DIFFERENCES IN THE EFFECTS OF HYPERCAPNIA AND HYPOXIA ON THE SWALLOWING REFLEX IN CATS

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Reflex swallowing is achieved by the integrated action of the respiratory centre and several cranial nerve nuclei under the control of a specific neural group, the swallowing centre (Doty, 1951; Miller, 1982). Mechanisms integrating swallowing and respiration have been studied in animals and man (Doty and Bosma, 1956; Sumi, 1964; Wilson et al., 1982). However, there is little information about the effects of factors such as \( P_{\text{CO}_2} \) and \( P_{\text{O}_2} \) on the swallowing reflex, of factors such as \( P_{\text{CO}_2} \) and \( P_{\text{O}_2} \), which influence the activity of the respiratory centres. In a previous study, in lightly anaesthetized cats (Nishino et al., 1985), we showed that continuous stimulation of the superior laryngeal nerve (SLN) at first suppressed ventilation, as judged by suppression of phrenic nerve (PN) activity, and then after a latent interval a swallow was induced, as indicated by a characteristic brief burst of PN activity and a large amplitude burst of hypoglossal nerve (HN) activity. Using this definition of the swallowing reflex, we studied the effects of changes in \( P_{\text{CO}_2} \) and \( P_{\text{O}_2} \) on the swallowing reflex under steady-state conditions.

MATERIALS AND METHODS

Studies were performed on healthy cats weighing from 2.4 to 4.0 kg. Anaesthesia was induced and maintained with 2–3% halothane in oxygen during the surgical preparation—which was similar to that described previously (Nishino et al., 1985). Briefly, the animals were prepared with tracheal, arterial and venous cannulae. The hypoglossal and phrenic nerves were isolated and prepared for recordings of their discharges. The internal branch of the right superior laryngeal nerve was sectioned, desheathed and placed on bipolar platinum electrodes to allow electrical stimulation. All nerves and electrodes were covered with warm mineral oil. Bilateral vagotomy was performed at the middle cervical level. Temperature was monitored by a rectal thermistor.
and maintained at 37–38 °C by a heating lamp. After the surgical preparations, halothane was discontinued and was replaced by α-chloralose 25 mg kg⁻¹ i.v.

Pancuronium 0.2 mg kg⁻¹ i.v. was administered and the lungs ventilated artificially at a fixed rate and volume (rate x volume = 25 x 50 ml). In 10 cats, the effects of changes in \( P_{\text{a}CO_2} \) and \( P_{\text{a}O_2} \) on the swallowing reflex were examined. The swallowing reflex was induced by electrical stimulation of the superior laryngeal nerve (0.08–0.2 V, 0.5-ms pulse duration with a frequency of 33 Hz). The strength of the stimulus was varied from animal to animal, but it was approximately three times the minimum voltage necessary to produce prolonged apnoea during normocapnic hyperoxia and was not changed throughout each individual investigation. The swallowing reflex induced by this method was identified by a characteristic brief burst of activity in the phrenic nerve and a large amplitude burst of activity in the hypoglossal nerve (Nishino et al., 1985).

In order to obtain various values of \( P_{\text{a}CO_2} \) and \( P_{\text{a}O_2} \), the inspired gas mixture was manipulated using various concentrations of carbon dioxide in oxygen or various concentrations of oxygen in nitrogen while end-tidal \( PCO_2 \) (\( PE_{CO_2} \)) and
end-tidal $P_O_2$ ($P'_O_2$) were monitored with an infra-red carbon dioxide analyser and a polarographic oxygen analyser, respectively.

Inspired $P_CO_2$ was increased in four steps under hyperoxia ($P'_O_2 > 46$ kPa) to obtain four different values of $Pa_CO_2$ (3.9, 5.1, 6.3 and 7.8 kPa). After a change in $P'_O_2$, 5–7 min was allowed to achieve a steady state, at which time an arterial blood sample was taken and analysed immediately for pH, $P_CO_2$ and $P_O_2$. Following blood sampling at each steady state of $Pa_CO_2$, the SLN was stimulated for 60 s as described above. The inspired $P_O_2$ was now decreased in four steps to obtain four different values of $Pa_CO_2$ (5.6, 11.3, 6.9 and 4.8 kPa) from hyperoxia to hypoxia while $P'_O_2$ was maintained constant (4.2 kPa). After a change in $P'_O_2$, 3–5 min was allowed to achieve a steady state. The effects of changes in $Pa_CO_2$ on the swallowing reflex were determined in the manner described for changes in $Pa_CO_2$. Most of the investigations were completed within 3 h. If prolonged, a further dose of $\alpha$-chloralose 5–8 mg kg$^{-1}$ i.v. was administered.

In addition to the above, in another four cats the effect of carotid chemoreceptor stimulation on the swallowing reflex was examined by comparing the response to SLN stimulation before and after the bolus i.v. injection of a small dose of doxapram (0.3 mg kg$^{-1}$) under normocapnic, hyperoxic conditions. Doxapram has been shown to be a potent stimulant of carotid chemoreceptor activity (Hirsh and Wang, 1974; Nishino, Mokashi and Lahiri, 1982).

Statistical analysis was performed using Student’s $t$ test where appropriate.

### RESULTS

#### Effects of increases in $Pa_CO_2$

Figure 1 shows an example of the changes in activity in the PN and HN in response to SLN stimulation at four different values of $Pa_CO_2$. Spontaneous inspiratory activity in both PN and HN increased with increasing values of $Pa_CO_2$. At all four $Pa_CO_2$ values, with the start of SLN stimulation, rhythmic PN activity ceased and apnoea ensued while the HN showed irregular bursts of activity. Following a latent period of 10 s, a swallowing act characterized by a brief burst of PN activity and a large amplitude burst of HN activity occurred. During continuing SLN stimulation for 60 s, the swallowing acts appeared repeatedly with intervals of 3–8 s, although the interval between successive swallows gradually increased and the peak height of HN activity decreased gradually. These changes were consistently observed at all four values of $Pa_CO_2$. In table I, the latent period between the start of SLN stimulation and the occurrence of the first swallow, and the number of swallows elicited during continuous SLN stimulation at the various $Pa_CO_2$ are listed. The values of the latent period and the number of swallows are almost the same at all four values of $Pa_CO_2$, indicating that changes in $Pa_CO_2$ have no effect on the swallowing reflex.
Effects of decreases in $P_{a_o_2}$

In contrast to the effects of changes in $P_{a_c_o_2}$, changes in $P_{a_o_2}$ exerted a considerable influence on the swallowing reflex. An example of the effects of decreasing $P_{a_o_2}$ at a constant $P_{a_c_o_2}$ on the swallowing reflex is shown in figure 2. Although spontaneous inspiratory activity in both PN and HN increased with decreasing values of $P_{a_o_2}$, the changes in activity in the PN and HN to SLN stimulation decreased progressively with decreasing $P_{a_o_2}$, and a considerable decrease in the number of swallows was observed during hypoxia.

The relationship between $P_{a_o_2}$ and the number of swallows elicited during a 60-s SLN stimulation in all animals is shown in figure 3. Unlike the effects of decreasing $P_{a_o_2}$ on the number of swallows, the latent period varied greatly and no consistent relationship between the latent period and $P_{a_o_2}$ was observed (table II).

Effects of doxapram

In order to examine whether the effects of the decreases in $P_{a_o_2}$ were mediated by increases in carotid chemoreceptor activity, the response to SLN stimulation before and after the administration of doxapram was compared in four animals. Although the spontaneous respiratory activity of PN and HN after doxapram administration was larger than that before doxapram, the responses to SLN stimulation after doxapram were similar to

### Table II. Latent period (LP) and number of swallows elicited during a 60-s SLN stimulation at different values of $P_{a_o_2}$ at a fixed $P_{a_c_o_2}$.

*Mean value of LP was not determined since, in two animals, no reflex swallowing occurred during SLN stimulation for 60 s.

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>$P_{a_o_2}$ (kPa)</th>
<th>$P_{a_c_o_2}$ (kPa)</th>
<th>LP (s)</th>
<th>No. swallows</th>
<th>$P_{a_o_2}$ (kPa)</th>
<th>$P_{a_c_o_2}$ (kPa)</th>
<th>LP (s)</th>
<th>No. swallows</th>
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<td>4.5</td>
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<td>6</td>
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<td>2</td>
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<td>4.8</td>
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<td>13</td>
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<td>3.89</td>
<td>7.2</td>
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</table>

Mean 56.0 4.29 9.6 8.0 11.29 4.22 9.5 6.8 6.86 4.23 14.6 4.6 4.79 4.21 2.6

The number of swallows was observed during hypoxia.

### Table III. Reflex swallowing before and after administration of doxapram under normocapnic hyperoxia.

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>LP (s)</th>
<th>Swallows (per min)</th>
<th>LP (s)</th>
<th>Swallows (per min)</th>
</tr>
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<td>11</td>
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<tr>
<td>14</td>
<td>12.5</td>
<td>6</td>
<td>12.0</td>
<td>6</td>
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</tbody>
</table>

Mean 12.4 ± 4.0 6.8 ± 1.7 11.3 ± 6.9 7.0 ± 1.8

**P < 0.05; **P < 0.01, compared with values under hyperoxia.
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FIG. 4. Responses of PNA and HNA to SLN stimulation before (the left panel) and after (the right panel) administration of doxapram 0.3 mg kg\(^{-1}\) i.v. For abbreviations, see legend to figure 1.

those before doxapram in terms of the number of swallows elicited and the latent period (fig. 4, table III).

DISCUSSION

In the present study, the swallowing act induced by SLN stimulation was identified by a characteristic brief burst of PN activity and a large amplitude burst of HN activity. Such identification of swallowing enabled us to assess the effects of changes in blood-gas tensions on the swallowing reflex in paralysed and artificially ventilated animals under steady-state conditions (Nishino et al., 1985).

The results of the present study demonstrated that graded hypoxia resulted in a graded inhibition of the swallowing reflex. Our results are in accordance with the observation of Sumi (1963) who showed that, during asphyxia, the hypoglossal motor neurones which discharge rhythmically in phase with respiration did not demonstrate a swallowing response to stimulation of the oropharyngeal cavity, indicating inhibition of the swallowing reflex during hypoxia. In contrast with the effect of hypoxia, our results showed that graded hypercapnia had no effect on the swallowing reflex, although graded hypercapnia and hypoxia similarly increased the spontaneous respiratory activity. This may suggest that the excitability of the swallowing reflex is independent of, rather than dependent on, the background level of respiratory activity.

The mechanism of the depressant effect of hypoxia on the swallowing reflex remains elusive. It is unlikely that the effects observed during hypoxia occurred at the level of sensory receptors in the larynx, since SLN was stimulated electrically at a constant frequency and intensity. It is also unlikely that the graded inhibition of the swallowing reflex during hypoxia occurred at the level of the motor neurones, because the respiratory activities in HN and PN progressively increased as \(P_{a\text{O}_2}\) decreased; therefore, there was no progressive deterioration of motor neurone activity. Accordingly, it would seem that inhibition of the swallowing reflex during hypoxia occurs at an internuncial level where the interneurones link both afferent and efferent limbs of the swallowing reflex (Doty, Richmond and Storey, 1967). It is possible that one reflex system is potentially capable of influencing another. The carotid chemoreceptor response to a decrease in \(P_{a\text{O}_2}\) is well recognized, and it is possible that hypoxia may exert an inhibitory effect on the swallowing reflex through an inhibitory interaction of carotid chemoreceptor input and SLN input in the central nervous system. One possible site of such an interaction is the nucleus tractus solitarius (NTS), since primary afferent fibres in the SLN synapse on to neurones of the NTS in which the
termination of carotid body chemoreceptor afferent fibres are located (Cottle, 1964; Davies and Edwards, 1973).

In fact, there is evidence (Weerasuriya, Bieger and Hockman, 1980) to suggest that some interaction of different inputs from different nerves occurs at the level of the NTS. However, the possibility of the inhibitory interaction of carotid chemoreceptor input and SLN input is not supported by the findings presented here, in that administration of a small dose of doxapram, which stimulates predominantly peripheral chemoreceptors (Hirsh and Wang, 1974), did not inhibit the swallowing reflex induced by SLN stimulation. Another possibility comes from the consideration of a direct depressant effect of hypoxia on the neural pathway relevant to the swallowing reflex. In terms of the direct effect of hypoxia on the central nervous system, there is no evidence that graded hypoxia results in a graded diminution of the ventilatory response in chemoreceptor-dener-vated animals (Lahiri, 1976). Thus, hypoxic depression of the swallowing reflex seems to resemble medullary respiratory depression by hypoxia. The effect of decreasing PaO2 is also analogous to the effect of increasing depth of anaesthesia on the swallowing reflex, in that the number of swallows elicited for a given period of SLN stimulation decreases progressively in a dose-related manner (Nishino et al., 1985). Also, in spite of progressive depression of the swallowing reflex, both hypoxia and anaesthesia did not change the characteristic activity in the PN and the HN during the swallowing reflex, once it was elicited. The latter finding is in agreement with the results of Doty and Bosma (1956), who showed that the motor pattern of swallowing is affected neither by asphyxia nor by anaesthesia, indicating a high degree of stability in the efferent mechanisms of the swallowing reflex.

Unlike the depression produced by anaesthesia, however, hypoxic depression of the swallowing reflex did not always accompany progressive prolongation of the latent period for elicitation of the swallowing reflex. This may indicate that the mechanism of the depression of the swallowing reflex by hypoxia is somewhat different from that by anaesthesia.

There has been no clinical study that is comparable to the present study. Although simple extrapolation of our results to clinical situations may not be entirely valid, it is possible that, as with anaesthesia, hypoxia depresses the swallowing reflex in man and enhances the chance of aspiration of regurgitated material.

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REFERENCES