medication. Sleep-disordered breathing in the control subjects was screened for using a questionnaire and overnight measurement of arterial oxygen saturation (SaO2) with a pulse oximeter (Pulsox 7; Minolta, Osaka, Japan). Oral informed consent was obtained from each subject before the study. The study protocol was approved by the Institutional Review Board of Asahikawa Medical College. All subjects were instructed to refrain from drinking caffeine-containing beverages on the day of the study.

Respiratory drives

The effects on respiratory drive of chemical stimuli were assessed by the ventilatory response and mouth occlusion pressure response. All subjects fasted and were in a stable resting state for at least 30 min before the tests. They were seated in a comfortable chair, breathed through a low-resistance valve (Model 2700; Hans Rudolph, St Louis, MO, USA) and wore a rubber mouthpiece, noseclips and headphones, which supplied music devoid of strong rhythm.

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The respiratory response to hypercapnia was measured using the rebreathing method [15]. In brief, a 6-L bag, which was filled with gas composed of 5% CO2, 50% O2 and 45% N2, was connected to the breathing valve and the subject rebreathed into the bag until PETCO2 was >9.3 kPa (70 mmHg). During the tests, the PETO2 was maintained >13.3 kPa (100 mmHg). One rebreathing test was usually terminated within 5 min. The respiratory response to hypoxia was measured by the isocapnic progressive hypoxia method [16]. In brief, PETO2 was lowered from 16.0 to 6.0 kPa (120 to 45 mmHg) over 7 min by the addition of N2. CO2 was added in amounts sufficient to maintain isocapnia. The respiratory drive was assessed by the slopes of V'I and P0.1 as functions of PETCO2 and SaO2.

Hypoxic withdrawal responses

The hypoxic withdrawal test [6–8] was used to evaluate the contribution of peripheral chemoreceptors to the ventilatory response. At the beginning of the test, V'I and PETCO2 were measured while the subject was breathing room air in a rubber bag. N2 and CO2 were then added to room air in the rubber bag. The PETO2 was gradually lowered to 8.0 kPa (60 mmHg). At the same time, the PETCO2 was elevated to 0.7 kPa (5 mmHg) above the PETCO2 during breathing of room air in order to stabilize ventilation. In this mildly hypercapnic hypoxic state, the hypoxic inspiratory gas was changed to 100% O2 during two breaths without indicating this to the subject. After two breaths of 100% O2, the inspiratory gas was switched back to the hypercapnic hypoxic gas. The V'I during room air breathing was defined as V'IN. The V'I before breathing 100% O2 during the mildly hypercapnic hypoxic state was defined as V'I0. The V'I between 5 and 20 s after changing the inspiratory gas was defined as V'I5–20. The difference between V'I0 and V'I5–20 was defined as the withdrawal response (ΔV'I) and %ΔV'I (ΔV'I/V'I0 × 100) was used as an index of the peripheral chemoreceptor activity (fig. 1). One exposure to hypoxia in this test was usually terminated within 7 min. This withdrawal test was performed three or more times at intervals of 20 min. The subject breathed room air between tests, to avoid the effects of hypoxic ventilatory depression.

Drugs and protocol

A double-blind study was performed to compare domperidone (Kyowa-Hakko, Tokyo, Japan) with placebo on separate test days in a random order. The dose of domperidone was 0.5 mg·kg−1 per os. The medicines were prepared
with the baseline determined with the awake subject in a supine position.

istical significance. were assessed by calculating Spearman correlations coef-
test for intragroup comparison and the Mann–Whitney U-
V calculated as the 4% desaturation ratio (DSR4%) and 10%
of desaturation as percentages of total sleep time were
P
metres [17].

were corrected by body surface area (BSA) in square
body size and sex, the indices of each ventilatory response
in the sleep study, apnoea was defined as cessation of
flow at the nose and mouth for at least 10 s. An apnoea
index (total number of apnoeic episodes divided by the
total sleep time in hours) was defined and computed as
described by Guilleminault et al. [1]. Baseline S\textsubscript{a}O\textsubscript{2} was
determined with the awake subject in a supine position. The
periods with desaturations of >4 or 10\% compared with
the baseline S\textsubscript{a}O\textsubscript{2} were calculated; then the durations of
desaturation as percentages of total sleep time were
calculated as the 4\% desaturation ratio (DSR4\%) and 10\%
desaturation ratio (DSR10\%), respectively. The slopes of
the \( V^1 \) and \( P_{O_2} \) responses to hypoxia and hypoxia were
calculated by least-squares regression analysis with
\( PETCO_2 \) and \( S\textsubscript{a}O\textsubscript{2} \), respectively. To eliminate the effects of
body size and sex, the indices of each ventilatory response
were corrected by body surface area (BSA) in square
metres [17].

Values reported in the text and tables are means±SEM.
Differences were tested for significance with the Wilcoxon
for intragroup comparison and the Mann–Whitney U-
test was used for two independent groups. Correlations
were assessed by calculating Spearman correlations coef-
ficients. A p-value <0.05 was considered to indicate statistical
significance.

Results

The characteristics of the two groups are shown in table
1. There was no significant difference in anthropometric
values between patients with OSAS and control subjects.
The mean values of forced expiratory volume in one sec-
ond (FEV\textsubscript{1})/forced vital capacity (FVC) and arterial oxy-
gen tension (\( P_{a,O_2} \)), although within the generally accepted
normal range [18], were lower in patients with OSAS. The
mean value of arterial carbon dioxide tension (\( P_{a,CO_2} \)) was
higher in the group of patients with OSAS, since this group
included five patients with chronic hypoventilation (\( P_{a,CO_2} \)
\geq 6.0 kPa (45 mmHg)).

The ventilatory responses to hypercapnia and hypoxia are
shown in table 3. The mean values of the hypercapnic
ventilatory response in the patient group was lower than
that in the control group. Domperidone increased the res-
piratory drive to hypoxia only in the patients with OSAS.
In the patients with OSAS, each parameter of respiratory
drive to hypoxia was significantly lower than that
in the corresponding value in the control group. Domperi-
done did not alter the respiratory drive to hypoxia in
either group.

There was no significant difference in \( V^1 \textsubscript{L} \) between
the two groups (table 4). The \( V^1 \textsubscript{L}/BSA, \Delta V^1/BSA \) and
\% \( \Delta V^1 \) for patients with OSAS were lower than those for the con-
trol subjects. Domperidone increased \( V^1 \textsubscript{L} \) in neither the
patients with OSAS nor the control subjects. Domperi-
done increased the \( \Delta V^1/BSA \) and \% \( \Delta V^1 \) in patients with OSAS,
but not in control subjects. No difference was found in
\( \Delta V^1/BSA \) or \% \( \Delta V^1 \) during administration of domperi-
done between the two groups. On subgroup analysis, no
differences were observed in ventilatory responses to che-
meal stimuli or peripheral chemoreception between the
OSAS patients without chronic hypcapnia and those
with chronic hypcapnia (data not shown).

Correlations between ventilatory drive parameters and the
results of polysomnography for the patients with OSAS
are given in table 5. There was no significant correlation
between the respiratory drive to hypoxia and any of
the indices of disturbance of ventilation during sleep. Hy-
poxic ventilatory response exhibited a negative correla-
tion with DSR4\% (fig. 2). There were significant correla-
tions between DSR4\% and \% \( \Delta V^1 \), and between DSR10\%
and \% \( \Delta V^1 \). The apnoea index was correlated with nei-	her hypoxic ventilatory response nor hypercapnic ventilatory
response. Scatter plots of significant correlations in table
5 are illustrated in figure 2. Values for the OSAS patients
with hypcapnia are indicated as open circles and they
appeared to superimpose on each relationship. These
findings showed that subgroup analysis was unlikely to
alter the comprehensive findings of this study.

Discussion

The present study showed that: 1) respiratory drive to
chemical stimuli was attenuated in patients with OSAS; 2)
peripheral chemosensitivity was reduced in patients with
OSAS; 3) domperidone increased the hypercapnic ventila-
tory response and the hypoxic withdrawal response in pa-
tients with OSAS; and 4) the hypoxic ventilatory response
and hypoxic withdrawal response during wakefulness were
negatively correlated with the severity of desaturation
during sleep in patients with OSAS.
The nature of the ventilatory response to chemical stimuli in awake patients with OSAS is still unclear. Ventilatory drive in OSAS patients has been reported to be diminished [19, 20]. In contrast, other investigators have concluded that ventilatory responses in OSAS patients are normal [21]. These discrepancies in findings concerning chemical ventilatory control in OSAS are due in part to differences in patient populations between these studies. Chronic hypercapnia is well recognized, though uncommon among OSAS patients during wakefulness [20, 22]. Hypocapnic OSAS patients have decreased respiratory drive compared with that in normocapnic OSAS patients [19, 20, 22] and the chronic hypercapnia observed during wakefulness in patients with OSAS has been thought to reflect the impact of oxygen desaturation during sleep [23]. The findings obtained for ventilatory drive in OSAS patients has been reported to be diminished [19, 20]. In contrast, other investigators have excluded factors other than the peripheral chemoreceptor activity. The merits of withdrawal tests in the evaluation of peripheral chemoreception have been reported by Miller et al. [27]. In the present study, the change in V'1 during the 5–20-s period following the end of the first O2 inspiration was defined as the withdrawal response. Since the time required for circulation from the lung to the central nervous system is considered to be about 20 s, the hypoxic withdrawal test eliminates peripheral chemoreceptor activity but leaves the humoral environment of the central respiratory regulatory system unchanged. ΔV’1 and %ΔV’1 are, therefore, due to the transient cessation of peripheral chemoreceptor activity.

A preliminary study by the authors estimated the spontaneous variation in five repeated tests of hypoxic withdrawal responses in single subjects. The mean of the coefficient of variance of ΔV’1 was 12.8% (range 8.8–15.6%) in six healthy subjects. This value was equal to indices of ventilatory responses given in previous reports.

### Table 3. Ventilatory responses to hypercapnia and hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Patients with OSAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Domperidone</td>
</tr>
<tr>
<td>ΔV’1/ΔPETCO₂/BSA L-min⁻¹-mmHg⁻¹-m²</td>
<td>0.96±0.09</td>
<td>0.85±0.16</td>
</tr>
<tr>
<td>ΔV’1/ΔPETCO₂ cmH₂O-mmHg⁻¹</td>
<td>0.79±0.15</td>
<td>0.65±0.15</td>
</tr>
<tr>
<td>ΔV’1/ΔSO₂/BSA L-min⁻¹-mmHg⁻¹-m²</td>
<td>0.55±0.08</td>
<td>0.62±0.11</td>
</tr>
<tr>
<td>ΔV’1/ΔSO₂ cmH₂O%⁻¹</td>
<td>0.65±0.10</td>
<td>0.56±0.06</td>
</tr>
</tbody>
</table>

Values are means±SEM. OSAS: obstructive sleep apnoea syndrome; V’1: inspiratory minute ventilation; PETCO₂: end-tidal carbon dioxide tension; BSA: body surface area; P0.1: mouth occlusion pressure; Δ: difference; SO₂: arterial oxygen saturation. (1 mmHg=0.133 kPa); p<0.05 placebo versus domperidone; †: p<0.05 control subjects versus patients with OSAS.

### Table 4. Results of hypoxic withdrawal test

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Patients with OSAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Domperidone</td>
</tr>
<tr>
<td>ΔV’1N/BSA L-min⁻¹</td>
<td>5.4±0.2</td>
<td>6.0±0.5</td>
</tr>
<tr>
<td>ΔV’1N/BSA L-min⁻¹</td>
<td>10.2±1.1</td>
<td>9.9±1.4</td>
</tr>
<tr>
<td>ΔV’1/BSA</td>
<td>3.2±0.4</td>
<td>3.0±0.4</td>
</tr>
<tr>
<td>%ΔV’1 %</td>
<td>31±3</td>
<td>32±4</td>
</tr>
</tbody>
</table>

Values are means±SEM. OSAS: obstructive sleep apnoea syndrome; V’1N: inspiratory minute ventilation during breathing of room air; BSA: body surface area; V’1: inspiratory minute ventilation during hypercapnic hypoxia; V’1S:5–20: V’1 between 5 and 20 s after changing the inspiratory gas; ΔV’1 = V’1S:5–20 – V’1. %ΔV’1 = V’1/S:5–20 × 100; †: p<0.05 placebo versus domperidone; *: p<0.05 control subjects versus patients with OSAS.

### Table 5. Coefficients of correlation between apnoea index (AI), oxygen desaturation ratios and ventilatory responses in patients with obstructive sleep apnoea syndrome

<table>
<thead>
<tr>
<th>AI</th>
<th>DSR4%</th>
<th>DSR10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercapnic response</td>
<td>ΔV’1/ΔPETCO₂/BSA</td>
<td>-0.073</td>
</tr>
<tr>
<td></td>
<td>ΔV’1/ΔPETCO₂</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypoxic response</td>
<td>ΔV’1/ΔSO₂/BSA</td>
<td>-0.378</td>
</tr>
<tr>
<td></td>
<td>ΔV’1/ΔSO₂</td>
<td>-0.112</td>
</tr>
<tr>
<td>Hypoxic withdrawal response</td>
<td>%ΔV’1</td>
<td>-0.141</td>
</tr>
</tbody>
</table>

DSR4%: 4% desaturation ratio; DSR10%: 10% desaturation ratio; Δ: difference; V’1: inspiratory minute ventilation; PETCO₂: end-tidal carbon dioxide tension; BSA: body surface area; P0.1: mouth occlusion pressure; SO₂: arterial oxygen saturation. *: p<0.05.
The magnitude of change in responses to treatment with domperidone appeared to be significant, compared with spontaneous variation in the indices of ventilatory responses observed in the present study.

Dopamine is a major transmitter in the carotid body [9, 10]. In an animal study, exogenous dopamine reduced ventilatory responses to chemical stimuli owing to the inhibition of carotid chemoreception and dopamine antagonists augmented the ventilatory response [28]. Human studies have also shown that i.v. dopamine administration reduces the ventilatory responses to both hypoxia and hypercapnia [12, 29]. Dopamine appears to be an inhibitory transmitter in the mammalian carotid body.

Domperidone is a selective dopaminergic receptor antagonist (D2) and only minimally crosses the blood–brain barrier [13]. It has been shown that, unlike other such antagonists, domperidone has no $\alpha_2$-adrenoreceptor-blocking activity [30]. Therefore, domperidone was used to examine the roles played by endogenous dopamine in peripheral chemoreceptors.

It has been demonstrated in animal studies that the hypercapnic ventilatory response [31] and carotid chemosensory discharge response to hypercapnia [32] are enhanced by domperidone. The hypercapnic ventilatory response was not enhanced by domperidone in carotid body-denervated animals [31]. These findings appear to support the hypothesis that domperidone potentiates hypercapnic ventilatory responses in humans via the effects on peripheral chemosensitivity. The findings of the present study appear to be compatible with those of the animal studies noted above.

DELPIERRE et al. [33] reported that i.v. administration of domperidone increased hypoxic ventilatory response in healthy subjects. In the present study, domperidone changed neither the ventilatory responses to chemical stimuli nor peripheral chemosensitivity in control subjects. This discrepancy in findings between the previous studies and the present investigation might be explained by differences in serum concentrations of domperidone. A safe dose of orally administered domperidone was used in the present study to avoid serious cardiac side-effects [34]. This dose of domperidone has been demonstrated clearly to modulate the effects of dopamine in the gastrointestinal tract [35]. However, the same dose of domperidone increased peripheral chemosensitivity in the patients with obstructive sleep apnoea syndrome in the present study. One interpretation of these findings is that patients with obstructive sleep apnoea syndrome have an abnormality of dopaminergic mechanisms in peripheral chemoreceptors. More specifically, the effects of dopamine on the peripheral chemoreceptors of patients with obstructive sleep apnoea syndrome might be increased and in such patients these receptors might be more sensitive to dopamine receptor antagonists than are those of healthy subjects. However, this hypothesis requires more systematic pharmacological study for testing and direct evidence of abnormality of dopaminergic mechanisms in patients with obstructive sleep apnoea syndrome.

Fig. 2. – Scatter plots of significant correlations between oxygen desaturation ratio during sleep and ventilatory response in obstructive sleep apnoea syndrome with normocapnia (●) and those with chronic hypercapnia (○). DSR4%: 4% desaturation ratio; DSR10%: 10% desaturation ratio; $\Delta$: difference; $V_I$: inspiratory minute ventilation; $S_{a, O_2}$: arterial oxygen saturation; BSA: body surface area.

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