Aconitine Induced Pulmonary Edema.* (27719)

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Injection of fibrinogen-thrombin mixtures into the cysterna(1), cutting of both vagus nerves in rabbits and guinea pigs(2), and the lesions of the preoptic areas of rats(3) have been reported to produce fatal pulmonary edema. During studies on temperature regulation, we made the incidental observation that hypothalamic injection of aconitine into rats resulted in rapidly developing pulmonary edema. The present report is an extension of this observation.

Method. Sprague-Dawley rats, usually weighing 200 g or over, were anesthetized with ether, pentobarbital, or fluothane. Drill holes were made in the skull and the heads secured in a stereotaxic instrument especially adapted for rats. Exploratory injections of varying dilutions of the drug were made; primarily in hypothalamic areas using a 25-gauge needle. The quantity of fluid injected was 0.02 cc to 0.04 cc. The animals were removed and the skin incision closed and observations made; usually for a 4-hour period and occasionally for 24 hours. Autopsies were made upon death of the animals. Animals surviving the 4-hour period were sacrificed at that time or at the end of a 24-hour period. In addition to aconitine, a wide variety of other compounds was tested. In one group of animals, lesions of the posterior hypothalamus were made by electric current prior to injecting aconitine into the anterior hypothalamus. Intraperitoneal injections of aconitine up to fatal levels were given to 2 groups of rats.

Results. After various exploratory injections of aconitine, it was found that the most marked edema of the lungs developed when the drug was injected bilaterally into the preoptic areas. Minimal or no edema occurred when injections were made 2 mm anterior, laterally or posteriorly to this area.

Injection of 0.02 cc of a 1 $\times$ 10-6 dilution of the drug bilaterally was found to produce a very severe, fatal edema in many animals. The lungs are enlarged and red and the trachea is filled with froth and fluid. Fluid in the trachea is clear in the early phases of edema but becomes sanguineous as it progresses.

The edema develops in the presence of a non-irritating volatile agent, fluothane; an irritant volatile agent, ether; or a longer acting non-inhalant anesthetic, pentobarbital.

As indicated in Table I, bilateral injection of aconitine in doses of 0.02 cc of a 2 $\times$ 10-6 dilution into the preoptic areas of rats under ether, fluothane or light pentobarbital anesthesia results in marked pulmonary edema with fluid and foam in the trachea and a 2- to 3-fold increase in lung weight (Table I). With lesions of the posterior hypothalamus and with deep pentobarbital anesthesia aconitine injections resulted in only a 25% increase in lung weight.

Atropine sulfate in doses up to 20 mg/kg did not significantly alter the development of edema. In a search for drugs that might produce similar effects to aconitine, some 30 compounds have been tried including sympathomimetics, sympatholytics, cholinergics, anticholinergics, procaine, hexocaine, hexamenthomium, decaethomium, strychnine, metrozole, cantharidine, dinitrophenol, veratrum alkaloids and bacterial toxins. None of these compounds caused edema. Systemic injections of aconitine up to fatal levels produced marked respiratory changes but failed to produce pulmonary edema.

Discussion. The area of the anterior hypothalamus giving the most marked response to dilute solutions of aconitine corresponds to the preoptic area, the ablation of which was shown by Gamble and Patton(3) to result in fatal pulmonary edema. Gamble and Patton (4) and Marie and Patton(5,6) have postulated that ablation of the preoptic areas produces a "release phenomenon" whereby caudal areas become more active and bring about marked vascular changes responsible for the

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TABLE I. Lung Weights of Control Animals and Animals Receiving Anterior Hypothalamic Injections of Aconitine.

Group	Ether, control	Ether, aconitine	Fluothane,* aconitine	Pentobarbital light (35 mg/kg), aconitine	Pentobarbital* (deep)	Ether, posterior hypothalamic lesions, aconitine
No. of animals	10	10	10	8	10	20
Mean wt/100 g rat	.71 ±.047	2.14 ±.911	1.72 ±.821	1.53 ±.466	.91 ±.397	.97 ±.425
P values		<.0005	<.0005	<.0005	<.07	<.055

* Pentobarbital sufficient to give marked depression of respiration and reflexes.

pulmonary edema. Our results showing that the edema produced by injections of aconitine into the preoptic areas is reduced by lesions of the posterior hypothalamus is compatible with their theory. Our observation that deep barbiturate anesthesia reduces the severity of the edema would be explainable on the basis that adequate depression of the "released" areas diminishes their capacity to produce the vascular changes responsible for the edema. It is difficult to account for the fact that drug-induced hypothalamic edema production appears to be a unique property of aconitine.

Summary. Acute pulmonary edema is induced by bilateral injections of dilute solutions of aconitine into the preoptic area of the hypothalamus of rats. The severity of the edema is greatly reduced but not abolished by lesions of the posterior hypothalamus. Deep barbiturate anesthesia greatly reduces aconitine edema. Systemic injections of aconitine up to fatal dose levels do not induce pulmonary edema.

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Effects of 6-Mercaptopurine on Susceptibility of Guinea Pigs to Experimental Allergic Encephalomyelitis.* (27720)

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Hoyer, Condie and Good(1) found that 6-MP, given intravenously and daily to rabbits prior to and following inoculation with an emulsion of homologous spinal cord and Freund's adjuvant, reduced the incidence of paralysis of experimental allergic encephalomyelitis, but did not completely prevent it. Larger doses completely suppressed the appearance of the paralysis, which appeared 7 to 10 days after 6-MP was discontinued. Field(2) reported that 6-MP, given to guinea pigs inoculated with brain antigen, not only afforded no protection against EAE, but 6-MP treated animals became paralyzed more quickly than did inoculated animals not given 6-MP.

The aim of the present investigation is to determine the effects of daily administration of a tolerated dose of 6-MP to guinea pigs inoculated with homologous brain plus Freund's adjuvant, particularly on time of appearance and severity of EAE; and to investigate, at

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