γ-aminobutyric acid (Killam & Bain, 1957), the depleting action of semicarbazide on the level of the acid is likely to be compensated for by a decreased use of the acid during altitude exposure, resulting in an anticonvulsant effect.

This work was supported by the training grant PH S-5 TO 1. ES00104-02.

Institute of Environmental Biology and
Department of Pharmacology,
University of Rhode Island,
Kingston, Rhode Island 02881, *U.S.A.*
November 25, 1968

IRWIN BAUMEL
ROBERT SHATZ
JOHN DEFEO
HARBANS LAL

REFERENCES

BAUMEL, I. P., ROBINSON, S. M. & BLATT, W. F. (1967). *J. pharm. Sci.*, **56**, 918–919.
FAIMAN, M. D. & HABLE, A. R. (1966). *Life Sci.*, **5**, 2225–2234.
GURDJIAN, E. S., WEBSTER, J. E. & STONE, W. E. (1949). *Am. J. Physiol.*, **156**, 149–157.
KILLAM, K. F. & BAIN, J. A. (1957). *J. Pharmac. exp. Ther.*, **119**, 255–262.
WOOD, J. D., WATSON, W. J. & DUCKER, A. J. (1968). *J. Neurochem.*, **15**, 603–608.
WOOD, J. D., WATSON, W. J. & DUCKER, A. J. (1967). *Ibid.*, **14**, 1067–1074.

On the locus of the airway constricting effect of histamine in the dog

Although the ability of histamine to constrict the airway smooth musculature of a variety of animal species (including man) has been recognized for a number of years, little evidence has appeared in the literature concerning the precise location within the tracheobronchial tree at which this effect of histamine manifests itself. We now report the results of experiments which shed light on the problem.

The experiments were made on five mongrel dogs (6 to 10 kg) anaesthetized with a solution containing 100 mg of allobarbitone, 400 mg of urethane and 400 mg of monoethylurea in each ml (0·6 ml/kg i.p.). The animals were intubated with a cuffed Murphy endotracheal tube and their interpleural spaces were cannulated. Airflow was measured with a Fleisch pneumotachograph in conjunction with a differential strain gauge (Sanborn 270). A volume signal was obtained by electrical integration of the flow signal. Transpulmonary pressure was measured with a differential pressure transducer (Sanborn 267B), one side being connected to the interpleural cannula and the other side to an opening in the endotracheal tube. Individual parameters of airflow, volume and transpulmonary pressure were recorded simultaneously on a Sanborn multi-channel recorder and from these tracings values for total lung resistance were obtained by the method of Amdur & Mead (1958).

Constriction of airway smooth muscle was induced by administering five inhalations of a 2% solution of histamine base from a DeVilbiss No. 42 nebulizer. Arterial blood samples were collected anaerobically via a polyethylene cannula inserted into a femoral artery. The oxygen tension (pO_2) of the arterial blood was determined with a Radiometer oxygen microelectrode. The pH of each blood sample was measured as drawn at 38° with a Radiometer ultra-micro capillary electrode unit and again after the blood was equilibrated with two different known CO_2 mixtures. The nomogram of Siggaard Andersen & Engel (1960) was then used to determine the carbon dioxide tension (pCO_2) of each sample.

The results of a typical experiment are presented in Table 1. Intrapulmonic administration of the histamine solution evoked a rapid increase in respiratory minute volume and total lung resistance. The increased minute volume was the

consequence of a highly elevated respiratory rate and not the result of an increase in tidal volume which, in most instances, was much diminished. As a rule, tachypnoeic breathing began after an initial period of apnoea lasting 10–30 s, reached a maximum within 2 or 3 min, then gradually subsided. The precise cause of the respiratory stimulation was not investigated. Certainly, the high arterial pCO_2 and low pO_2, produced as a result of the histamine inhalations, must have contributed to the observed increase in respiratory frequency. However other factors, such as reflex stimulation of the respiratory centre through reflexes originating in the carotid sinuses and homologous regions sensitive to the hypotensive effect of histamine, may also have played a significant role. The important finding here is that a nearly twofold increase in respiratory minute volume was virtually ineffective in restoring the arterial blood gas values to normal. As shown in Table 1, the histamine induced hypercapnic hypoxia began within 30 s after the last breath of histamine was administered and persisted for the duration of the measurement period. It is apparent then, that the observed increase in respiratory minute volume merely reflected enhanced movement of dead space air and was not associated with augmented alveolar ventilation.

Table 1. *The effect of histamine inhalation on the respiratory minute volume, pulmonary resistance and blood gases of an anaesthetized, spontaneously breathing dog*

	Minute volume (litres/min)	Pulmonary resistance (cm H_2O/litres s^{-1})	pO_2 (mm Hg)	pCO_2 (mm Hg)
Control	3·39	8·3	97	42
30 s	4·69	16·7	70	50
1 min	4·75	21·8	62	52
2 min	5·96	19·6	62	52
3 min	6·04	18·2	67	54
5 min	4·35	14·4	72	51

These findings suggest that when histamine is administered intrapulmonically it exerts a strong constricting action on the peripheral airways (i.e., the terminal bronchioles or alveolar ducts) thereby diminishing the total number of lung units being ventilated. This effect manifests itself as an increase in total lung resistance and a decrease in alveolar ventilation. It should be pointed out that these results do not preclude a possible secondary effect of histamine on the proximal airways, either directly or reflexly via pulmonary vagal efferents. Additional studies will be required to determine the extent to which the increase in pulmonary resistance was due to an effect on the upper air passages.

Department of Pharmacology,
University of Maryland,
School of Pharmacy,
Baltimore, Maryland 21201, *U.S.A.*

L. DIAMOND*

December 3, 1968

* Present address: Materia Medica Department, University of Kentucky, College of Pharmacy, Lexington, Kentucky 40506, U.S.A.

REFERENCES

AMDUR, M. O. & MEAD, J. (1958). *Am. J. Physiol.*, **192**, 364–368.
SIGGAARD ANDERSON, O. & ENGEL, K. (1960). *Scand. J. clin. Lab. Invest.*, **12**, 177–186.