Pulmonary Surface Activity Alterations Associated with Pulmonary Edema Following Preoptic Hypothalamic Lesions in Rats[1] (37168)

C. Dick Park and Alton I. Sutnick
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Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104; and the Institute for Cancer Research, Fox Chase Center for Cancer and Medical Sciences, Philadelphia, Pennsylvania 19111

Clinical central nervous system lesions including intracranial tumors and cerebral trauma are commonly accompanied by pulmonary edema (1–5). In the experimental animal cerebral trauma produced in a variety of ways or the intracranial injection of certain substances results in pulmonary edema (6–12). In the rat pulmonary edema has been readily produced by electrolytic lesions in the preoptic area of the hypothalamus (13). The mechanisms whereby these clinical and experimental lesions cause pulmonary edema are not understood. There is much evidence that deficiency or destruction of the normal pulmonary surface active material causes alveolar collapse and atelectasis (14, 15). A decrease in alveolar surface activity may also result in pulmonary edema (16). Furthermore, experimental neurologic lesions (vagotomy) cause a diminished surface activity of extracts of the lung of the animal (17). On the other hand, a loss in surface activity can apparently be a result of the pulmonary edema itself (18).

The purpose of this study was to determine if alterations in surface activity of rat lung extracts occurs in experimental neurogenic pulmonary edema, and if this does occur, to determine whether surfactant loss may be the cause of pulmonary edema in these animals.

Materials and Methods. Forty-five male Sprague–Dawley rats weighing 181 to 215 g were used and divided into four groups. Group I consisted of 12 rats in which stereotaxic lesions were produced resulting in pulmonary edema. Group II (15 rats) had similar operations but did not develop pulmonary edema. Group III consisted of 9 non-operated control rats. Group IV (11 rats) were given aqueous epinephrine intravenously and developed pulmonary edema.

The animals in Group I and II were lightly anesthetized with intraperitoneal hexabarbitol (Evipal) (120 mg/kg) and placed in a stereotaxic instrument. Animals were positioned in the instrument and bilateral electrolytic lesions were produced in the preoptic area of the anterior hypothalamus utilizing coordinates described by DeGroot (19). Bilateral electrolytic lesions were produced 7.1 mm anterior to the interaural line, 2.0 mm below the horizontal zero plane and 1.0 mm on either side of the midline using a current of 4 mA for 30 sec. The location of the lesions is shown in Fig. 1. Following production of the lesions, the animals were allowed to recover. Some animals developing acute pulmonary edema became acutely dyspneic, cyanotic and died within 1.5 to 4 hr postoperatively, while others with less severe pulmonary edema or those which did not develop pulmonary edema were alive 4 hr postoperatively. All animals alive 4 hr postoperatively were sacrificed by the intraperitoneal injection of sodium pentabarbitol (Toxital) (500 mg/kg).

A group of 9 rats which did not receive stereotaxic lesions were sacrificed with intraperitoneal sodium pentabarbitol (500 mg/kg) and used as controls (Group III). The rats

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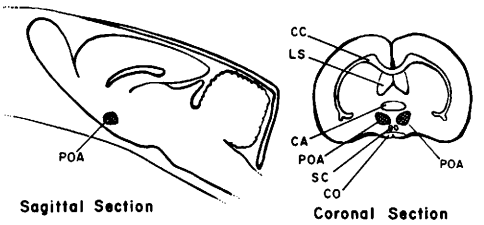

FIG. 1. Location of bilateral lesions in the preoptic area of the hypothalamus is indicated by the cross hatched areas labeled POA (Area preoptica) in the sagittal and coronal sections. Other adjacent areas are labeled as follows: CC = corpus callosum, LS = nucleus lateralis septi, CA = commissura anterior, SC = nucleus suprachiasmaticus, CO = chiasma opticum.

in Group IV were lightly anesthetized with intraperitoneal hexabarbitol (120 mg/kg) and a femoral vein was exposed and cannulated. Aqueous epinephrine 1:1000 (2 mg/kg) was injected intravenously to produce pulmonary edema. These animals died within 1 to 5 min and exhibited massive pulmonary edema.

All animals were weighed immediately following death and the lungs were removed and weighed. Both lungs were minced into pieces less than 3 mm in diameter and extracted in 0.9% saline. The extract was filtered through gauze to remove pieces of tissue and poured into the trough of a modified Wilhelmy surface film balance. After "aging" for 30 min the surface was contracted to 20% of the original area and reexpanded in 15 min cycles. When the minimum surface tension was the same on three successive cycles, this was recorded as the minimum surface tension for that animal.

Results. Table I shows the median lung weight:body weight ratios and median minimum surface tension of the lung extracts in the four groups of rats in the study. The scatter diagram in Fig. 2 clearly shows the higher lung weights in Groups I and IV. The lung weight:body weight ratios were always higher than 10×10^{-3} in these groups and consistently lower than 10×10^{-3} in the other two groups. This difference was statistically significant ($p < 0.001$) when the data from these groups were compared using the median test (18). Figure 3 demonstrates that the minimum surface tensions were higher only in Group I, also significantly higher than the other three groups ($p < 0.01$).

Discussion. The results of this study show that the extracts of lungs of rats which develop pulmonary edema following preoptic lesions have significantly higher minimum surface tensions than the extracts of lungs from the control rats or from animals with similar operations but which did not develop pulmonary edema. Furthermore, the extracts of lungs of animals in which pulmonary edema was produced by intravenous injection of epinephrine did not show elevation of minimum surface tensions. It would appear, therefore, that the loss in surface activity of lungs extracted following this type of neurogenic pulmonary edema is not a result of pulmonary edema alone since the animals

TABLE I. Median Lung Weight:Body Weight Ratios and Median Minimum Surface Tensions in the Four Groups of Experimental Animals.[a]

	Group	Median LW:BW $\times 10^3$	Median minimum surface tension (dyn cm^{-1})
I	Operated rats with pulmonary edema	13.25	31.95
II	Operated rats without pulmonary edema	6.6	27.8
III	Control (unoperated) rats	7.0	25.7
IV	Rats with epinephrine-induced pulmonary edema	26.0	25.0

[a] Group I > II or III and Group IV > II or III ($p < .001$). Group I > II, III or IV ($p < .01$).

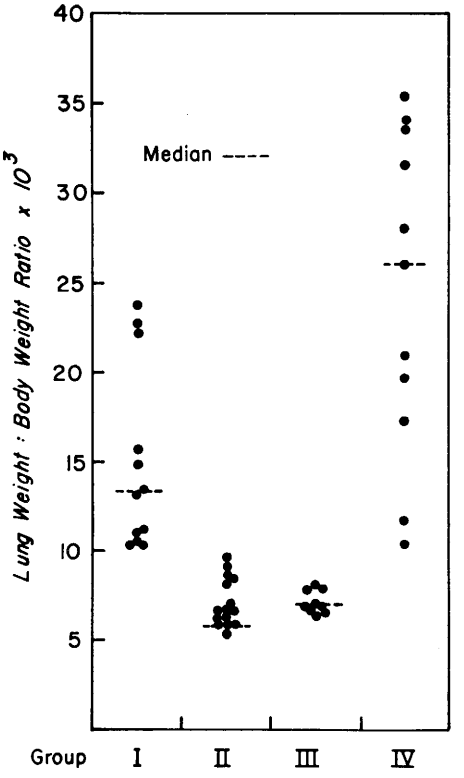

FIG. 2. Scatter diagram illustrating individual lung weight:body weight ratios in each group of rats. (Group I, operated animals developing pulmonary edema; Group II, operated animals not developing pulmonary edema; Group III, controls; Group IV, animals with epinephrine-induced pulmonary edema).

developing massive pulmonary edema (median LW:BW, 26.0 $\times$ 10^{-3}) from epinephrine had no alteration in surface activity.

There is much evidence in man and experimental animals that central nervous system lesions lead to pulmonary edema. Clinically, pulmonary edema has been shown to occur with a variety of central nervous system lesions. Cameron (1) has reported autopsy evidence that pulmonary edema occurs in 67% of patients dying following nontraumatic cerebral hemorrhage and in 63% of patients following skull fracture. Weisman (2) reviewed the autopsies of 686 patients dying following either spontaneous or traumatic intracranial hemorrhage and found evidence of pulmonary edema in two-thirds of the cases while only 2% of 200 randomly selected patients had evidence of pulmonary edema at autopsy. The same proportion of patients with pulmonary edema was found in both the post-traumatic and the spontaneous hemorrhage groups. He also noted that pulmonary edema was often present in those patients dying within 1 hr of the onset of the intracranial hemorrhage. Ducker (3) described 11 patients, 10 of whom died, who were all young and with no cardiopulmonary disease, who developed acute pulmonary edema in response to a central nervous system lesion. The common feature in all of these was an increase in the intracranial pressure and the development of pulmonary edema occurred with 2 hr of the increase in intracranial pressure.

Urabe and co-workers (4) who reported

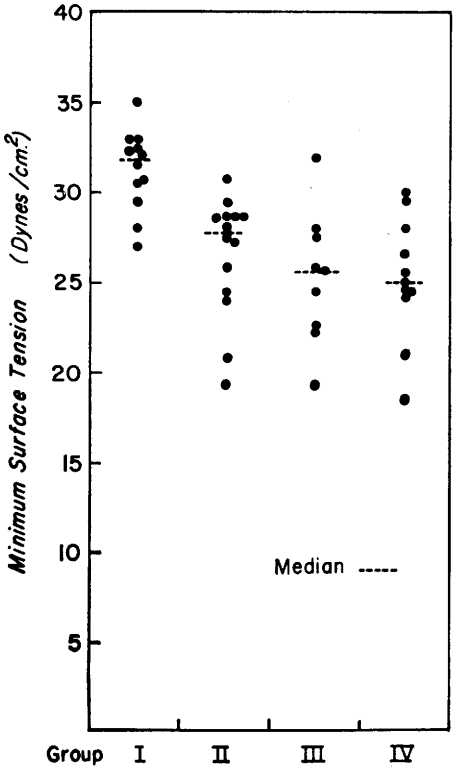

FIG. 3. Scatter diagram illustrating individual minimal surface tensions in each group of rats. (Group I, operated animals developing pulmonary edema; Group II, operated animals not developing pulmonary edema; Group III, controls; Group IV, animals with epinephrine-induced pulmonary edema).

a 12% incidence (8/67) of pulmonary edema following intracranial surgery found that five of these patients had operative procedures performed adjacent to the preoptic area and the hypothalamus. The remaining three cases occurred following surgery in the area of the medulla and pons. They also reported that 10 of 11 patients developing pulmonary edema following brain trauma had lesions in the preoptic area and one had a lesion in the medulla.

Baker (5) carried out a detailed histopathologic study of the nervous system in 10 fatal cases of bulbar poliomyelitis with extensive pulmonary edema and in five cases without lung changes in order to determine if pulmonary edema could be attributed to specific neurological lesions. He found that all cases with pulmonary edema had extensive damage to both the dorsal nuclei of the vagus and the medial reticular nuclei (vasomotor) of the medulla and that pulmonary edema was not seen when only one of these areas was involved. Cases without pulmonary edema did not have the same consistent damage to these two areas.

Thus many of the clinical and pathological observations suggest that lesions of the preoptic area and the dorsal nuclei of the vagus are responsible for neurogenic pulmonary edema. However, not all authors have found such a consistent relationship (21).

Gamble and Patton (13) first described the production of pulmonary edema in rats following the creation of electrolytic lesions in the preoptic area of the hypothalamus. Maire and Patton (22) suggest the existence of an edemagenic center located 1 to 2 mm caudal to the preoptic area. They felt that lesions in the preoptic area caused a release phenomenon in the edemagenic center since lesions in the edemagenic area abolished the pulmonary edema producing effects of preoptic lesions. Bilateral cervical vagotomy in animals with preoptic lesions did not prevent the occurrence of pulmonary edema. However, cord transection did modify the production of pulmonary edema with increased protection occurring at higher levels of cord transection. Pulmonary edema following preoptic lesions could also be prevented by midline transection of the caudal portion of the hypothalamus. They concluded that the preoptic lesions cause a release phenomenon and that interruption of the descending pathways from the edemagenic center (which is located caudal to the preoptic area) either at the caudal portion of the hypothalamus or by spinal cord transection exerted a protective effect.

The vagus nerves are known to play an important role in the production of pulmonary edema. Vischer, Haddy and Stephens (23) have reviewed some of the mechanisms related to the production of pulmonary edema by bilateral cervical vagotomy. Work from their laboratory has shown that vagotomy exerts a protective effect when pulmonary edema is produced in guinea pigs by elevations in intracranial pressure (24). Similarly, they showed that atropine was effective in protecting dogs from pulmonary edema when intracranial pressure was increased (6).

Borison and Kovacs (9) studied the various roles played by different parts of the central nervous system in production of pulmonary edema by vagotomy in the guinea pig. They found that bilateral cervical vagotomy resulted in lethal pulmonary edema within 8 hr of vagotomy. They also demonstrated that discrete bilateral lesions in the dorsal vagal nuclei caused pulmonary edema to occur in otherwise intact animals and in decerebrate animals though to a less severe degree. These data are consistent with the pathological findings of Baker (5) in patients with bulbar poliomyelitis. Pulmonary edema was also produced in guinea pigs by Staub and Sagawa (25) utilizing bilateral cervical vagotomy. In the rapidly frozen lung of these animals they found partial constriction of pulmonary arterial sphincters and capillary congestion but normal appearing veins. They postulated a circulatory agent that altered capillary permeability or inhibited alveolar surfactant as the mechanism responsible for this type of pulmonary edema. Tooley *et al.* (17) showed that the minimum surface tension of extracts of guinea pig lungs was elevated 2 to 4 hr following bilateral cervical vagotomy. Also they reported that 24 hr following unilateral vagotomy the extracts of a lung on the side of the vagotomy had an elevated surface tension compared to the lung from the side with intact vagus.

The presence of an alveolar lining layer was histologically demonstrated in guinea pig lungs as a thin fluorescent line by Bolande and Klaus (26) using ultraviolet microscopy. When pulmonary edema was produced by bilateral cervical vagotomy a loss or diminution of the fluorescent lines was noted and was accompanied by the abnormal surface tension of lung extracts.

In an attempt to localize the source of surface active material to the lung, Klaus *et al.* (27) demonstrated the presence of a strong surfactant in the washed mitochondrial fraction of the guinea pig lung. They also noted a loss of mitochondrial lamellar forms accompanying the loss of lung surface activity following vagotomy and the absence of strong surface activity in the extracts of lungs of animals whose alveolar lining cells showed no lamellar forms.

In this study the operated animals with pulmonary edema developed it 1.5 to 4 hr after the lesions were produced while epinephrine-induced pulmonary edema developed almost instantaneously. Previous studies in dogs suggested that adequate surfactant exists to maintain stability of alveoli for about 3 hr after production ceases (28). Thus, the temporal relationship of the development of pulmonary edema 1.5 to 4 hr following the production of preoptic lesions is consistent with surfactant loss as a mechanism for its production. However, since the epinephrine-induced pulmonary edema occurred within 5 min after the injection of epinephrine it is unlikely that surfactant loss plays an important role in the production of this type of pulmonary edema and may explain why the surface activity of lung extracts from this group of animals did not differ from control animals.

This study has shown that alterations in pulmonary surface activity take place when the production of pulmonary edema follows preoptic lesions in the rat but not when pulmonary edema follows the intravenous injection of epinephrine. This is the first demonstration of altered pulmonary surface activity associated with a specific intracranial lesion and might suggest a neural mechanism involving the preoptic nuclei and the vagus nerve causing alterations in pulmonary surface activity in this type of neurogenic pulmonary edema.

Summary. Neurogenic pulmonary edema occurring in a group of rats 1.5 to 4 hr following bilateral preoptic lesions in the hypothalamus was associated with alterations in pulmonary surface activity. A group of animals with similar operations but in whom pulmonary edema did not develop had pulmonary surface activity which did not differ from that in a group of unoperated control animals. A fourth group of animals with pulmonary edema induced by the intravenous injection of epinephrine also had pulmonary surface activity similar to control animals. This study suggests that the pulmonary edema developing following preoptic lesions may be caused by a decrease in pulmonary surface activity possibly mediated by the vagus nerves.

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