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THE ROLE OF THE CHEMORECEPTORS IN THE HYPERPNOEA CAUSED BY INJECTION OF AMMONIUM CHLORIDE

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Anitschkov (1936) investigated the effect of chemoreceptor denervation on the respiratory response of anaesthetized cats and dogs to the intravenous injection of ammonium chloride. He found that section of the sinus nerves scarcely altered the hyperpnoea resulting from administration of ammonium chloride. He maintained, however, that the hyperpnoea was due to a respiratory reflex originating from the stimulation of pulmonary vagal receptors; thus vagotomy abolished the response.

Winterstein & Gökhan (1953) obtained quite different results in experiments on dogs. They asserted that carotid chemoreceptor denervation converted the usual hyperpnoeic response to ammonium chloride, seen in the intact anaesthetized animal, to one of mild respiratory depression.

In view of these conflicting opinions we have investigated the matter, using cats as experimental animals. A brief report of our findings has already been published (Joels & Neil, 1961).

METHODS

Cats were anaesthetized by the intraperitoneal injection of either sodium pentobarbitone (50 mg/kg body weight) or chloralose (50 mg/kg body weight) and urethane (250 mg/kg body weight).

A T-cannula inserted in the trachea led to inspiratory and expiratory valves. Respiration was qualitatively recorded on a kymograph by a lever operated by a tambour placed distal to the expiratory valve. On some occasions the volume of air expired during a timed period was measured by collecting it in a spirometer bell of 650 ml. capacity.

Femoral arterial blood pressure was recorded with a mercury manometer. Both sinus and vago-aortic nerves were dissected free from their surroundings. Loose ligatures placed round them enabled them to be lifted and divided without causing undue disturbance. In some experiments carotid chemoreceptor potentials were led off from fine slips of the sinus nerve (prepared as described by Heymans & Neil, 1958) by saline-wick electrodes connected to a RC coupled amplifier and displayed on one beam of a double-beam oscilloscope. The second beam of the oscilloscope displayed either an electromyogram (e.m.g.) of the diaphragm, sampled by a concentric needle electrode, or the efferent impulse activity of a thin slip of the recurrent laryngeal nerve. Recording was photographic. Ammonium chloride (3% solution in Ringer-Locke fluid) was injected through the femoral vein.

RESULTS

Two groups of experiments were performed. In one group the respiratory response to ammonium chloride was examined before and after cutting the carotid sinus and vago-aortic nerves. In the other we studied the effect of ammonium chloride injections on chemoreceptor impulse activity, simultaneously recorded with the diaphragm e.m.g. or the impulse activity in the recurrent laryngeal nerve.

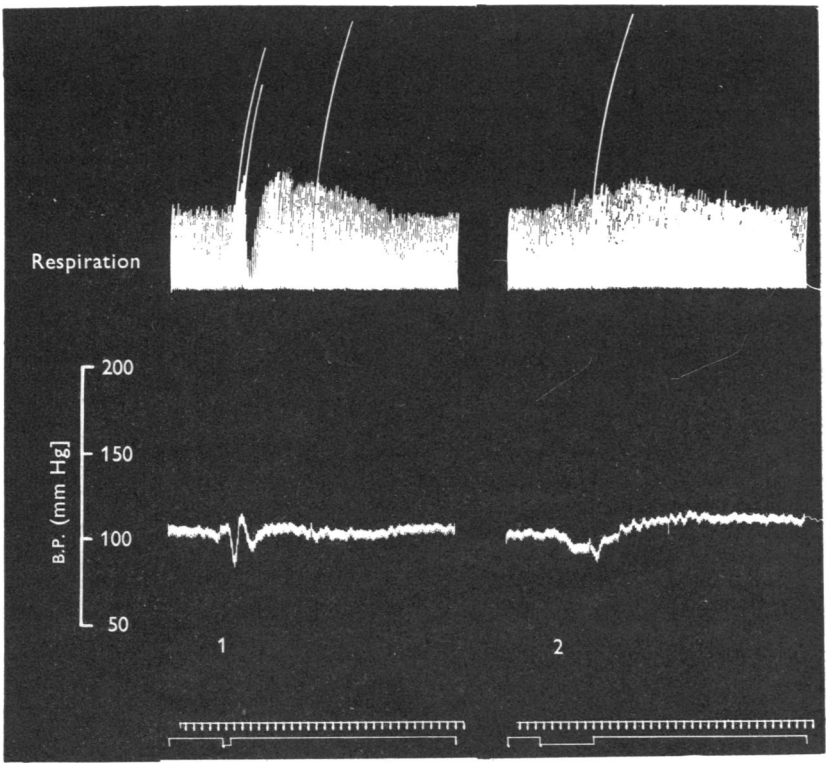

Fig. 1. Cat, 3·0 kg, anaesthetized with chloralose and urethane. Records from above downwards: respiration, femoral blood pressure, time marker (10 sec), signal marker. 75 mg NH_4Cl injected I.V. at signals, (1) during 10 sec, (2) during 60 sec.

The influence of sino-vagotomy on hyperpnoea induced by ammonium chloride

In doses of 25–50 mg/kg body weight, ammonium chloride invariably caused hyperpnoea within 35–40 sec; the increase of breathing usually lasted some minutes. The immediate response of the breathing to the injection of the drug depended on the rate of administration. When the injection was made slowly (Fig. 1, right), hyperpnoea developed smoothly;

when the drug was rapidly injected there occurred successive phases of evanescent tachypnoea and transient hypopnoea before the hyperpnoea developed (Fig. 1, left).

Sino-vagotomy did not prevent the development of sustained hyperpnoea (Fig. 2), although it did modify the transient initial responses to rapid injection of ammonium chloride. There was no evidence of the respiratory depression which Winterstein & Gökhan (1953) claimed to occur after injection of the drug into chemoreceptor-denervated dogs. In some experiments the measurements of expired air volumes confirmed the observation that ammonium chloride still caused an increase in ventilation volume after sino-vagotomy. Table 1 exemplifies such results.

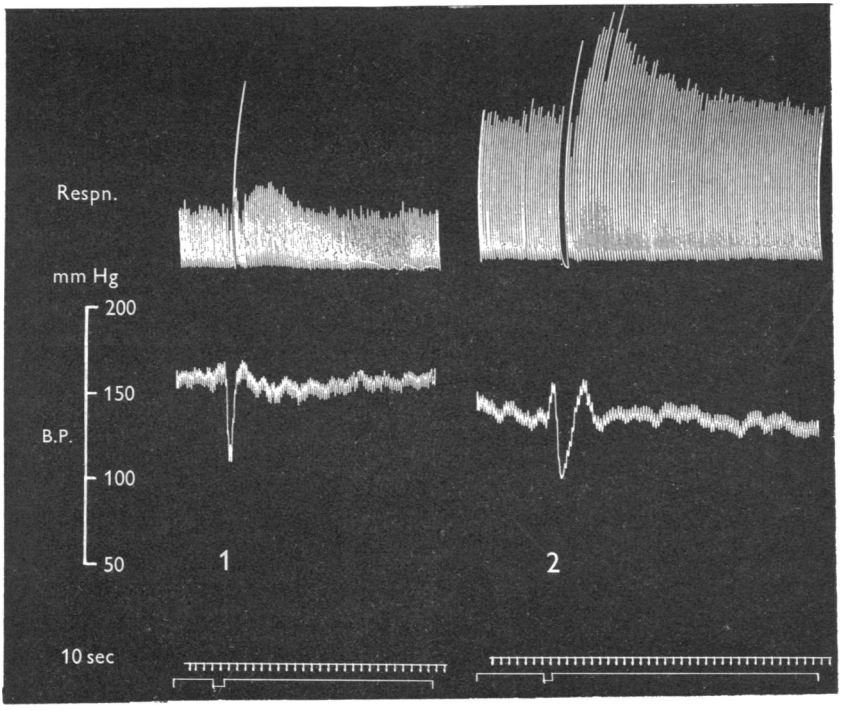

Fig. 2. Cat, 3·75 kg, anaesthetized with chloralose and urethane. Records from above downwards: respiration, femoral blood pressure, time marker (10 sec), signal marker. At signals, 100 mg NH_4Cl I.V. (1) before cutting sinus and vago-aortic nerves; (2) after cutting nerves.

Chemoreceptor and respiratory motor responses to ammonium chloride injection

In these experiments one sinus nerve was used for the chemoreceptor preparation. The remaining sinus nerve and both vago-aortic nerves were thus still available to mediate chemoreceptor reflexes.

Injection of ammonium chloride generally evoked a transient increase in chemoreceptor potentials (Fig. 3). However, the recurrent laryngeal record reveals that respiratory stimulation had already begun before chemoreceptor activity changed. The subsequent increase in both respiratory rate and impulse activity with each breath persisted even when the sinus nerve impulse traffic fell much below that immediately prior to

TABLE 1. Pulmonary ventilation during infusion of saline at 0·2 ml./min and during infusion of ammonium chloride 10 mg/min. Cat, 3·0 kg. chloralose–urethane anaesthesia.

	Pulmonary ventilation (ml./min)			
	Before chemoreceptor denervation		After chemoreceptor denervation	
	Saline (0·2 ml./min)	NH_4Cl (10 mg/min)	Saline (0·2 ml./min)	NH_4Cl (10 mg/min)
	1200	1372	814	889
	1170	1372	774	889
	1263	1297	800	—
	1333	1412	787	—
	1170	1454	787	—
	—	1548	—	—
Mean	1281	1409	792	889
Increase		10%		12%

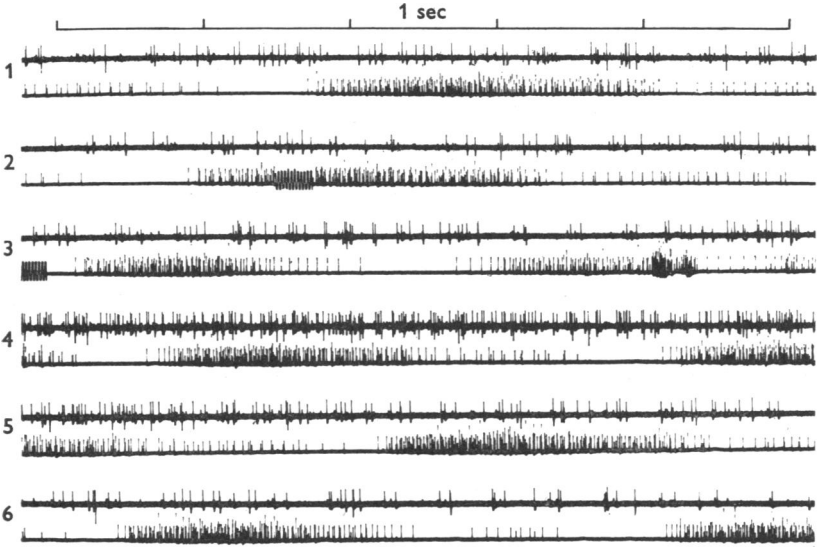

Fig. 3. Cat, 2·3 kg, sodium pentobarbitone anaesthesia. Strips 1–6 form a continuous record. In each record: upper trace, action potentials in chemoreceptor slip of sinus nerve; lower trace, efferent impulse activity in slip of recurrent laryngeal nerve. Between signals (50-cycle interruption of recurrent laryngeal record), 350 mg NH_4Cl injected I.V. Other sinus nerve and both vago-aortic nerves intact.

administration of the drug (Fig. 4). Thus chemoreceptor excitation cannot be responsible for the hyperpnoea.

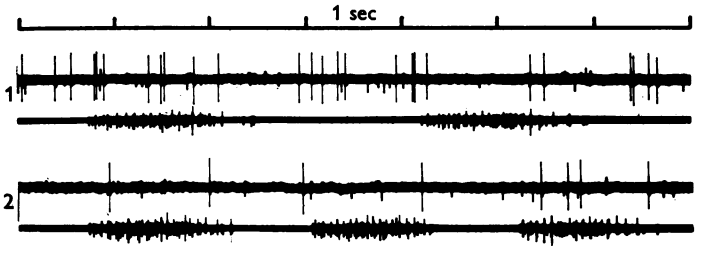

Fig. 4. Cat, 2·3 kg, sodium pentobarbitone anaesthesia. In each record: upper trace, action potentials in chemoreceptor slip of sinus nerve; lower trace, e.m.g. of diaphragm. (1) Immediately before and (2) 15 sec after I.V. injection of 150 mg NH_4Cl.

DISCUSSION

These results show that the hyperpnoea provoked by the injection of ammonium chloride is not dependent upon chemoreceptor reflexes. Such findings are in marked disagreement with those of Winterstein & Gökhan (1953).

Such changes in chemoreceptor discharge as occur after ammonium chloride injection must be largely secondary to circulatory and respiratory changes induced by the drug. The increased chemoreceptor discharge which ensues shortly after the injection is probably due to the brief hypotension which the drug causes. Such hypotension reduces glomus blood flow and excites the chemoreceptors (Landgren & Neil, 1951). The subsequent considerable reduction of impulse activity may be related to improved oxygenation of the blood brought about by the hyperpnoea. Anitschkov (1936) also found that the abolition of chemoreceptor reflexes from the carotid area had no effect on the response to ammonium chloride. He opined, however, that the hyperpnoea was due to stimulation of lung receptors by the drug, rather than to direct stimulation of the respiratory centre, claiming that it was abolished by division of the vagi. As vagal section had little effect on the hyperpnoea in the present experiments this does not seem to be the case. It therefore seems likely that the injection of ammonium chloride provokes hyperpnoea by a direct stimulation of the respiratory centre caused by the increase in hydrogen ion concentration of the blood plasma.

SUMMARY

1. Chemoreceptor denervation by section of both sinus and vago-aortic nerves failed to abolish hyperpnoea provoked by intravenous injection of ammonium chloride.

2. Any increase in chemoreceptor impulse traffic aroused by injections of this drug is slight and does not parallel the increase in respiratory motor activity.

3. Chemoreceptor excitation is therefore not responsible for the stimulation of respiration which follows injection of ammonium chloride.

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