Influence of Autonomic Blockade on Aconitine Induced Pulmonary Edema.* (29380)

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Gamble and Patton(1) and Marie and Patton(2,3) have shown that destructive lesions of the preoptic areas in rats lead to a fatal pulmonary edema. We have reported our observations (Seager and Wood(4)) that bilateral injection of aconitine into the preoptic areas of the rat likewise produces a rapidly developing fatal pulmonary edema. The present report concerns an attempt to explain the mechanism of the edema so produced.

Methods. Sprague-Dawley rats weighing in excess of 200 g were etherized and drill holes were made 1 mm lateral to the midline just anterior to the cruciate suture. The heads were placed in a stereotaxic instrument and aconitine in doses of 0.02 cc of a 10^{-5} dilution was injected into the preoptic areas bilaterally. One control group was sham operated and injected with saline. Animals dying acutely from edema were autopsied at the time. Those surviving a 4-hour period were sacrificed and autopsied. Lung weights were determined in all animals. The location of the injection was confirmed by section of the brain. An additional control group was injected with lethal doses of aconitine intraperitoneally.

Groups of animals were pretreated with atropine (20 mg/kg), phentolamine (10 mg/kg), and dibenzyline, respectively. Due to slow absorption and long duration of action dibenzyline was given in a dose of 10 mg/kg 12 to 16 hours and again one hour prior to the aconitine. The other drugs were given intraperitoneally 20 to 40 minutes prior to aconitine. In a 7th group of rats, using larger animals, femoral arteries were cannulated and pressure was measured before and after the injections of aconitine. Pressures were measured by Statham strain gauges and recorded on a Sanborn or Grass instrument. In an 8th group of rats under ether anesthesia epinephrine was infused at a rate necessary to raise and maintain the femoral blood pressure at a level of 200 to 220 mm Hg. In a 9th group of animals the chest was opened under ether anesthesia, and the pulmonary artery and vein of a lobe of the lung were cannulated and the pressures measured along with femoral, arterial and venous pressures.

Results. Fig. 1 shows typical examples of the edema produced by aconitine as compared to a control. Sham operated animals showed a lung weight-body weight ratio of 0.72% with no edema while animals receiving bilateral injections of aconitine into the preoptic areas without pretreatment had lung body ratios of 1.98% (Table I). Pretreatment with atropine (20 mg/kg) did not significantly modify the extent of the edema. Phentolamine (10 mg/kg) and especially dibenzyline (10 mg/kg) significantly reduced the extent of the edema. Animals injected with fatal doses of aconitine intraperitoneally failed to develop pulmonary edema.

In animals not pretreated but injected with aconitine, the systemic blood pressure starts to rise soon after the hypothalamic injection of aconitine and reaches a peak of 185 to 240 mm Hg within 2 to 32 minutes (Table II). Usually within a few minutes after peak pressures are attained, pulmonary edema, as evidenced by foam and fluid in the mouth and nose, is present. Death of all animals occurred within 10 to 82 minutes. At autopsy all of these animals were found to have severe pulmonary edema. All of the group of animals infused with epinephrine at a rate producing and maintaining femoral pressures at 200 to 220 mm Hg developed fatal pulmonary edema.

In the group of animals whose pulmonary as well as systemic pressures were measured the preoptic injection of aconitine resulted in a marked rise in systemic arterial pressure, an appreciable rise in pulmonary venous pres-

* This work was supported by NIH grants HE03383 and HE07567.

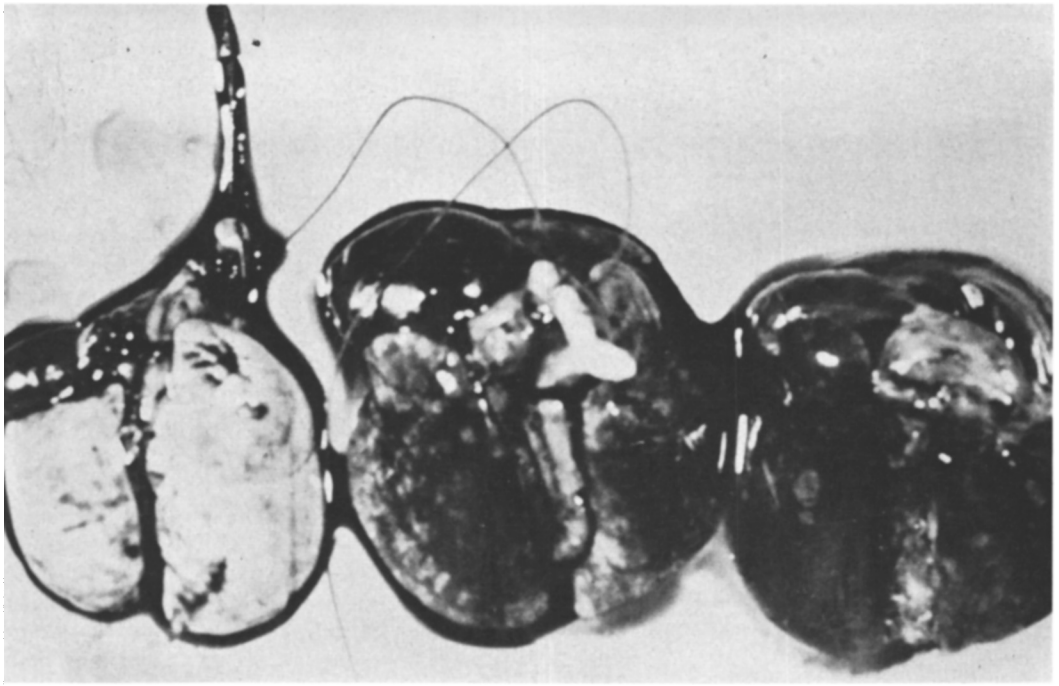

FIG. 1. Typical examples of lungs from rats given injections of Aconitine into anterior hypothalamus as compared to a saline injected control at left.

sures and little change in pulmonary arterial or systemic venous pressures.

Discussion. Gamble and Patton(1) and Marie and Patton(2,3) have postulated that the pulmonary edema resulting from destructive lesions of the preoptic areas of rats is due to a mass sympathetic discharge resulting in a shunting of blood to the pulmonary circuit. They believe the preoptic lesions result is a "release" of the sympathetic centers from inhibitory impulses. They found that section of the sympathetic outflow minimized the extent of the edema. Our experiments would indicate that aconite induced edema is due to increased central sympathetic activity. The marked rise in systemic arterial pressure associated with pulmonary edema resulting from preoptic injection of aconitine, both of which are largely prevented by adrenergic blocking agents, would indicate that catecholamines are the chief agents involved in the two phenomena.

Though most investigators(5) point to pulmonary edema as the cause of death from large doses of epinephrine in the rabbit, guinea pigs, and dog Nickerson *et al*(6) postulate that in the rat the fatality is due to respiratory failure. In our experiments pulmonary edema developed from epinephrine or from the preoptic injection of aconitine when blood pressure rose to levels near 200 mm Hg. Respiratory failure did not occur until terminally, after marked pulmonary edema as evidenced by rales or foam in the mouth or nares had developed.

The marked rise in systemic arterial and

TABLE I. Influence of Pretreatment with Autonomic Blocking Agents on Lung Edema Produced by Hypothalamic Injections of Aconitine.

Group	Sham operated control	Aconitine injected control	Atropine, 20 mg/kg pretreatment	Phentolamine, 10 mg/kg pretreatment	Dibenzyline, total 20 mg/kg pretreatment
No. of animals	10	10	8	12	20
Mean lung wt/100 g rat	.71 ±.047	1.98 ±.9	2.0 ±.86	1.22 ±.89	.97 ±.27

TABLE II. Blood Pressure Responses to the Bilateral Injections of Aconitine into Preoptic Areas.

Rat No.	Control B.P.	Peak pressure, mm Hg	Time in min: Inj to peak pressure	Time in min: Inj to death
1	120	185	6	21
2	90	185	6	30
3	105	210	10.2	59
4	90	212	18	137
5	100	190	10.5	103
6	120	217	3	12
7	90	215	3	18.5
8	85	205	39	82
9	105	230	13	50
10	107	196	8	18
11	101	206	8.5	119
12	90	200	9	25
13	95	207	4.5	17
14	98	220	14	24
15	92	240	5.5	13
16	82	212	9	38
17	80	195	6	25
18	90	243	2	10
19	104	210	7	23
20	98	206	9	31

appreciable rise in pulmonary venous pressures as compared to pulmonary arterial and systemic venous pressures would indicate that the pulmonary edema results from inability of the left heart to maintain its output against the increased resistance thus leading to back pressure effects in the pulmonary venous and capillary systems.

Though Auer and Gates(7) found that atropine ameliorated the pulmonary edema produced by epinephrine in rabbits and Campbell *et al*(8) found protection against edema in dogs resulting from increased intracranial pressure, large doses of atropine failed to give protection in our experiments from either epinephrine or central aconitine induced edema.

Summary. 1. Bilateral injection of aconitine into the preoptic areas of rats results in a marked rise in systemic arterial pressure and a rise in pulmonary venous pressure followed or accompanied by development of severe pulmonary edema. 2. Pulmonary edema from preoptic injection of aconitine or from infused epinephrine occurs at femoral arterial pressures near 200 mm Hg. 3. Since the rise in blood pressure and the accompanying edema is largely prevented by the sympatholytic agents, phentolamine and dibenzyline, the preoptic injection of aconitine appears to act primarily by causing a central sympathetic discharge. 4. It is postulated that the pulmonary edema produced by preoptic injection of aconitine results, as with epinephrine, from inability of the left ventricle to maintain its output against an increased peripheral resistance which leads to back pressure effects on the pulmonary venous and capillary vessels. 5. Atropine in doses of 20 mg/kg does not significantly modify the edema production.

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Received April 13, 1964. P.S.E.B.M., 1964, v116.