Hypertension, Bradycardia, and Pulmonary Edema in the Conscious Rabbit after Brainstem Lesions Coinciding with the A1 Group of Catecholamine Neurons

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SUMMARY We studied the effects of lesions in the ventrolateral medulla, in a region coinciding with the cell bodies of the A1 group of catecholamine neurons. After bilateral electrolytic lesions at three contiguous rostrocaudal levels (obex and at 1 and 2 mm caudal to the obex), mean arterial pressure increased by 40 mm Hg in the conscious rabbit. This rise in pressure was associated with increased resistance in the distal aortic vascular bed and with profound bradycardia. Many lesioned animals developed respiratory distress in the first few postoperative hours and died with hemorrhagic pulmonary edema. In surviving rabbits, the distal aortic resistance remained raised throughout the 2-week observation period, but the blood pressure and heart rate returned to preoperative levels within 2 hours and then remained normal. Bilateral electrolytic lesions restricted to the level of the obex or to a level 1 mm caudal to the obex also caused transient hypertension and bradycardia, but most of the animals survived this more restricted damage and did not develop pulmonary edema. Micro-injections of kainic acid, a neurotoxin that specifically damages cell bodies, also caused transient hypertension and bradycardia, and after larger doses the rabbits died with acute pulmonary edema. Injections of 6-hydroxydopamine caused similar changes in pressure and heart rate, but doses necessary to destroy the A1 cells caused nonspecific histological damage of an extent similar to that produced by electrolytic lesions. Sham-lesioned animals and those with control lesions in adjacent sites did not develop these cardiovascular changes. These experiments suggest that the persistent increase in peripheral resistance after lesions of the ventrolateral medulla results from destruction of neurons that normally act to inhibit sympathetic vasoconstrictor tone. It is our hypothesis that the increase in vascular resistance after the lesions results from destruction of the A1 catecholamine cells within this ventrolateral region.

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THE existence of separate excitatory and inhibitory areas in the medulla oblongata, controlling sympathetic activity, was established by the work of Alexander (1946). Recent studies in which electrolytic lesions were used have defined some of these areas in the rabbit. Dorsomedial lesions in the rostral part of the medulla oblongata, well above the obex, have been shown to cause a marked fall in resting arterial pressure and to abolish the vasomotor responses to cerebral ischemia in the anesthetized rabbit (Kumada et al, 1979). Ventrolateral lesions in the rostral medulla also depress arterial pressure in the anesthetized rabbit (Kumada et al., 1979). Ventrolateral lesions in the rostral medulla also depress arterial pressure in the anesthetized rabbit, possibly by damaging a projection passing through the dorsomedial medulla at the same level (Dampney and Moon, 1980).

More caudally in the medulla, lesions destroying the nucleus tractus solitarius, the site of the primary synapse from arterial baroreceptor afferents, are known to produce hypertension with an increase in the lability of the blood pressure in the rat and cat (Reis et al, 1977; De Jong et al., 1977). The nucleus tractus solitarius is rich in catecholamine nerve endings, and selective destruction of these terminals with 6-hydroxydopamine also produces an increase in lability of pressure, with transient hypertension (Snyder et al., 1978), whereas injection of noradrenaline analogues into the nucleus tractus solitarius causes a fall in pressure (Zandberg and De Jong, 1977). Catecholamine neurons of the A2 cell group (Dahlstrom and Fuxe, 1964) within the nucleus tractus solitarius also cause a transient increase in pressure followed by a permanent increase in lability (Talmann et al., 1980).

There are no reports of ventrolateral lesions in the more caudal parts of the medulla at the level of the obex and caudal to it. Furthermore, there are no reports to date of lesions aimed at elucidating the role of the A1 group of catecholamine neurons (Dahlstrom and Fuxe, 1964) which lies caudal to this level in the ventrolateral medulla and also contributes to the innervation of the nucleus tractus solitarius (Ungerstedt, 1971; Blessing, Furness,
Costa, West, and Chalmers, submitted for publication). In the present study we have investigated the effects of making discrete lesions of the ventrolateral medulla at the level of the obex and caudad to it, coinciding with the A1 collection of catecholamine neurons. In the rabbit, they form a rather compact group (Blessing et al., 1978), and we now report that lesion of the ventrolateral medulla destroying these cells are followed by hypertension, bradycardia, and pulmonary edema.

Methods

A preliminary operation was performed on New Zealand white rabbits weighing approximately 2 kg, under halothane anaesthesia, after induction with propanidid (Epontol, Bayer, 30 mg/kg, iv). A Doppler ultrasonic cuff-type blood flow transducer (inner diameter = 4 mm) was placed around the lower abdominal aorta through an abdominal incision and an inflatable balloon occluder was placed around the abdominal aorta just below the diaphragm. The wires and tubing were then buried subcutaneously in the back for subsequent use. Two weeks later, resting measurements of blood pressure, heart rate, and distal aortic blood flow were made in conscious animals according to a fixed protocol over a period of half an hour. The rabbits were then anesthetized to permit the production of discrete electrolytic or chemical lesions in the ventrolateral medulla under stereotaxic control. After the cessation of halothane administration, observations of the same cardiovascular variables were made at fixed time intervals for a period of 4 hours in conscious animals, and repeated during a half-hour observation period on the following day and at 2 weeks. Arterial blood pH, Po2, PCO2, and base deficit were determined from 1-ml samples of blood at 37°C using a Radiometer ABL1a blood gas analyzer. Animals then were killed for histological and histochemical assessment of the lesion site.

Measurement of Circulatory Variables

On each day of study, a polyethylene catheter was inserted into the central ear artery under 0.5% lignocaine anesthesia, the subcutaneous wires of the Doppler flow probe were connected to the flowmeter (Baker Institute) and the rabbit placed in a box for about 1 hour prior to the start of recording. Arterial pressure (mm Hg) was measured using a Statham P23D strain gauge and recorded on a Grass polygraph. Heart rate (beats/min) was obtained from the arterial pressure record, and distal aortic blood flow (kHz, Doppler shift) was measured using a Doppler ultrasonic flowmeter consisting of a cuff transducer, a flowmeter, and frequency-to-voltage converter (Baker Institute). In previous studies, we showed in pump-calibration experiments that under conditions similar to those existing in the present experiments the relationship between volume flow and Doppler shift was linear and not altered by changes in perfusion pressure (West et al., 1975). In the present study, the sensitivity of the frequency-to-voltage converter was adjusted so that electrical zero was set at zero aortic flow after occlusion of the abdominal aorta, using the previously implanted inflatable cuff. Errors in tuning were minimized by re-tuning the flowmeter several times prior to each recording period. Distal aortic resistance (mm Hg/kHz) was calculated by dividing the mean arterial pressure by the distal aortic blood flow.

Stereotaxic Lesions

Neurosurgical procedures were carried out under halothane anesthesia administered through an endotracheal tube. The rabbit's head was immobilized in a maximally flexed position in a Kopf stereotaxic animal holder, and its eyes protected by pads. The dorsal surface of the medulla was exposed by separation of the posterior neck muscles and division of the atlanto-occipital membrane. Because of the degree of neck flexion used, it was not necessary to remove any occipital bone or cerebellum. The animal was then paralyzed with suxamethonium (1 mg/kg, iv, every 15 minutes) and mechanically ventilated during the production of lesions. Electrolytic or chemical lesions were made in the ventrolateral medulla at one or more of the sites shown in Figure 1. After the lesions were made, the atlanto-occipital membrane was repaired, the wound closed, and mechanical ventilation and anesthesia ceased. The rabbits recovered rapidly and were able to sit in their boxes after 5-10 minutes.

The site of each lesion was defined with reference to the midline, the dorsal surface of the medulla in the region of the obex, and the rostral border of the area postrema, as shown in Figure 1. Electrolytic lesions were made with insulated stainless steel wires (diameter 0.1 mm) ground to a fine point and protruding from 27-gauge steel tubing. The electrode was inserted at right angles to the dorsal surface of the medulla under stereotaxic control. With the negative electrode attached to the exposed neck muscles, an anodal d.c. current of 1 mA was passed for 5 seconds at each lesion site. In sham-operated control animals, electrodes were inserted without passage of current. In other control animals, lesions were made more medially, adjacent to the sites described in Figure 1. Chemical lesions were made with kainic acid (Sigma), a substance which has been shown to selectively damage nerve cell bodies with minimal or no damage to nerve terminals or to axons passing through the lesioned area (McGeer et al., 1978). The kainic acid was dissolved in 0.1 M sodium phosphate buffer (pH 7.2), and 0.5-μl aliquots were injected through a glass micropipette (outer diameter 40 μm) ground to a sharp point, carried in a micro-manipulator. The kainic acid was injected gradually over 2 minutes and the pipette left in situ for another minute. Sham-operated animals received 0.5 μl of the vehicle alone into the sites shown in Figures 1 and 2.
while an additional group of control animals received 0.5 μl kainic acid into adjacent sites, dorsal to those in Figure 2. Chemical lesions were also made with 6-hydroxydopamine hydrobromide (6-OHDA; Sigma), a substance which has been shown to damage catecholamine-containing neurons, especially norepinephrine neurons (Snyder et al., 1978). 6-OHDA was freshly dissolved in ice-cold physiological saline containing ascorbic acid (1 mg/ml) and 4–8 μg of free base contained in a volume of 0.25 μl was injected in a similar manner to kainic acid into sites shown in Figure 1. Control animals received the vehicle alone.

Lesioned rabbits recovering from the effects of surgery rested in their experimental box breathing spontaneously. After unilateral electrolytic or kainic acid lesions, the rabbits exhibited a temporary postural deficit and leaned toward the side of the lesion; the defect gradually cleared in the hours and days that followed. Postural changes were much less frequent and less marked after bilateral lesions. After the lesions, the rabbits were fed by intragastric tubes daily for 3 days so as to minimize the weight loss which otherwise occurred. Surviving lesioned animals used in these experiments all ate and drank normally after 1 week and resumed their normal weight gain at this time. Sham-operated animals appeared normal in every way by the 2nd postoperative day.

**Histological and Histochemical Assessment**

Brains of most rabbits were processed for catecholamine fluorescence histochemistry by the formaldehyde glutaraldehyde (Faglu) perfusion procedure (Blessing et al., 1978). Transverse sections (30 μm) of the medulla were cut on a Vibratome and photographed at low magnification, providing an atlas for each animal. The same sections were then air dried on slides, mounted in liquid paraffin, and examined with a Leitz Ortholux II fluorescence microscope. Catecholamine cells, axons, and terminals were related to the lesions and mapped on the photographs. Sections then were rehydrated and stained with cresyl fast violet for Nissl substance. Representative electrolytic lesions from one...
rabbit are shown in Figure 2 and the histological appearance of the A1 group of catecholamine cells, after the injection of kainic acid or of vehicle, is shown in Figure 3. Examination of the ventrolateral medulla 4 days after the injection of 4 $\mu$g of 6-OHDA revealed that the A1 catecholamine cells had not been destroyed but appeared brighter than those of uninjected sites. However, the injection of 8 $\mu$g of 6-OHDA produced non-specific damage to all cells in the ventrolateral medulla, not limited to the catecholamine cells. Examination 10 days after the injection of 8 $\mu$g of 6-OHDA revealed a necrotic area similar in extent to the damaged area observed after electrolytic lesions.

Statistical Methods

The significance of the changes in different circulatory variables following lesions was assessed by analysis of variance (Wallenstein et al., 1980). In analyzing the immediate effects of lesions (Figs. 4, 5, and 7) the variance was partitioned so as to derive a standard error of the mean for the entire pre-lesion period and for any single time interval during the post-lesion period (Shaw et al., 1971). The long-term effects of lesions were analyzed using a randomized block design where the total variance was partitioned into differences between animals, variation over time, and residual variance. Comparisons between values before lesions and at different times after lesions were carried out using the Bonferroni procedure (Wallenstein et al., 1980).
HYPERTENSION AFTER BRAINSTEM LESIONS/Blessing et al.

Results

Acute Effects of Electrolytic Lesions in the Ventrolateral Medulla

Bilateral electrolytic lesions in the ventrolateral medulla at all three levels (sites 1-6, Fig. 1; Fig. 2) in 10 animals caused the mean arterial pressure to rise from 85 ± 0.6 (SEM) mm Hg to a peak value of 127 ± 3.9 mm Hg at 40 minutes, in contrast to a group of 10 sham-operated control rabbits in which there was little change in pressure (Figs. 4 and 6). There was a concomitant fall in heart rate from 205 ± 2 beats/min to a minimum of 137 ± 9 beats/min 30 minutes after the lesions were made, compared with a gradual slight increase in heart rate of sham-operated animals (Fig. 4). Distal aortic blood flow was also reduced after electrolytic lesions, and resistance in this bed rose to a peak value of 350% of control at 40 minutes (P < 0.01; Fig. 4). There was no significant change in blood flow or resistance in the distal aortic bed of sham-operated controls. These changes in the lesioned animals subsided during the 2nd hour, and, at 2 hours, only the

![Image of a graph showing mean arterial pressure (MAP) and heart rate (HR) during the pre-lesion control period and the post-lesion period after the production of bilateral electrolytic lesions in the ventrolateral medulla at various levels.](http://circres.ahajournals.org/)

![Image of a graph showing mean arterial pressure, heart rate, and distal aortic resistance prior to the production of lesions and at various times after the production of bilateral electrolytic lesions at all three levels in lesion animals (hatched columns) and after sham operations (open columns).](http://circres.ahajournals.org/)
vascular resistance remained significantly different from pre-lesion control values, and from values obtained in sham-operated control rabbits (Fig. 4).

After these bilateral electrolytic lesions at all three rostro-caudal levels, many of the animals became acidic and hypoxaemic and died in the first few post-operative hours, whereas the sham-operated controls survived with no permanent ill-effects. Autopsy of the lesioned rabbits that died revealed punctate, sometimes confluent, hemorrhagic areas throughout both lungs, with pink frothy fluid in the large airways and on the cut surface of the lungs. Histological examination confirmed the presence of pulmonary edema with erythrocytes and a homogeneous eosinophilic material in the alveolar spaces and respiratory bronchioles; there were numerous areas of atelectasis. These changes were not seen in control animals. In subgroups of lesioned animals that survived, from which the cardiovascular data shown in Figures 4–7 are derived, there was no significant hypoxemia after the lesions, but there was a transient fall in arterial PCO₂ and a compensated metabolic acidosis manifest in the normal pH with increased base deficit (Table 1). In sham-operated animals, arterial blood gases and pH remained normal and there was no evidence of a metabolic acidosis.

The effects of bilateral ventrolateral medullary lesions at each of the three separate levels shown in Figures 1 and 2 were tested in three separate groups of five animals, as illustrated in Figure 5. At the level of the obex and at a level 1 mm caudal to the obex, bilateral lesions produced increases in blood pressure and reductions in heart rate very similar to those observed with bilateral lesions in all three levels (Figs. 4 and 5). However, after bilateral lesions restricted to a level 2 mm caudal to the obex, there was no significant increase in pressure, although the bradycardia was once again observed (Fig. 5, bottom panel). Distal aortic flow was not measured in these experiments. Animals with lesions restricted to a single rostro-caudal level survived and maintained normal arterial pH and PO₂, but punctate hemorrhagic areas were occasionally seen in the lungs at autopsy.

Long-Term Effects of Electrolytic Lesions in the Ventrolateral Medulla

The effects of bilateral lesions at all three rostro-caudal levels during a two week post-operative period are given for sub-groups of animals that survived the immediate post-lesion period (Fig. 6). The blood pressure and heart rate both returned to control values 1 day after the lesion (Fig. 4) and then changed very little in the ensuing 2 weeks (Fig. 6). However, there was a persistent increase in distal aortic vascular resistance in the lesioned animals which was increased to 170% of control 2 weeks after the operation (Fig. 6). The resistance in the sham-operated controls was unchanged from corresponding pre-lesion values, indicating that the operation per se did not increase the distal aortic vascular resistance in a non-specific manner (Fig. 6). The preoperative resistance in the two groups of animals, both those that were lesioned and those that had a sham operation, was also similar (Fig. 6).
Acute Effects of Micro-injections of Kainic Acid into the Ventrolateral Medulla

When 2.5 nmol of kainic acid were injected bilaterally at all three rostro-caudal levels, the pressure rose immediately after cessation of anesthesia, and the rabbit died within 1 hour with severe hypertension and pulmonary edema. Unilateral injection of 1 nmol of kainic acid into the ventrolateral medulla at a single level, 1 mm caudal to the obex, caused an increase in blood pressure from 77 ± 0.8 mm Hg to a peak of 126 ± 5.6 mm Hg 15 minutes after the injection (Fig. 7, top panel). Injection of 1 nmol of kainic acid into the dorsolateral medulla 1 mm caudal to the obex as an additional control experiment did not cause an increase in blood pressure or a bradycardia (Fig. 7, top panel).

Acute Effects of Control Electrolytic Lesions in the Ventromedial Medulla

Bilateral electrolytic lesions were also made in the ventromedial medulla 1 mm medial to the site of the ventrolateral lesions at a rostro-caudal level 1 mm caudal to the obex, as an additional control. These bilateral lesions produced an increase in heart rate (Fig. 7, bottom panel) in contrast to the bradycardia observed with all the ventrolateral medullary lesions. A slowly developing increase in pressure was observed after these ventrolateral lesions (Fig. 7, bottom panel), but the time course of the pressure change was quite different to that seen after ventrolateral lesions and the magnitude of the changes was much smaller.

Discussion

The association of hypertension, bradycardia, and pulmonary edema has not previously been reported after discrete intracerebral lesions, although hypertension and bradycardia occur with activation of the nasopharyngeal reflex, the arterial chemoreceptor reflexes, and the cerebral ischaemic reflex (Kumada et al., 1979). Lesions within the nucleus tractus solitarius (Reis et al., 1977) and just lateral to it (De Jong et al., 1977) produce hypertension, but this results from interruption of baroreceptor afferent fibers and their first synaptic relay and is associated with a tachycardia. Lesions of the hypothalamus have also been reported to cause hypertension (Nosaka, 1966) and pulmonary edema (Gamble and Patton; 1953; Reynolds, 1963), but not together, and not in association with bradycardia. In fact the occurrence of hypertension after localized intracerebral lesions is quite rare (Reis et al., 1975). The cardiovascular changes reported after ventrolateral medullary lesions in the present studies cannot be attributed to non-specific damage such as hemorrhage into the cerebrospinal fluid or operative distortion of the brainstem, since sham-operated animals and animals with control lesions in adjacent areas underwent similar procedures but did not manifest the same responses. The increase in pressure and bradycardia cannot be attributed to stimulation of arterial chemoreceptors, since lesioned animals had normal arterial oxygen tension and pH (Table 1).

Vasomotor Changes

Lesions of the nervous system can have both destructive and irritative effects so that the acute hypertensive response in the present studies could have resulted from ablation of a vasodepressor system or from excitation of a vasopressor system. It might be argued, for example, that both the chemical and electrolytic lesions of the ventrolateral medulla evoked degeneration release of the transmitter (Geffen and Hughes, 1972) in a pressor system, thus causing the transient increase in pressure which was noted in Figures 4-7. On the other hand, the increase in pressure is associated with vasoconstriction (Fig. 4) and, whereas the increase in pressure is not sustained, the increase in peripheral resistance is still present 2 weeks postoperatively (Fig. 6). We therefore suggest that the changes in pressure observed after ventrolateral medullary lesions probably result from destruction of neurons that normally act to inhibit peripheral sympathetic vasomotor activity. The present experiments do not

### Table 1: Arterial Blood Gases and pH in Animals with Bilateral Electrolytic Lesions at Three Levels

<table>
<thead>
<tr>
<th>Time post-lesion</th>
<th>n</th>
<th>pH</th>
<th>PCO₂ (mm Hg)</th>
<th>PCO₂ (mm Hg)</th>
<th>Base deficit (meq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>10</td>
<td>7.42 ± 0.01</td>
<td>85 ± 2</td>
<td>34 ± 1</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>1 Hour post-lesion</td>
<td>10</td>
<td>7.29 ± 0.07</td>
<td>92 ± 9</td>
<td>31 ± 4</td>
<td>7.1 ± 2.5</td>
</tr>
<tr>
<td>4 Hours post-lesion</td>
<td>21</td>
<td>7.41 ± 0.01</td>
<td>95 ± 3</td>
<td>24 ± 2</td>
<td>6.8 ± 1.0</td>
</tr>
<tr>
<td>1 Day post-lesion</td>
<td>6</td>
<td>7.40 ± 0.03</td>
<td>79 ± 7</td>
<td>33 ± 3</td>
<td>3.1 ± 1.0</td>
</tr>
<tr>
<td>2 Weeks post-lesion</td>
<td>3</td>
<td>7.37 ± 0.03</td>
<td>89 ± 5</td>
<td>31 ± 2</td>
<td>6.9 ± 1.6</td>
</tr>
</tbody>
</table>
permit us to deduce whether the distal aortic vasoconstriction evoked by the lesions is mediated by sympathetic vasoconstrictor nerves, or through a humoral mechanism; however, the results of an accompanying series of experiments (West et al., 1981) investigating the effects of ventrolateral medullary lesions on the baroreceptor-vasoconstrictor reflex suggest that the vasoconstriction is mediated through activation of vascular a adrenoceptors by sympathetic nerves.

The present finding that lesions of the ventrolateral medulla coinciding with the A1 cells produce transient hypertension is reminiscent of the effects of destruction of catecholamine nerve endings terminating in the nucleus tractus solitarius (Reis et al., 1977). The presence of a projection from the A1 catecholamine neurons toward the nucleus tractus solitarius (Ungerstedt, 1971; Blessing, Furness, Costa, West and Chalmers, submitted for publication) could be relevant in this respect, though it should be noted that in the rat the A1 neurons also send a projection to the hypothalamus (Sakumoto et al., 1978; Day et al., 1980). Our results are also in accord with those of Coote and McLeod (1974a, 1974b) who have reported depressor effects after electrical stimulation of the ventrolateral medulla in the anesthetized cat, at sites coinciding with the A1 cells. However, these authors attribute the depressor actions to A1 neurons projecting caudally into the spinal cord of the cat, whereas we have recently found that any direct projection from A1 catecholamine neurons to the spinal cord of the rabbit is at most miniscule, though there are non-catecholamine containing nerve cells projecting caudally from the ventrolateral medulla (Blessing et al., in press). This agrees with recent findings in the rat (McKellar and Loewy, 1979).

The present studies in conscious rabbits suggest that ventrolateral medullary neurons at and below the level of the obex act to inhibit the activity of sympathetic vasoconstrictor nerves. On the other hand, experiments in anesthetized rabbits suggest that in the ventrolateral medulla rostral to the obex there is a group of non-noradrenergic neurons which act to facilitate the activity of sympathetic vasoconstrictor neurons (Kumada et al., 1979; Dampney and Moon, 1980). The pressor area studied by Dampney and Moon (1980) in the rostral part of the ventrolateral medulla is closely related to the C1 group of adrenaline synthesizing neurons (Hokfelt et al., 1974; Howe et al., 1980), whereas the depressor area in the more caudal region of the ventrolateral medulla coincides with the A1 group of noradrenaline neurons (Blessing et al., 1978).

Heart Rate Changes

The bradycardia produced by both electrolytic and kainic acid lesions develops more rapidly than the increase in pressure or the vasoconstriction (Figs. 4 and 7) and reaches a peak about 10 minutes before the peak increase in pressure and peripheral resistance (Figs. 4, 5, and 7). Furthermore, the bradycardia was produced by selective bilateral electrolytic lesions 2 mm caudal to the obex (Fig. 5) which did not produce any increase in pressure. These experiments suggest that the bradycardia does not result solely from activation of baroreceptor reflexes stimulated by the increase in pressure, and is at least in part independent of the arterial baroreflexes. This is confirmed and the mechanism studied in an accompanying series of experiments analyzing the effects of ventrolateral medullary lesions on the baroreceptor-heart period reflex (West et al., 1981).

Pulmonary Edema

Pulmonary edema occurs after lesions of the nucleus tractus solitarius in the dorsomedial medulla of the rat and, in that situation, is thought to be due to acute left ventricular failure secondary to severe hypertension (Reis et al., 1977). It is possible that a similar mechanism could be responsible for the pulmonary edema after lesions in the ventrolateral medulla of the rabbit in the present study. It should be noted that terminals of the A1 group of catecholamine nerves recently have been shown to innervate the preoptic area of the hypothalamus (Day et al., 1980), another region in which lesions have also been shown to cause pulmonary edema (Gamble and Patton, 1953; Reynolds, 1963). Whereas intracerebral injection of kainic acid has been reported to cause myocardial necrosis, histological examination of rabbit hearts in the present experiments did not reveal any necrotic areas. The pulmonary edema could also result from a direct neural effect on the pulmonary vasculature, and, in fact, neurogenically mediated changes in the pulmonary vessels have been noted in association with systemic vasoconstriction and bradycardia in the cat (Hoff et al., 1976) and the rat (Chen et al., 1980) subjected to neurological trauma. It is well recognized that, in patients with expanding structural lesions in the brain, a rising blood pressure and a slowing of the pulse are clinical signs of deterioration (Cushing, 1903; Moss, 1975); furthermore, rapidly progressive pulmonary edema is a lethal complication of acute brain damage and is at times associated with hypertension and bradycardia. The rabbit with pulmonary edema, hypertension, and bradycardia after discrete ventrolateral lesions of the medulla could provide a useful animal model of the clinical disorder.

Nature of Ventrolateral Medullary Neurons Mediating the Cardiovascular Changes—Possibly the A1 Catecholamine Neurons

Electrolytic lesions within the central nervous system destroy all structures within the target areas, including nerve cell bodies, nerve endings, and fibers of passage as well as glial and vascular
elements. However, kainic acid is thought to act on nerve cell bodies, sparing axons of passage and nerve terminals (McGeer et al., 1978). Since ventrolateral medullary lesions produced with this neurotoxin also caused hypertension, bradycardia, and pulmonary edema, it is likely that these cardiovascular effects result from destruction of cell bodies in the target area, which was specifically chosen to coincide with the A1 group of catecholamine cell bodies. However, both catecholamine cells and the cell bodies of neurons utilizing other transmitters were destroyed by the lesions. The chemical lesions produced with microinjections of 6-OHDA into the ventrolateral medulla were performed to try to destroy the A1 catecholamine neurons specifically. Unfortunately, while 6-OHDA exhibits significant specificity for catecholamine containing nerve endings after administration into the cerebrospinal fluid or the bloodstream, its toxicity for catecholamine cell bodies is much less selective after direct intracerebral administration; micro-injection of 6-OHDA into the ventrolateral medulla in the doses used in our studies appeared to produce quite non-specific damage, so that these experiments did not resolve the issue. However, it is interesting that selective destruction of catecholaminergic nerve endings in the nucleus tractus solitarius (with 6-OHDA) (Snyder et al., 1978), which receives nerve endings from the A1 neurons (Ungerstedt, 1971; Blessing, Costa, Furness, West and Chalmers, submitted for publication), also produces a transient increase in pressure in the rat. Furthermore, Korner et al. (1978) have reported that intracisternal injections of 6-OHDA also produce transient hypertension and bradycardia in the conscious rabbit. It is our hypothesis that the transient hypertension and the persistent vasoconstriction observed in our experiments results from destruction of A1 catecholamine neurons that normally act to inhibit sympathetic vasoconstrictor tone.

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