

THE HYPERPNOEA PRODUCED BY INTRAVENOUS ADMINISTRATION OF SALICYLATES

BY

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(RECEIVED FEBRUARY 16, 1956)

An increase in pulmonary ventilation after administration of salicylate is well known and has been shown to be associated with a respiratory alkalosis (Rapoport and Guest, 1945; Boyle, Smull, and Wégria, 1947). Graham and Parker (1948) have suggested that this alkalosis is due to a primary action on respiration through stimulation of peripheral vagal nerve endings. This suggestion was based on their observation that the hyperpnoea produced by intravenous administration of salicylate to the anaesthetized cat and rabbit is abolished by bilateral vagotomy.

The development of a respiratory alkalosis after salicylate administration was confirmed by Reid, Watson, and Sproull, 1950; but its close association with a pronounced increase in protein katabolism, together with the later finding that salicylate is a powerful metabolic stimulant (Cochran, 1952, 1954) acting at the cellular level (Sproull, 1954), indicated that the primary action may be metabolic and not respiratory. For this reason, re-examination of Graham and Parker's claim to have localized the action at peripheral vagal nerve endings has been undertaken.

METHODS

Nine cats were used in the first series. These were anaesthetized with chloralose or with pentobarbitone sodium and then placed in an airtight box. The lungs were connected to the outside air by a tracheal cannula and tube. Intravenous injections were made from outside the box through a tube connected to a venous cannula. Changes in the volume of air inside the box were recorded by a tambour; these changes gave indirectly the volume of air respired. This method was found to be useful for qualitative measurements only.

More accurate and quantitative records of the ventilation were obtained by adaptation of the spirometer of Bernstein and Mendel (1953) to small animals. The arrangement is shown diagrammatically in Fig. 1. The water valves were later replaced by sensitive rubber

flap valves. With this apparatus records were made from 9 decerebrate cats.

RESULTS

Qualitatively, the results obtained from anaesthetized animals were the same as those from decerebrate animals. A preliminary report has been published in which evidence is presented that anaesthesia does not affect the respiratory response resulting from increases in metabolism caused by injection of metabolic stimulants or by exercise (Ramsay, 1956). However, only the quantitative results from decerebrate cats are given here.

The effect of an intravenous injection of 0.05 g./kg. body weight sodium salicylate in a decerebrate

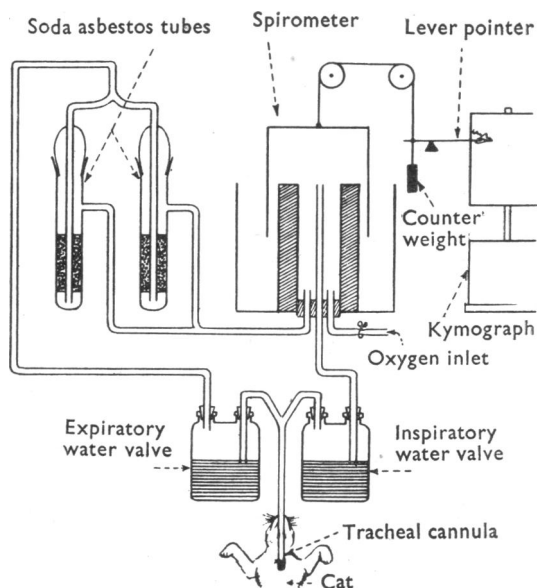


FIG. 1.—Schematic diagram of respirometer. The water valves were later replaced by sensitive rubber flap valves.

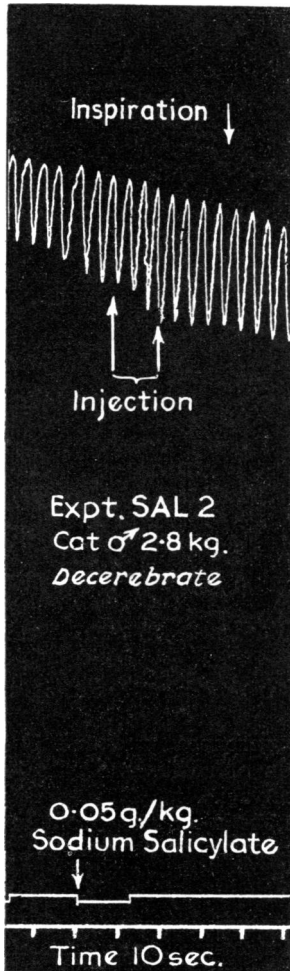


FIG. 2.—Cat, ♂, 2.8 kg., decerebrate. Respiratory response to 0.05 g./kg. body weight sodium salicylate intravenously. Inspiration, downstroke. Time, 10 sec.

cat is shown in Fig. 2. The pulmonary ventilation is increased from a resting level of 0.77 l./min. to 1.06 l./min. within a few seconds of the injection being made. (All values for ventilation are corrected to BTPS.)

After bilateral vagotomy the response is as seen in Fig. 3. The dose of sodium salicylate was 0.05 g./kg. body weight. This dose increased ventilation from 0.94 l./min. resting to 1.2 l./min. after injection.

An injection of 0.1 g./kg. body weight sodium salicylate produced up to a three-fold increase in ventilation in cats with intact vagi. After vagotomy, such a dose will also produce a stimulation of respiration. It was found, however, that vago-

tomized animals could not always maintain ventilation, respiratory movements becoming gasping and inadequate for survival.

In further experiments the effects on respiration of isomers of sodium salicylate were investigated. The absence of effect of doses of 0.1 g./kg. body weight of sodium *para*- and sodium *meta*-hydroxybenzoate when injected intravenously in decerebrate cats is shown in Fig. 4.

DISCUSSION

In the experiments on vagotomized animals by Graham and Parker (1948) it would seem that the slowing and deepening of respiration produced by vagotomy, combined with the insensitive stethographic recording method used, masked the respiratory response to salicylate administration.

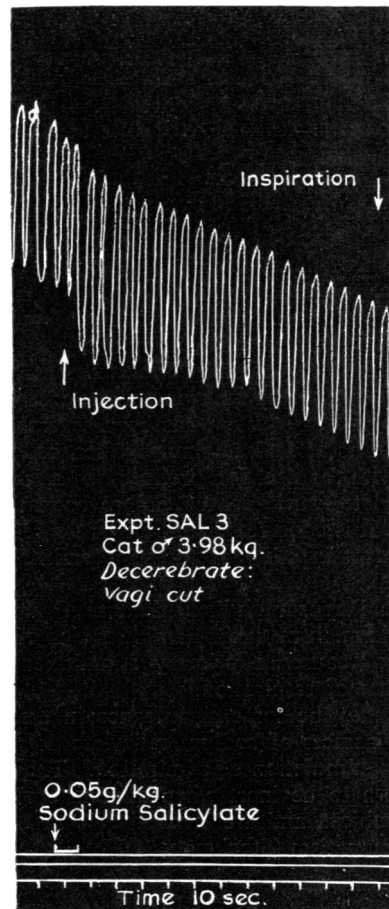


FIG. 3.—Respiratory response of a decerebrate, vagotomized cat to intravenous sodium salicylate (0.05 g./kg. body weight).

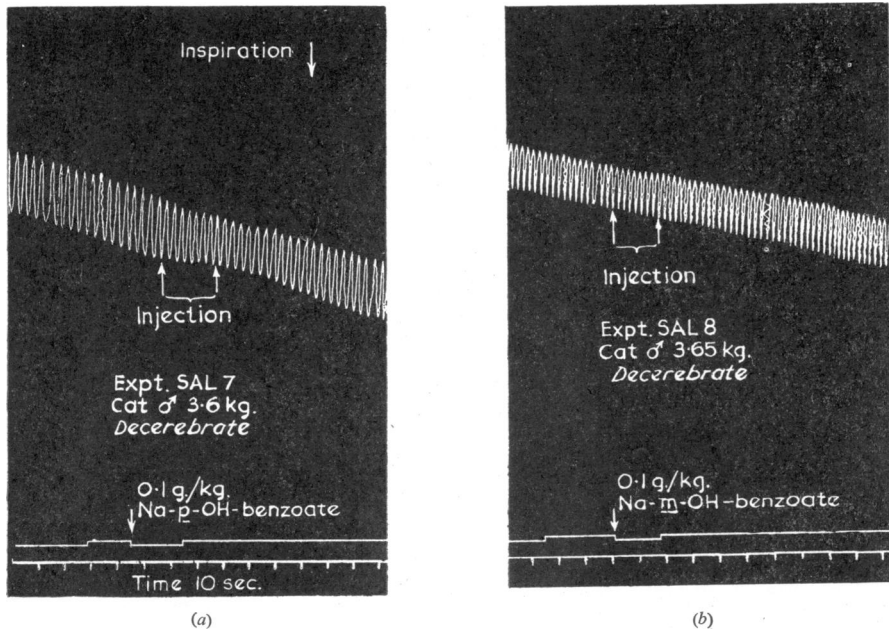


FIG. 4.—Respiratory responses of decerebrate cats during intravenous injection of 0.1 g./kg. sodium *parahydroxy*-benzoate (a) and sodium *metahydroxy*benzoate (b) respectively.

The use of more accurate methods of recording respiration shows that vagotomy does not, in fact, abolish an immediate stimulatory effect on the respiration of the intravenous injection of sodium salicylate.

The site of stimulation cannot therefore be confined to receptors sending impulses along ingoing vagal fibres as suggested by Graham and Parker.

In vagotomized animals one of the control loops of the respiratory system has been severed. Thus the system is at a disadvantage when called upon to deal with the situation produced by a large dose of salicylate—such as 0.1 g./kg. as earlier described. It is considered that this is the reason for the frequent inability of the vagotomized animal to survive.

It would appear unlikely that, as Graham and Parker claim, intravenous administration of sodium salicylate “causes a primary stimulation of the mechanism of respiration.”

There may be some significance in the finding that the isomers of sodium salicylate do not produce any stimulation of respiration. The isomers are known to be inert when administered to the human subject, and are ineffective in the relief of acute rheumatism (Stockman, 1920).

SUMMARY

1. Intravenous injection of sodium salicylate (0.05 g./kg. body weight) produces an immediate

hyperpnoea in decerebrate and in anaesthetized cats.

2. The hyperpnoea produced by intravenous administration of sodium salicylate is seen after section of the vagi.

3. Intravenous injections of solutions of isomers of sodium salicylate do not produce a stimulation of breathing.

We wish to thank Professor R. C. Garry and Dr. James Reid for their help and encouragement. Part of the expenses were defrayed by the Rankin Medical Research Fund of the University of Glasgow.

We would also like to thank Miss Jane Wylie for invaluable technical assistance.

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