Central Nervous Integration of the Circulatory and Respiratory Responses to Arterial Hypoxemia in the Rabbit

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ABSTRACT

Neural integration during arterial hypoxia was studied in sham-operated, rhinencephalic, thalamic, high mesencephalic, and pontine rabbits, 3 hours after operation under halothane anesthesia. All preparations except the pontine recovered normal movement and posture 40 to 60 minutes after the operation, and effects on the resting circulation specifically ascribable to transection were small. Activation of diencephalic, and to a lesser extent of rhinencephalic, centers was necessary to produce the large increase in autonomic peripheral resistance effect and the autonomic slowing of heart rate characteristic of normal rabbits. In animals with only pontine and high mesencephalic centers, the autonomic peripheral resistance effect was smaller and there was an autonomic rise in heart rate. The neocortex and rhinencephalon exerted inhibitory influences related to the effects of hyperventilation. Suprabulbar respiratory mechanisms were also activated during hypoxia, with diencephalic mechanisms limiting the reflex response mediated by the pontine centers and the cortex exerting disinhibitory effects on the diencephalic centers. The cardiorespiratory response at different degrees of hypoxia probably depends on differences in relative magnitude of inputs from the arterial chemoreceptors, baroreceptors, and lung inflation receptors, producing different degrees of excitation and inhibition of the various suprabulbar and bulbar centers.

ADDITIONAL KEY WORDS rhinencephalic thalamic pontine preparations neural ablation suprabulbar control of respiration and circulation

A number of regions in the cortex and diencephalon when stimulated electrically can influence the activity of the autonomic effectors to the circulation (1-5), and some of these effects can be modified in turn by stimulation of the arterial baroreceptors and chemoreceptors (6-11). It remains uncertain whether the suprabulbar regions contribute significantly to cardiorespiratory integration of physiologically evoked reflex activity arising from these peripheral receptors (12, 13). We have examined this question in the present experiments in the rabbit by comparing the respiratory and circulatory responses to arterial hypoxia and the autonomic effects in a number of acute unanesthetized prepara-
tions, including sham-operated, rhinencephalic, thalamic, high mesencephalic and pontine animals (14-16). The circulatory effects of different levels of hypoxia in the normal unanesthetized rabbit, the role of the autonomic effectors, and the contribution to the autonomic effects of peripheral inputs from the arterial chemoreceptors, baroreceptors and lung inflation receptors, have been the subject of considerable analysis in this species (17-23). The results of the present studies suggest that suprabulbar regions of the nervous system are normally important in the rabbit's cardiovascular and respiratory responses to arterial hypoxia.

Methods

Ninety-two offspring of New Zealand White rabbits crossbred with the New Zealand Giant strain, of average body weight 2.6 kg (range 2.3 to 3.4 kg) were used in this study.

Operations.—In all rabbits except the "deafferented" ones, a thermistor catheter was inserted into the aorta at a preliminary operation 3 to 7 days before an experiment, as previously described (24). To prepare autonomically "deafferented" animals, bilateral adrenalectomy was performed 10 to 14 days before an experiment. A thermistor was inserted into the aorta at the same time, and the animals were maintained on fixed adrenal steroid replacement therapy (25); from the fourth postoperative day they were given guanethidine sulfate (12.5 mg/kg/day iv), the last dose being given on the morning of the experiment; just before the test the animals were fully atropinized (see below) (20,26).

On the day of the experiment, the central ear artery and right atrium were cannulated and a tracheotomy tube was inserted under local lidocaine anesthesia (24).

The neurosurgical procedures were performed under open-circuit halothane anesthesia. The dura was opened through a bilateral frontoparietal craniotomy, and appropriate regions of the brain were removed by a sucker fitted with a blunt needle tip (16-21 gauge Luer). The tip formed the active lead of a diathermy apparatus, and the force of suction was controlled by partial digital occlusion of a side-hole in the handle. With this arrangement, brain stem distortion was minimal, blood vessels were coagulated as they were exposed during removal of brain tissue, and the blood loss was small (3 to 8 ml measured as hemoglobin from the sucker bottle and eluted from swabs). The operations required about 1 hour. We prepared: (1) Sham-operated animals, in which bilateral craniotomy was performed and 8 ml of blood removed from the arterial catheter during anesthesia, which was extended to 1 hour. In most experiments the dura remained intact, but in some it was accidentally torn, with consequent escape of cerebrospinal fluid, but this was without apparent effect on the postoperative resting values of the different cardiorespiratory variables or on the response to hypoxia. (2) Rhinencephalic animals, in which the superior colliculus was exposed by removing the occipital lobe and the parietal cortex removed, leaving a layer of white matter overlying the anterior portion of the lateral ventricle. The cortical removal extended ventrolaterally to the rhine fissure and medially to the lateral sagittal fissure, leaving the area paracentralis (37) intact over the middle of the hemisphere; in the anterior quarter the area paracentralis was removed to the midline (Fig. 1B). (3) Thalamic animals in which the cortex, olfactory tract, hippocampus, fornix, basal ganglia, and septum pellucidum were removed; thalamus, subthalamus, and hypothalamus including preoptic regions were preserved intact (Fig. 1C). (4) High mesencephalic animals in which the transection extended from the anterior border of the superior colliculus to just behind the mamillary body (Fig. 1D). (5) Pontine animals, in which transection was from the lower margin of the inferior colliculus to the anterior pontine border near the point of emergence of the oculomotor nerve (Fig. 1E). In three pontine animals, the carotid sinuses and aortic nerves were sectioned after decerebration (24).

After all bleeding had stopped, the exposed brain was covered with moist absorbable gelatin sponge (Sterispon, Allen & Hanbury, Ltd.), and the skin was sutured. The animals recovered in a sound-proof box, and were given 5.5% dextrose in distilled water, 15 ml iv hourly. Body temperature was maintained when necessary by an electric blanket. At the end of the experiment, the brains were fixed in 10% formal saline and examined macroscopically. The lesions were reproducible, and histological examination showed that there was no underlying damage of parts of the brain covered with pia mater (e.g., superior colliculus in Fig. 1C); small, irregular patches of edema and hemorrhage did not extend more than 200 to 500 μ from the cut surfaces.

Cardiorespiratory Measurements.—Cardiac output was measured by recording thermodilution curves from the upper abdominal aorta, after rapid injection into the right atrium of 0.46 ml of 5.5% dextrose in distilled water at room temperature (24). Mean ear artery and right atrial pressures were recorded using Statham P 23 AC strain gauges, and the heart rate was obtained from the arterial pressure record. Total peripheral
resistance was calculated as (ear artery pressure —
right atrial pressure)/cardiac output. The animal
breathed room air through a low-resistance
respiratory flap-valve (17, 24) during control and
recovery periods, and a freshly prepared low O₂-
N₂ mixture from a light latex balloon during the
treatment period. Respiratory rate was measured
by counting the respiratory movements and the
minute volume (liters/min, ATPS) was deter-
mined by collecting expired gas. Arterial Po₂,
Pco₂ and pH were measured with a blood gas
analyzer and pH meter. (Instrumentation Labora-
tory Inc., Model 113).

Experimental Procedure.—After the initial can-
nulation procedures, each animal rested for 1
hour in a small rabbit box, kept in a larger sound-
proof box. Four measurements of the different
resting cardiorespiratory variables (cardiac out-
put, arterial and right atrial pressures, heart rate,
respiratory rate and minute volume) were made
over a period of 10 minutes in each animal.
Neurosurgery or sham operation (craniotomy)
were then performed, and the main part of the
experiment began 3 hours later.

In the first series of experiments, all animals
were studied inside the sound-proof box 3 hours
after surgery while sitting in their normal posture,
except for the pontine animals, which required a
special holder. The experiment consisted of a
resting period of 16 minutes breathing room air
(5 sets of cardiorespiratory measurements), a
treatment period of 44 minutes breathing 7.5%
to 12% O₂ (17 sets of measurements), and a
recovery period of 13 minutes breathing room air
(4 sets of measurements). In each experiment,
measurements of arterial Po₂, Pco₂, and pH were
obtained while the animal was breathing room
air, and at 12 and 32 minutes after the start of
hypoxia. The changes in Pao₂ minute by minute
were not studied, since previous studies showed
that the arterial O₂ saturation falls close to its
new equilibrium level in less than 3 minutes (28,
29). The effects of only one level of hypoxia were
examined in each animal. In each preparation
three groups of rabbits were studied at Pao₂
approximately 50, 40, or 30 mm Hg, using mostly
3 to 5 animals per group; two other groups of
normal animals were also studied at Pao₂ 35 mm
Hg and 26 mm Hg.

In the second series of experiments, the animals
again recovered from the effects of operation
while breathing spontaneously. Three hours after
operation they were connected to a respiratory
pump and ventilated at the average minute
volume (1 liter/min) and rate (60/min) of
normal rabbits. Muscular relaxation was induced
by decamethonium iodide, 1 mg/kg iv, with supplements of 0.5 mg/kg iv every 20 to 30 minutes (26). No operative intervention was undertaken while the animals were under the influence of decamethonium, and they were placed supine on a warm platform, wrapped in cotton wool, and Dow Silicone Medical Fluid No. 360 instilled into their eyes to minimize somatic stimuli. Each animal was subjected to three levels of hypoxia in random order, each test consisting of a resting period of 8 minutes (room air, four measurements); a period of hypoxia of 10 minutes (five measurements); a recovery period of 6 minutes (room air, three measurements). During the treatment and recovery periods the ventilation was raised to 2 l/min for all levels of arterial Po2 to imitate the respiratory response to severe hypoxia of a spontaneously breathing normal animal (17, 19); this degree of hyperventilation during hypoxia resulted in approximately the same changes in Paco2 and pH as in the spontaneously breathing animal subjected to PaO2 of about 30 mm Hg (Table 2); these changes in blood composition being known to be tolerated by the latter without apparent distress. Arterial blood composition was determined before, and 8 minutes after, the start of hypoxia. A period of 30 minutes was allowed between tests.

A third series of experiments was performed in the same way under controlled ventilation, but the animals were given atropine sulfate, 3 mg iv 10 minutes before the test followed by a continuous infusion of 0.2 mg/min iv. The method estimates autonomic effects on the arteriolar smooth muscle (32), the magnitude of which is probably not altered by the de-efferentation procedure (20) or by the difference in transmural pressure between the preparations in the present experiments (33), we have assumed that the direct local effects of hypoxia on the peripheral arterioles in normal animals are relatively independent of the degree of neural constrictor tone and can be estimated approximately from the responses of autonomically de-efferented animals (23). The method estimates autonomic effects and not autonomic neural activity, and is suitable for studying only relatively gradual changes in each variable were averaged per larger time interval, except for the first interval after the start of hypoxia, for which only one set of measurements was obtained. The timing of measurements was the same in each animal, and the mean absolute value of each variable was obtained by averaging the results of all animals in a particular group at each time interval. To facilitate comparisons between the different preparations, the average changes at each time interval during hypoxia and recovery have been expressed as a percent of the mean resting value of the particular group. The standard error of the mean at a single time interval was calculated from analysis of variance, after subtracting between-time-intervals from the total sums of squares, as (EMS/n)½, where n is the number of animals in the group. In the second or third series of experiments, the standard error of the mean at a single time interval was calculated similarly, but in these series all time intervals were of only 2 minutes duration, with one measurement per time interval from each animal, and mostly three animals per group.

Assessment of Autonomic Effects.—Changes in autonomic effects were assessed indirectly from the differences in the circulatory responses between the various neurological preparations on the one hand, and autonomically de-efferented animals on the other, as discussed in detail elsewhere (23, 26, 31). The cardiorespiratory variables of the latter preparation at rest differ only slightly from normal, and they have a normal respiratory response to hypoxia. Since hypoxia appears to have a direct action on the arteriolar smooth muscle (32), the magnitude of which is probably not altered by the de-efferentation procedure (20) or by the difference in transmural pressure between the preparations in the present experiments (33), we have assumed that the direct local effects of hypoxia on the peripheral arterioles in normal animals are relatively independent of the degree of neural constrictor tone and can be estimated approximately from the responses of autonomically de-efferented animals (23). The method estimates autonomic effects and not autonomic neural activity, and is suitable for studying only relatively gradual changes in these effects.

Figure 2 illustrates the calculation in sham-operated normal animals of the autonomic effects at PaO2 of 50, 40, and 30 mm Hg. To assess net autonomic effects on total peripheral resistance, the resting values in sham-operated and de-efferented animals were superimposed, and the changes in each preparation expressed as the percent of its own resting value at the various longer time intervals. The differences in total peripheral resistance values at each time interval.
Graph showing calculation of autonomic effects on heart rate (H.R.) and total peripheral resistance (T.P.R.). Low O₂-N₂ mixtures breathed between arrows, room air at other times. Results at Pao₂ 50 mm Hg from 3 normal (solid line) and 3 de-efferented (broken line) rabbits; at Pao₂ 40 mm Hg from 5 normal and 3 de-efferented rabbits; at Pao₂ 30 mm Hg from 4 normal and 3 de-efferented rabbits. In the top row, mean heart rate changes have been expressed as percent of resting, in each group, the symbol on the left being the standard error of the mean at a single time interval. In the second row, the difference in percent response between normal and de-efferented animals is the autonomic heart rate effect, and the time-effect curves obtained by joining successive time intervals; the standard error of the autonomic effect at a single time interval is on the left. In the third row, the total peripheral resistance percents are plotted; the net autonomic effect on total peripheral resistance in the fourth row has been obtained at each time interval from the difference in percent response between the normal and de-efferented animals.

and the differences in heart rate response are used to construct time-autonomic total peripheral resistance and heart rate effect curves. As seen in Figure 2, at Pao₂ 50 mm Hg, the heart rate increases during hypoxia in both sham-operated and de-efferented groups, the rise being approximately twice as great in the former. The autonomic component of the tachycardia is thus less than the total rise in heart rate in the sham-operated animal. When, as at Pao₂ 50 mm Hg, the rise in heart rate is relatively greater in sham-operated than in de-efferented animals, the autonomic response is called an autonomic rise in heart rate, and when the sham-operated animal responds with more cardiac slowing than the de-efferented animal (as at Pao₂ 30 mm Hg), it is termed autonomic cardiac slowing. The standard error of the mean autonomic effect at a single time interval, \( \text{SE}_{\text{aut}} = \sqrt{\text{SE}_{\text{normal}}^2 + \text{SE}_{\text{de-ef}}^2} \), the values in parentheses being the standard error of a single time interval in the total peripheral resistance or heart rate change of sham-operated and de-efferented animals for \( (n_1 + n_2 - 2) \) degrees of freedom, where \( n_1 \) and \( n_2 \) are the number of normal and de-efferented animals, respectively. When calculating the significance of differences between two groups of neurological preparations with \( n_1 \) and \( n_2 \) animals respectively, the degree of freedom is \( (n_1 + n_2 - 2) \), and the de-efferented results contribute only to the calculation of \( \text{SE}_{\text{aut}} \) of each group. The standard error of the mean autonomic effect over the whole period of hypoxia in any group is \( \text{SE}_{\text{aut}} / (N) \), where \( N \) is the number of larger time intervals during hypoxia.

The above method was used in the other neurological preparations to construct time-autonomic effect curves at Pao₂ approximately 50, 40, and 30 mm Hg. Small corrections were applied to the data from de-efferented rabbits using more detailed response curves to allow for differences in arterial Pao₂ and pH between corresponding neurological groups. The de-efferented animals were not subjected to halothane anesthesia and craniotomy because of a high mortality during induction of anesthesia in these areflexic animals (26). Since the same basic data from de-efferented rabbits have been used with each neurological preparation, any changes in local circulatory responsiveness due to preceding anesthesia and operation will systematically affect the estimates of the autonomic effects in all the preparations. However, it is unlikely that local vessel sensitivity was much affected, since in one de-efferented animal the circulatory response to hypoxia was the same before as 3 hours after anesthesia and craniotomy.

Assumptions and Limitations.—The use of acute neural preparations in the analysis of central nervous function requires that the ablation procedures should produce few nonspecific effects and that differences in resting state will not preclude valid comparisons between the prepara-
TABLE 1
Comparisons of Mean Normal Resting Values with Values Three Hours after Surgery

<table>
<thead>
<tr>
<th>Group*</th>
<th>Variable</th>
<th>Pre-op</th>
<th>Post-op</th>
<th>SE</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>( \bar{V}_E )</td>
<td>1.03</td>
<td>1.37</td>
<td>±0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Sham operation (13)</td>
<td>f</td>
<td>67</td>
<td>112</td>
<td>±12.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Rhinencephalic (8)</td>
<td>( \bar{V}_E )</td>
<td>1.32</td>
<td>1.97</td>
<td>±0.15</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Thalamic (12)</td>
<td>f</td>
<td>81</td>
<td>101</td>
<td>±15.1</td>
<td>NS</td>
</tr>
<tr>
<td>High mesencephalic (9)</td>
<td>( \bar{V}_E )</td>
<td>1.11</td>
<td>1.91</td>
<td>±0.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pontine (11)</td>
<td>( \bar{V}_E )</td>
<td>1.15</td>
<td>1.31</td>
<td>±0.12</td>
<td>NS</td>
</tr>
</tbody>
</table>

\( \bar{V}_E \) = respiratory minute volume (liters/min, STPD); \( f \) = respiration rate (breaths/min); \( \bar{V}_O_2 \) = oxygen consumption (ml/min, STPD); \( \bar{V}_T \) = tidal volume (ml). SE and P are standard error and significance of difference between pre- and postoperative values obtained from the same animal; NS = not significant.

*Number in parentheses is number of rabbits.

Marked changes in the circulatory response of a particular preparation (e.g., pontine) from normal will then indicate that the centers remaining after ablation by themselves account inadequately for cardiorespiratory integration. However, conclusions regarding the normal function of these centers in animals with intact brains must be more tentative, since the hemodynamic changes may lead to a different profile of stimulation of the peripheral receptors normally involved in the response. Supplementary information about the activation of various centers from electrophysiological studies using the evoked potential method would be valuable, but has not been obtained in this study.

In the spontaneously breathing pontine animals, the mechanical effects of decerebrate rigidity were minimized by using a special holder which kept them in the same posture as normal animals, and allowed free chest movements. In these animals, resting respiratory minute volume was not significantly different from that observed after sham operation, but the depth of breathing was somewhat greater. This could possibly be related to change in discharge rates from the stretch receptors of skeletal muscles, including those of respiration, associated with the decerebrate rigidity. We have, however, assumed that these differences do little to modify the pontine animal's respiratory response to hypoxia, since it is closely similar to that of normal (Fig. 4) and high mesencephalic rabbits (Table 3), in which decerebrate rigidity is absent. No data are available on the work and efficiency of breathing in the pontine rabbits but the overall effects of decerebrate rigidity on muscle tone are not large enough to affect total body oxygen consumption (Table 1).

The muscle relaxant decamethonium when used in large doses is known to affect chemoreceptor discharge during hypoxia and also autonomic ganglionic transmission (34, 35). In the present dose, the effect on chemoreceptor discharge is probably minimal (35), and even with
three times the present dose, the magnitude of the heart rate changes produced by electrical stimulation of the vagus is virtually unaffected. Furthermore, in sham-operated animals the reflex autonomic effects evoked by severe hypoxia are closely similar during spontaneous respiration and after decamethonium (with ventilation controlled at approximately the same level). The dose of atropine used in the present study prevents heart rate changes during electrical stimulation of the vagus in the anesthetized rabbit (31), but has no apparent toxic effect in the unanesthetized animal (26). We have assumed that its main action is to block vagal efferents, that its effect on chemoreceptor discharge can be neglected in the doses used (34), and that when used by itself in series 3, its recently demonstrated effects on sympathetic ganglionic transmission can probably be neglected in the presence of the normal nicotinic component (36).

The use of 'de-efferented' animals to assess the local effects of hypoxia requires that their autonomic effects have been completely inactivated. The adrenalectomy is complete, and the animals do not survive when adrenal steroid replacement therapy is discontinued (25); the dose of guanethidine blocks sympathetic nerve transmission to the hindlimb (37) and in normal rats and rabbits depletes peripheral tissue catecholamines except in the central nervous system and adrenal medulla (38-40).

Results

Resting Behavior

The sham-operated, rhinencephalic, thalamic, and high mesencephalic animals regained normal posture and movement within 30 to 40 minutes after operation. The sham-operated animals made normal sniffing and washing movements typical of unoperated rabbits, and appeared to be in no distress. The rhinencephalic and thalamic animals would sit in a quiet, limp manner, with head drooping, but after a painful stimulus or loud noise they would arch their backs and with pupils dilating, would run forward vigorously (sham rage). We did not observe the placidity described by Bard and Mountcastle (16) in chronic rhinencephalic cats. The pontine animals lay on their side, with the classic posture of decerebrate rigidity (14).

Resting Measurements

The preoperative normal resting values in each animal were compared with the results obtained 3 hours postoperatively. Respiratory minute volume increased significantly in sham-operated \( P < 0.01 \), rhinencephalic \( P < 0.01 \), and thalamic \( P < 0.001 \) animals, but not in the high mesencephalic and pontine animals (Table 1). In the rhinencephalic and thalamic animals, the rise in minute volume was greater than after sham operation \( P = 0.05, P < 0.02 \), respectively, but the rise in respiratory rate was somewhat less marked. In both these groups, there was some hypocapnia, with a slight respiratory alkalosis in thalamic animals (Table 2); alkalosis was absent in the rhinencephalic animals.

In the first series of experiments, the postoperative results were obtained during spontaneous respiration (Fig. 3). In the sham-operated animals there was a moderate rise in heart rate and fall in arterial pressure to 111% and 87% of the respective preoperative values \( P < 0.05 \), while the changes in cardiac output and total peripheral resistance were not statistically significant. In the rhinencephalic and thalamic animals the changes in heart rate, arterial pressure, and cardiac output also differed significantly from the effects in the sham-operated animals, but the differences were small. In the thalamic animals, the rise in heart rate was again greater than after sham operation, and the changes after operation in blood pressure and cardiac output also differed slightly \( P < 0.05 \). In the pontine animals, the heart rate and blood pressure remained unchanged from the preoperative value, but the reduction in cardiac output to 79% of preoperative and the rise in total peripheral resistance to 127%, were significantly different \( P < 0.05 \) from the effects of sham operation.

In the second series of experiments, the normal preoperative values (spontaneous respiration) were compared with the postoperative values obtained during controlled ventilation (Fig. 3). The circulatory variables after operation were now more closely similar in sham-operated, rhinencephalic, and thalamic animals, suggesting that the differences in the spontaneously breathing animals reflected differences in respiratory or muscular activity or both, rather than different degrees of trauma. However, in the pontine group the
### TABLE 2

**Mean Values of Arterial Oxygen Pressure, Carbon Dioxide Pressure, and pH during Rest and during Hypoxia**

<table>
<thead>
<tr>
<th>Group</th>
<th>Arterial oxygen pressure* (mm Hg)</th>
<th>Arterial carbon dioxide pressure (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R 12 min</td>
<td>Hypoxia 12 min</td>
<td>Hypoxia 32 min</td>
</tr>
<tr>
<td>Normal</td>
<td>3 97 ± 1.0</td>
<td>50 ± 0.4</td>
<td>51 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>6 96 ± 3.1</td>
<td>41 ± 1.6</td>
<td>40 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>4 95 ± 1.8</td>
<td>36 ± 1.9</td>
<td>35 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>4 99 ± 3.6</td>
<td>32 ± 1.8</td>
<td>30 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>6 96 ± 2.0</td>
<td>27 ± 0.8</td>
<td>26 ± 0.7</td>
</tr>
<tr>
<td>Rhinencephalic</td>
<td>3 108 ± 3.8</td>
<td>53 ± 1.6</td>
<td>52 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>4 104 ± 2.8</td>
<td>41 ± 3.0</td>
<td>42 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>4 98 ± 2.0</td>
<td>32 ± 1.1</td>
<td>33 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>3 112 ± 4.2</td>
<td>39 ± 2.3</td>
<td>38 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>5 110 ± 4.0</td>
<td>32 ± 1.5</td>
<td>31 ± 1.5</td>
</tr>
<tr>
<td>High mesencephalic</td>
<td>2 96 ± 2.0</td>
<td>39 ± 2.2</td>
<td>38 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>6 96 ± 1.3</td>
<td>31 ± 1.3</td>
<td>30 ± 0.9</td>
</tr>
<tr>
<td>Pontine</td>
<td>3 103 ± 1.2</td>
<td>53 ± 1.5</td>
<td>52 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>4 100 ± 3.0</td>
<td>39 ± 2.7</td>
<td>40 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>4 107 ± 3.8</td>
<td>32 ± 1.4</td>
<td>32 ± 1.0</td>
</tr>
<tr>
<td>De-erfected</td>
<td>3 90 ± 1.7</td>
<td>52 ± 2.0</td>
<td>51 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>3 93 ± 2.4</td>
<td>42 ± 1.0</td>
<td>41 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>3 92 ± 3.0</td>
<td>32 ± 1.3</td>
<td>31 ± 1.1</td>
</tr>
</tbody>
</table>

*Respiration was spontaneous in all animals.*

*Mean ± SEM of each individual group to indicate range of variation. †Obtained by analysis of variance based on within-animal comparisons. R = at rest.*
NEURAL INTEGRATION IN HYPOXIA

FIGURE 3
Left: Comparisons of the mean normal resting preoperative value, with the value obtained 3 hours after surgery in 13 sham-operated (Sh), 8 rhinencephalic (Rh), 12 thalamic (Th), and 11 pontine (Po) rabbits, breathing spontaneously. The variables were heart rate/min (H.R.), arterial pressure, mm Hg (B.P.), cardiac output (C.O.) in ml/min and total peripheral resistance (T.P.R.) in arbitrary units. A significant (P < 0.05) change from preoperative value in each group is shown as stippled postoperative value. Solid circle above a preparation indicates that its response differs (P < 0.05) from effect of sham operation. The height of a rectangle equals mean value, and the height of the line near the upper edge of the preoperative rectangle is twice SE of the mean pre- or postoperative value, obtained by Analysis of Variance.

Right: Similar comparisons in 3 normal, 4 rhinencephalic, 3 thalamic and 3 pontine animals. The preoperative normal value was obtained during spontaneous respiration; the postoperative value was obtained during artificial ventilation after administration of decamethonium.

total peripheral resistance again rose more markedly than after sham operation (P = 0.05), thus showing the same effect as in spontaneously breathing animals.

BEHAVIOR DURING HYPOXIA
The normal (sham-operated) animals became restless for about half a minute after the start of hypoxia, especially with the lower inspired oxygen mixtures, often sniffing near the front of their box as though looking for a means of escape. However, they quickly settled down and remained quiet at all levels of PaO2 studied, without apparent loss of consciousness. In rhinencephalic and thalamic animals, the initial movements were less purposeful, but of about the same duration as in normal animals. There was little increased activity in the high mesencephalic and pontine animals. No ill effects were observed after hypoxia in any of the preparations.

RESPIRATORY RESPONSE
In each preparation we studied the responses to at least three levels of hypoxia at approximately PaO2 50, 40, and 30 mm Hg (Table 2, Fig. 4). In the normal animal at PaO2 50 mm Hg, the respiration increased...
### TABLE 3
Percent Change from Resting Values in Respiratory Minute Volume and Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>No. rabbits</th>
<th>( \text{PaO}_2 )</th>
<th>( \text{Ve} )</th>
<th>( \text{f} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>3</td>
<td>146 ± 4.9</td>
<td>102 ± 2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>179 ± 3.2</td>
<td>128 ± 2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>202 ± 2.9</td>
<td>142 ± 3.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>194 ± 5.8</td>
<td>118 ± 3.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6*</td>
<td>176 ± 7.3</td>
<td>121 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Rhinencephalic</td>
<td>3</td>
<td>129 ± 3.8</td>
<td>108 ± 1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>174 ± 6.3</td>
<td>140 ± 5.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>180 ± 2.4</td>
<td>127 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>Thalamic</td>
<td>4</td>
<td>135 ± 2.6</td>
<td>115 ± 2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3†</td>
<td>123 ± 3.4</td>
<td>114 ± 2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5†</td>
<td>138 ± 3.7</td>
<td>107 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>High mesencephalic</td>
<td>2‡</td>
<td>249 ± 4.6</td>
<td>150 ± 3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6‡</td>
<td>222 ± 5.0</td>
<td>145 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Pontine</td>
<td>3</td>
<td>139 ± 3.2</td>
<td>116 ± 1.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4‡</td>
<td>207 ± 6.1</td>
<td>131 ± 2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4‡</td>
<td>218 ± 6.6</td>
<td>138 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>De-efferented</td>
<td>3</td>
<td>147 ± 2.7</td>
<td>130 ± 3.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>187 ± 8.1</td>
<td>133 ± 5.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>170 ± 7.3</td>
<td>127 ± 6.6</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± se of the mean difference based on comparisons within animals. \( \text{PaO}_2 \) values are means from samples 12 and 32 minutes after start of hypoxia. Mean respiratory effects were calculated from the integrated time-response curves (Fig. 4).

*VE and f significantly lower \((P = 0.01)\) than in normal animal at \( \text{PaO}_2 \) 36 mm Hg.
†VE significantly less \((P < 0.001)\) than in other preparations at corresponding \( \text{PaO}_2 \).
‡VE significantly greater \((P < 0.05)\) than in normal, rhinencephalic, and thalamic animals at corresponding \( \text{PaO}_2 \).

soon after the onset of hypoxia, and rose within about 5 minutes to an approximate plateau level. At \( \text{PaO}_2 \) 40 and 30 mm Hg, ventilation increased to a maximum within 1 minute from the onset of hypoxia, settling to a lower plateau level 5 to 10 minutes later. The rise in respiratory rate was less marked than the rise in minute volume. Two other groups of normal animals were studied at \( \text{PaO}_2 \) 35 mm Hg and 26 mm Hg. The results in Table 3 indicate that the greatest mean respiratory response was attained at approximately \( \text{PaO}_2 \) 35 mm Hg \((202 ± 2.9 \text{ (se)% of resting)}\); at \( \text{PaO}_2 \) 30 mm Hg, the response was almost unaltered, but at 26 mm Hg, it had fallen off significantly to a mean of 176 ± 7.3% of resting.

At each level of \( \text{PaO}_2 \), respiratory response in rhinencephalic animals was closely similar to normal (Table 3, Fig. 4). In the thalamic animals the response was considerably less at \( \text{PaO}_2 \) 40 and 30 mm Hg than in the other preparations. On the other hand, the pontine and high mesencephalic animals had an essentially normal or somewhat increased response at all levels of \( \text{PaO}_2 \). The mean pH change during hypoxia in normal and de-efferented animals was in agreement with previous findings (17, 20, 31) and showed some respiratory alkalosis (Table 2). This was somewhat less marked in thalamic and high mesencephalic animals. However, the pontine and rhinencephalic animals developed a moderate acidosis toward the end of hypoxia, possibly related to greater epinephrine release (see Discussion).
Neural integration in hypoxia

Mean changes during severe hypoxia (Pao2 30 mm Hg) in heart rate (H.R.), arterial pressure (B.P.), cardiac output (C.O.), and total peripheral resistance (T.P.R.), all expressed as percent of resting, in 4 normal, 4 rhinencephalic, 5 thalamic, 6 high mesencephalic and 4 pontine rabbits, breathing spontaneously. Symbol on left of each variable is ± 1 se of mean at a single time interval.

Circulatory changes at Pao2 30 mm Hg

The results in the sham-operated group were similar to findings in rabbits subjected to only the minor cannulation procedures and previous implantation of the thermistor (17, 19). During severe hypoxia, there was bradycardia, transient early reduction in cardiac output followed by a subsequent increase above the resting value, and transient early elevation in arterial pressure and in total peripheral resistance (Fig. 5). The circulatory findings in the thalamic animals were closely similar. In the rhinencephalic animals, marked bradycardia was also present, but the cardiac output increased more rapidly than normal, and the early rise in total peripheral resistance was less pronounced. In the pontine animals, the early bradycardia was either minute or absent, and in all animals, heart rate and cardiac output increased rapidly soon after the onset of hypoxia, while the total peripheral resistance fell to 80% of resting. The circulatory response of the pontine group thus differed more markedly from normal than that of the other groups. In the high mesencephalic animals in which posture and movement were essentially normal, a response closely similar to that of pontine animals was observed.

In the normal rabbit, the reflex changes in respiration and circulation during hypoxia are primarily evoked from the receptors of the carotid sinus and aortic arch region (17-20). After section of the carotid sinus and aortic nerves in animals with an intact central nervous system, the resting total peripheral resistance was about 50% higher than before nerve section, and during hypoxia the respiration no longer rose, the bradycardia was greatly reduced, and the arterial pressure and total peripheral resistance fell markedly instead of rising (Fig. 6). In pontine animals, the resting total peripheral resistance was also increased by about 50% after section of the carotid sinus and aortic nerves, and during hypoxia the rise in respiration and tachycardia were virtually abolished. The same large reduction in arterial pressure and total peripheral resistance now occurred as in animals with intact central nervous system (Fig. 6), probably as a result of the local dilator effects of hypoxia (17, 20). The reason for the greater magnitude of vasodilatation compared

Circulation Research, Vol. XXIV. June 1969
Mean changes in respiratory minute volume ($V_e$), heart rate (H.R.), arterial pressure (B.P.) and total peripheral resistance (T.P.R.), all expressed as percent of resting, during hypoxia ($P_{ao2}$ 30 mm Hg) in spontaneously breathing animals with intact central nervous system (normal), and in pontine animals. The former group comprises 4 animals with carotid sinus and aortic nerves (C & A) intact (broken lines), and 3 animals with section of these nerves (solid lines). A similar notation is used to show responses of 4 pontine animals with these nerves intact and 3 pontine animals with section of these nerves. Mean absolute values of the variables in order, with nerves intact, then after section: Normal rabbits: $V_e$ = 1.37 liters/min; H.R. = 273/min, 306/min; B.P. = 84 mm Hg, 126 mm Hg; T.P.R. = 175 units, 261 units. Pontine rabbits: $V_e$ = 1.31 liters/min; H.R. = 245/min, 261/min; B.P. = 92 mm Hg, 110 mm Hg; T.P.R. = 218 units, 340 units.

The findings suggest that the carotid and aortic reflex zones are the primary sources of respiratory and autonomic excitation during hypoxia in pontine as well as in normal animals.

with de-efferented rabbits probably depends on differences in $P_{aco2}$, since de-efferented animals hyperventilate normally (31). The findings suggest that the carotid and aortic reflex zones are the primary sources of respiratory and autonomic excitation during hypoxia in pontine as well as in normal animals.

**FIGURE 6**

Mean changes in respiratory minute volume ($V_e$) heart rate (H.R.), arterial pressure (B.P.) and total peripheral resistance (T.P.R.), all expressed as percent of resting, during hypoxia ($P_{ao2}$ 30 mm Hg) in spontaneously breathing animals with intact central nervous system (normal), and in pontine animals. The former group comprises 4 animals with carotid sinus and aortic nerves (C & A) intact (broken lines), and 3 animals with section of these nerves (solid lines). A similar notation is used to show responses of 4 pontine animals with these nerves intact and 3 pontine animals with section of these nerves. Mean absolute values of the variables in order, with nerves intact, then after section: Normal rabbits: $V_e$ = 1.37 liters/min; H.R. = 273/min, 306/min; B.P. = 84 mm Hg, 126 mm Hg; T.P.R. = 175 units, 261 units. Pontine rabbits: $V_e$ = 1.31 liters/min; H.R. = 245/min, 261/min; B.P. = 92 mm Hg, 110 mm Hg; T.P.R. = 218 units, 340 units.

**FIGURE 7**

Time-autonomic total peripheral resistance effect curves at approximately $P_{ao2}$ 50, 40, and 30 mm Hg in the various preparations of animals breathing spontaneously. The number of animals is the same as in Figure 4.

**AUTONOMIC EFFECTS DURING SPONTANEOUS RESPIRATION**

Autonomic Total Peripheral Resistance Effect.—In the normal animals, the mean autonomic total peripheral resistance effect over the whole period of hypoxia at $P_{ao2}$ 50, 40, and 35 mm Hg increased by a small but statistically significant amount ($P < 0.02$) to an approximately constant value ($516 \pm 115$, $603 \pm 130$, $490 \pm 140$ arbitrary units, respectively) and then increased sharply at $P_{ao2}$ 30 mm Hg to 1530 ± 214 units, following attainment of the maximum respiratory response (Table 3). A similar rise in mean autonomic total peripheral resistance effect was observed at $P_{ao2}$ 26 mm Hg ($1730 \pm 214$ units), when there was some falling off in respiratory response.

The time-autonomic total peripheral resistance effect curves (Fig. 7) in the three
Neural Integration in Hypoxia

Suprabulbar preparations typically showed a transient increase in autonomic total peripheral resistance effect, and a smaller late effect, both components increasing in magnitude with increasing severity of hypoxia. The early transient response was completely suppressed in normal and rhinencephalic animals at \( P_{aO_2} 50 \) mm Hg and was most pronounced in the thalamic animals. In the rhinencephalic animals at \( P_{aO_2} 40 \) mm Hg, the early rise in autonomic effect was maintained during the latter part of hypoxia at a higher level than in the thalamic animals. In the thalamic animals at \( P_{aO_2} 50 \) mm Hg, the early rise in autonomic effect was maintained during the latter part of hypoxia at a higher level than in the normal animal at \( P_{aO_2} 50 \) mm Hg. At \( P_{aO_2} 30 \) mm Hg, each of the three suprabulbar preparations had prominent early and late autonomic total peripheral resistance effects. In the pontine animals at \( P_{aO_2} 50 \) and 40 mm Hg, the autonomic effects did not change significantly from the resting level, while at \( P_{aO_2} 30 \) mm Hg, the mean response during hypoxia averaged 40% of the value observed in the suprabulbar preparations, but only the early effect was statistically significant.

Autonomic Heart Rate Effect.—In the three suprabulbar preparations, the autonomic effect typically consisted of cardiac slowing during the early part of hypoxia, becoming less marked with time (Fig. 8). The early autonomic slowing became more pronounced with increasing severity of hypoxia in all suprabulbar preparations, and was most prominent in the thalamic animals at each \( P_{aO_2} \). In normal animals at \( P_{aO_2} 50 \) mm Hg, the early autonomic slowing was completely suppressed and there was a gradual autonomic rise in heart rate. Late autonomic cardiac slowing was more pronounced in rhinencephalic animals at \( P_{aO_2} 40 \) mm Hg than in the other preparations (\( P < 0.01 \)).

In the pontine animals, there was a gradual autonomic increase in heart rate at \( P_{aO_2} 50 \) and 40 mm Hg, rising to a plateau during the first 10 to 20 minutes of hypoxia, with a time course similar to that of the normal animal at \( P_{aO_2} 50 \) mm Hg. At \( P_{aO_2} 30 \) mm Hg, the response of the pontine animal was biphasic, with a very brief period of autonomic cardiac slowing followed by the more gradual autonomic rise in heart rate. The transient cardiac slowing in the pontine animal corresponds to the time of initial rise in arterial pressure (Fig. 5). In one experiment in a pontine animal, raising the carotid sinus pressure in the isolated sinus by 100 mm Hg for a few seconds resulted in reflex bradycardia due to increased vagal and reduced cardiac sympathetic activity. However, hypoxia never resulted in prolonged autonomic cardiac slowing in the pontine animal.

Autonomic Effects During Controlled Ventilation (2 liters/min)

The differences in autonomic total peripheral resistance effects observed during the early part of hypoxia between spontaneously breathing normal, rhinencephalic, and thalamic animals were now greatly reduced (Fig. 9), as were corresponding differences in autonomic heart rate effects (Table 4). In the pontine animals, the autonomic total periph-
TABLE 4
Mean Change in Autonomic Heart Rate Effect over Ten-Minute Period of Hypoxia

<table>
<thead>
<tr>
<th>Group</th>
<th>PaO₂ 50 mm Hg</th>
<th>PaO₂ 40 mm Hg</th>
<th>PaO₂ 30 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drug</td>
<td>-3.0 ± 2.4</td>
<td>-19.0 ± 2.9*</td>
<td>-35.0 ± 2.5*</td>
</tr>
<tr>
<td>Atropine</td>
<td>-2.0 ± 1.7</td>
<td>-3.0 ± 3.6†</td>
<td>-12.0 ± 1.8†</td>
</tr>
<tr>
<td>Rhinencephalic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drug</td>
<td>+3.6 ± 1.4</td>
<td>-22.0 ± 3.7*</td>
<td>-26.0 ± 2.2*</td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drug</td>
<td>+4.4 ± 1.3</td>
<td>-17.0 ± 3.3*</td>
<td>-28.0 ± 5.2*</td>
</tr>
<tr>
<td>Atropine</td>
<td>+1.2 ± 2.3</td>
<td>-15.0 ± 2.7*</td>
<td>-10.0 ± 1.8†</td>
</tr>
<tr>
<td>Pontine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drug</td>
<td>+2.0 ± 1.6</td>
<td>-0.2 ± 2.4</td>
<td>+3.8 ± 1.9</td>
</tr>
<tr>
<td>Atropine</td>
<td>+5.2 ± 1.6</td>
<td>+10.6 ± 3.0†</td>
<td>+6.4 ± 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SE of means for three rabbits with ventilation controlled at 2 liters/min.

*P < 0.05. †P < 0.05 for difference from response with no drug.

eral resistance effect was still significantly smaller (P < 0.01), its greatest increase at PaO₂ 30 mm Hg being again about 40% of the value in the suprabulbar groups. In the pontine animals there was either no change or an increase in autonomic effect on heart rate, while in the suprabulbar animals there was progressively more marked autonomic cardiac slowing with more severe hypoxia.

In normal animals at PaO₂ 50 mm Hg, the small autonomic change in heart rate was little affected by atropine (Table 4), but at 40 mm Hg the autonomic cardiac slowing was almost completely abolished, suggesting that it was largely vagal in origin at this PaO₂; at 30 mm Hg, it was reduced by about two-thirds after atropine, suggesting that there was now an additional component due to reduction in cardiac sympathetic activity. In thalamic animals the autonomic cardiac slowing at PaO₂ 40 mm Hg was unaffected by atropine, suggesting that it was predominantly due to reduced cardiac sympathetic activity, but at 30 mm Hg, it appeared to depend on increased vagal activity and reduced sympathetic activity in the same way as in normal animals. In the pontine group the autonomic rise in heart rate was slightly greater after atropine (0.1 > P > 0.05), suggesting slight masking of the early autonomic increase in heart rate by increased vagal activity.
Discussion

NEUROLOGICAL PREPARATIONS

The results suggest that nonspecific factors resulting from the surgical interventions exert relatively few effects 3 hours postoperatively since (1) the effects of sham operation on the cardiorespiratory variables are slight; (2) controlling ventilation almost abolishes the differences in resting circulatory variables between the three suprabulbar preparations; (3) all groups can withstand prolonged hypoxia without apparent ill effect. The somewhat greater muscular activity in response to slight stimuli observed in rhinencephalic and thalamic animals is probably a specific release phenomenon after ablation of the neocortex (14-16), and the rise in respiratory minute volume may be associated with this. The elevation in resting total peripheral resistance in the pontine animals is probably a specific effect of the lesion; it does not appear to result from baroreceptor involvement due to greater blood loss, since after section of the carotid sinus and aortic nerves there is a further rise in total peripheral resistance similar in magnitude to that found in normal animals (19, 24).

CARDIORESPIRATORY CONTROL DURING HYPOXIA

The peripheral receptors which contribute to the normal rabbit's cardiorespiratory response to hypoxia include the arterial chemoreceptors and baroreceptors, which produce autonomic excitation (17-19), and the effects of lung inflation mediated through vagal afferents, which inhibit the primary circulatory effects of strong chemoreceptor stimulation (22, 41, 42). The maximum initial autonomic effects suggest involvement of rate-sensitive elements in the control system at a time when the PaO2 is changing rapidly, but equilibrium between the local and autonomic effects at the periphery has not yet been reached, while the attenuated late response suggests proportional elements responding primarily to the gradual changes in state of the peripheral beds with prolonged exposure to the severe hypoxic stress.

RESPIRATORY CONTROL

The respiratory response to hypoxia of the pontine animals is slightly greater than normal and arises from arterial chemoreceptor stimulation. In the thalamic preparation the rise in respiration is markedly smaller, and this is

FIGURE 10

Schema of suggested inputs to, and outputs from, cardiovascular and respiratory centers in pons and medulla (pontine animals), diencephalon (thalamic animals), rhinencephalon and neocortex concerned with cardiorespiratory integration in hypoxia. Centers A and B in rhinencephalon influence the early and late components, respectively, of the autonomic effector response, and have no special anatomical significance. High mesencephalic centers are not considered to contribute to reflex response to hypoxia in view of identity of effects in pontine and high mesencephalic animals. Inputs arising from arterial chemoreceptors, baroreceptors, and lung inflation receptors relay in the bulb and along ascending relays suggested by upward flowing arrows (solid lines, known projections; broken lines, suggested projections); projections including vagal afferents to pons and medulla concerned with Hering-Breuer reflex, possible baroreceptor afferents to pontine respiratory center and possible afferents from muscle stretch receptors, are not shown in this schema. Downward flowing large black arrows indicate excitation of underlying centers or effectors; white arrows indicate inhibition of underlying centers; half white and half black arrows from diencephalon to bulbar heart rate centers indicate that autonomic cardiac slowing results from increased vagal and reduced cardiac sympathetic activity. Effectors: V = vagus; C.S. = cardiac sympathetic; S.-A. = sympatho-adrenal effects on systemic vessels; Resp. = Respiration. For further description see text.
probably not just a mechanical limitation of respiratory performance due to high resting ventilation, since the rhinencephalic animal has an almost normal response to hypoxia.

The net chemoreceptor drive during hypoxia probably differs little in the various preparations. In normal and thalamic animals, the arterial blood composition is similar, and the potentially stronger stimulus in rhinencephalic and pontine rabbits due to lower pH appears to be offset by greater reduction in \( \text{Paco}_2 \) in these animals (Table 2), and their respiratory responses are approximately the same as in normal rabbits.

The present results suggest that (1) the diencephalon limits the increase in respiration during hypoxia by exerting inhibitory influences on the pontine centers and (2) that this inhibitory influence is in turn inhibited by activation of rhinencephalic centers (with probably a small additional contribution from the neocortex), thus allowing the normal animal to have almost as great a respiratory response as the pontine animal down to a \( \text{Pao}_2 \) of 35 to 30 mm Hg, and a greater response than the thalamic animal (Fig. 10). The afferent sources for activating the suprabulbar respiratory mechanisms have not been studied in these experiments. In the cat and monkey, suprabulbar respiratory centers in the diencephalon and cortex have been identified in electrical stimulation studies (1, 4, 13), and these may correspond to the suprabulbar respiratory centers in the rabbit and also participate in the reflex control of respiration.

**CIRCULATORY CONTROL**

The autonomic effector response of the suprabulbar preparations differs from that of pontine animals in having a greater rise in autonomic total peripheral resistance effect at each \( \text{Pao}_2 \) and in having directionally different heart rate effects. The transition from suprabulbar to pontine autonomic effector response is sharp, between the thalamic and high mesencephalic preparations. The differences between the three suprabulbar preparations are at least partly related to differences in respiration, muscular activity, or both, since they are greatly reduced during controlled ventilation plus decamethonium, but the differences between suprabulbar and pontine responses are still present after controlling ventilation. The difference in heart rate effects does not depend on a different profile of baroreceptor stimulation, since the arterial pressure response during hypoxia is the same in normal and pontine animals (Fig. 5). The elevated resting total peripheral resistance of the pontine animal could have contributed to the difference in estimated autonomic total peripheral resistance effect. However, an even larger difference in resting total peripheral resistance is observed between pontine and normal animals subjected to section of the carotid sinus and aortic nerves, and in these the fall in resistance due to identical local effects of hypoxia is the same when expressed as a percent of each group's resting value.

The smaller autonomic total peripheral resistance effect during hypoxia in the pontine animal could be due to a smaller rise in sympathetic neural constrictor activity, a greater amount of beta-receptor dilator activity owing to greater secretion of epinephrine —virtually the rabbit's sole adrenal medullary hormone (43)—or both. The moderate 'metabolic' acidosis which occurs in pontine (and rhinencephalic) rabbits (Table 2) probably reflects a greater epinephrine secretion (44); it is not observed in autonomically de-efferented animals, suggesting that it results from a reflex change in autonomic effector activity rather than from prolonged hypoxia in a preparation with inadequate circulatory response.

**CARDIORESPIRATORY INTEGRATION**

Figure 10 presents a tentative hypothesis for the integration of cardiorespiratory effects during hypoxia in the rabbit, relating the present findings to the inputs from the various peripheral receptors (17, 19, 22). Afferents from lung inflation receptors (Hering-Breuer afferents) and possible baroreceptor afferents to the pontine respiratory centers may have relevance in cardiorespiratory integration in hypoxia, but are not shown in Figure 10 since they were not investigated in this study.

In pontine animals, the primary stimulus
arises, as in normal animals, from the carotid and aortic regions, and the circulatory findings suggest autonomic excitation through the arterial baroreceptor system (17, 19). Normally an autonomic rise in heart rate would occur in response to a fall in arterial blood pressure, but the present findings in hypoxia can be explained if we postulate that chemoreceptor and baroreceptor afferents terminate on common neurones in the bulbar circulatory centers. If we suppose that the increased chemoreceptor activity renders these neurones less than normally responsive to incoming baroreceptor traffic, through inhibitory mechanisms (45), this will alter the "set" reference blood pressure level for the baroreceptor reflex to a value somewhat above resting. Under these conditions: (1) Autonomic cardiac slowing will occur only during the largest blood pressure rise in the first minute of hypoxia (Figs. 5 and 8). (2) An autonomic rise in heart rate will occur even though the blood pressure is slightly elevated above resting, and the heart rate effect will increase further as the blood pressure tends to fall during the latter part of hypoxia. (3) Sympathoadrenal activity to the peripheral vessels will also increase while the blood pressure is somewhat raised.

Since the thalamic animal, unlike the pontine and high mesencephalic animals, has an autonomic effector response similar to hypoxia in a normal animal, the diencephalic vasomotor centers would appear to play a major part in the normal response. The autonomic effects depend on an important extent on arterial chemoreceptor stimulation (17-19), and occur during perfusion of the carotid chemoreceptors with hypoxic blood (46), suggesting that the diencephalic vasomotor center is one important suprabulbar projection site for chemoreceptor afferents (8, 9). Chemoreceptor afferents, baroreceptor afferents, or both (8-10, 26) may also project to the rhinencephalon, accounting for the late sustained effects in the rhinencephalic animals at Pao2 40 mm Hg.

The autonomic effects of strong chemoreceptor stimulation are inhibited by the effects of hyperventilation mainly through vagal afferents (22, 41, 42). The vagus has known cortical projections (47), and if we postulate that the main input from lung inflation receptors terminates in the rhinencephalon and neocortex this could explain (1) the attenuation of the early autonomic total peripheral resistance effect in rhinencephalic animals compared with the thalamic at Pao2 50 and 30 mm Hg; (2) the complete absence of autonomic cardiac slowing in normal animals at Pao2 50 mm Hg; and (3) the attenuation in the normal animal at Pao2 40 mm Hg of the late rhinencephalic response. The similar time course of the autonomic rise in heart rate in normal and pontine animals at Pao2 50 mm Hg suggests that it probably normally arises from the bulbar heart rate centers as a result of neocortical inhibition of rhinencephalic and thalamic mechanisms. Vagal afferents may also project to the diencephalon, since the circulatory findings are similar in artificially ventilated thalamic animals to those in the other suprabulbar preparations.

The various regions of the central nervous system probably compare information arising from the various peripheral receptors during hypoxia. In mild and moderate hypoxia, the relative magnitudes of input from lung inflation and from the chemoreceptors will result in inhibition of most of the early autonomic effects arising from the diencephalic centers in the normal animal. This inhibition would allow each peripheral bed to adjust its blood flow according to its needs, with a modest degree of control of the blood pressure. With more severe hypoxia the input from the chemoreceptors will increase more than the input from the lung inflation receptors, and the autonomic cardiac slowing and increased total peripheral resistance effects become more prominent, resulting in major redistribution of peripheral blood flow (20). The falling off in respiratory response in the normal animal (Table 3) can be explained if strong stimulation of the diencephalic vasomotor centers is associated with stimulation of the diencephalic (inhibitory) respira-
tory centers rendering the cortical respiratory disinhibition less effective, and would reduce
the work of breathing at a time when the alveolar ventilation could no longer maintain
the animal's oxygen supply (29).

The rabbit is a 'small-lung' burrowing animal, with a cardiorespiratory response to hypoxia intermediate between that of diving animals to submersion asphyxia (with maximum bradycardia and peripheral vasoconstriction and complete respiratory inhibition (48-50)), and that of man or the dog to hypoxia (with a large hyperventilation response [51] and only slight circulatory adjustments [17, 52]). However, the effects of hypoxic stimulation of the isolated chemoreceptors, the reflex effects through baroreceptors, and the effects of lung inflation are qualitatively similar in the rabbit and dog (17, 19, 22, 41, 42, 46, 53) and the species differences appear thus to be mainly quantitative. The large lung and greater respiratory response to hypoxia in man or the dog will maintain a relatively high $P_{\text{aO}_2}$ for a given inspired oxygen pressure, resulting in a preponderance of reflex effects due to lung inflation with inhibition of primary circulatory chemoreceptor effects. In the rabbit, however, the limited respiratory response will be associated with more marked circulatory chemoreceptor effects at higher inspired oxygen pressure and its capacity for circulatory adjustments through activation of the various suprabulbar mechanisms becomes unmasked more easily than in the dog (17, 41, 53).

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Central Nervous Integration of the Circulatory and Respiratory Responses to Arterial Hypoxemia in the Rabbit
PAUL I. KORNER, John B. Uther and Saxon W. White

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