Brit. J. Pharmacol. (1959), **14**, 219.

THE EFFECTS OF SODIUM SALICYLATE ON THE OXYGEN CONSUMPTION OF RATS

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(RECEIVED FEBRUARY 6, 1959)

The effects of sodium salicylate on oxygen consumption of intact rats and rats treated with tubocurarine have been studied. Intraperitoneal injections of sodium salicylate in untreated rats produced varying results which depended on both the dose and the concentration used. Intravenous injections in rats treated with curare gave rise to an increase in oxygen consumption which was proportional to the log dose over a range of 0.0625 mg./g. to 0.5 mg./g. body weight. It was concluded that sodium salicylate stimulated the oxygen consumption of rats when the concentration of the drug in the plasma was high.

In man, a rise in oxygen consumption after administration of salicylates has been demonstrated (Cochran, 1952). The interpretation of the effects of salicylates on the oxygen consumption of laboratory animals has, however, been complicated by the direct action of these drugs on respiratory rate and by changes in the degree of activity of the animals during the experiments. The present paper reports the effects of sodium salicylate on oxygen consumption by rats, untreated and treated with tubocurarine.

METHODS

Experiments with Untreated Rats. — Thirty-two male albino rats were divided into 8 groups of 4 each. Four groups received intraperitoneal injections of sodium salicylate solutions made up in two concentrations (10% and 2.5% w/v) which produced two blood concentrations, namely 0.5 mg./g. and 0.125 mg./g. body weight (see Table I). The remaining 4 groups received intraperitoneal injections of NaCl solutions of comparable molarity and volume. Oxygen consumption was recorded during three 30 min. periods (one before injection and two after), by a closed circuit method. The CO_2 evolved by the animal was absorbed in a soda-lime tower and the oxygen consumed was replaced from a calibrated spirometer. The change in volume of the spirometer, representing oxygen consumption, could be read to 2.2 ml. This resulted in a "reading error" of about 1% when oxygen consumption was calculated for a 30 min. period.

Experiments with Rats Treated with Tubocurarine. —Twenty-four male albino rats were divided into 6 groups of 4 each. Sodium salicylate was given intraperitoneally to 2 of the groups and intravenously to the remaining 4 groups. Under ether anaesthesia, the trachea was cannulated and 360 μg. tubocurarine chloride was injected into an external jugular vein; a further 180 μg. was given 1 hr. later. Ventilation was maintained by a pump with a stroke volume of about 5 ml. The expired air was directed by a valve system through a Pauling-Beckman oxygen analyser into a spirometer. The rate of the pump was regulated to maintain the oxygen tension of the expired air at about 130 mm. Hg. The oxygen consumption of the rats was calculated every 5 to 10 min. from the oxygen tension of the expired air and the ventilatory rate. By this method oxygen consumption could be determined to within 5%.

RESULTS

Untreated Rats.—The oxygen consumptions of the rats receiving NaCl solutions increased slightly during the first 30 min. after injection and decreased slightly during the second period, but these responses were not significant. The injection of 0.5 mg./g. body weight of sodium salicylate in 10% solution was followed by a 20% increase in oxygen consumption. When this dose was given in 2.5% solution there was no significant change in oxygen consumption. The administration of 0.125 mg./g. body weight sodium salicylate in 10% solution did not alter oxygen consumption significantly. However, when this dose was given in 2.5% solution a small but significant reduction (about 8%) in oxygen consumption occurred (Table I).

Rats Treated with Tubocurarine. — Intraperitoneal injections of 0.5 mg./g. body weight of sodium salicylate in 10% solution were followed by an increase in oxygen consumption of about 15%; when a quarter of this dose was given in

TABLE I

THE EFFECTS OF INTRAPERITONEAL INJECTIONS OF SODIUM SALICYLATE AND SODIUM CHLORIDE ON THE OXYGEN CONSUMPTION OF UNTREATED RATS

Oxygen consumption is mean ml./kg.$^{3/4}$±S.E.: for control period, total consumption; for test periods, mean difference (control period − test period). n=4 in all groups. All periods 30 min. Groups 1 and 5, 2 and 6, 3 and 7, 4 and 8 form comparable pairs with respect to molarity and volume of fluid injected.

Group	Mean Body Weight		Conc. %w/v	Dose (mg./g.)	O_2 Consumption		
					Control	After Injection	
	g.	kg.$^{3/4}$				1	2
Sodium salicylate							
1	200	0·299	10·0	0·50	561·8±31·1	+146·4±38·7	+77·4±23·8
2	233	0·335	10·0	0·125	525·5±26·4	+15·5±15·9	−32·4±18·9
3	219	0·320	2·5	0·50	648·3±23·0	+0·7±10·4	−17·0±17·7
4	228	0·330	2·5	0·125	608·8±28·0	−22·6± 9·9	−69·5±11·7
Sodium chloride							
5	225	0·327	3·6	0·18	611·0±38·7	+27·8±28·5	−25·1± 4·6
6	231	0·333	3·6	0·045	594·0±31·0	+22·7±12·2	−23·7± 7·5
7	221	0·322	0·9	0·18	611·0± 8·8	+21·1±19·4	−26·0±16·0
8	237	0·336	0·9	0·045	540·0±21·5	+24·9±18·5	−21·1±20·7

TABLE II

THE EFFECT OF INTRAPERITONEAL INJECTIONS OF SODIUM SALICYLATE ON THE OXYGEN CONSUMPTION OF RATS TREATED WITH TUBOCURARINE

Oxygen consumption calculated as in Table I. n=4 in both groups.

Group	Mean Body Weight		Conc. %w/v	Dose (mg./g.)	O_2 Consumption		
					Control	After Injection	
	g.	kg.$^{3/4}$				1	2
9	206	0·306	10·0	0·50	550·6±31·9	+80·8±25·9	+72·6±22·6
10	212	0·312	2·5	0·125	578·2±35·4	+31·1±43·3	+34·2±38·9

TABLE III

THE EFFECT OF INTRAVENOUS INJECTIONS OF SODIUM SALICYLATE ON THE OXYGEN CONSUMPTION OF RATS TREATED WITH TUBOCURARINE

Oxygen consumption calculated as in Table I. n=4 in all groups. (Two animals in Group 14 died during the final period.)

Group	Mean Body Weight		Dose (mg./g.)	O_2 Consumption		
				Control	After Injection	
	g.	kg.$^{3/4}$			1	2
11	223	0·324	0·0625	552·2±43·7	+25·4±26·6	−7·1±38·9
12	248	0·351	0·125	548·7±35·9	+50·8±37·1	+39·5±35·0
13	226	0·328	0·25	514·2±44·2	+150·5± 8·9	+116·4±21·3
14	213	0·313	0·50	538·9±47·6	+246·8±59·2	—

2.5% solution there was no significant change (Table II).

During the first 30 min. after intravenous injection of sodium salicylate, the change in oxygen consumption of the rats varied linearly with the log dose ($r=0.76$, $P<.001$). With the highest dose (0.5 mg./g. body weight), the increase in oxygen consumption was about 50% during the first 30 min. (Table III). Two of the rats, however, died during the second 30 min. after injection, presumably due to the toxic effect of the drug.

DISCUSSION

Interpretation of the results obtained from the untreated rats is subject to the limitations mentioned in the introduction. However, the results do show that, in rats, intraperitoneal injections of sodium salicylate can produce varying effects on oxygen consumption. The dose of sodium salicylate which reduced the oxygen consumption of the untreated rats produced no such response in those given tubocurarine (compare group 4, Table I, with group 10, Table II). Thus, it is possible that the reduction in the oxygen consumption of the untreated rats is an indirect effect due to some sedative action. Certainly the rats of group 4 were less active during the test period.

The results from rats treated with tubocurarine clearly indicate that sodium salicylate stimulated oxygen consumption. By extrapolation from Table III, the intravenous dose of sodium

salicylate necessary to produce a significant response is found to be about 0.18 mg./g. body weight. The concentration of the drug in the plasma falls gradually as it is distributed in the body fluid (Smith, Gleason, Stoll, and Ogorzalek, 1946). However, the initial concentration in the plasma is about 4.5 mg./ml. (plasma volume, 0.175 × weight as $g.^{.725}$: Wang and Hegsted, 1949). It is possible that the stimulating effect of sodium salicylate depends upon the attainment of a fairly high plasma concentration. The necessary concentration in the plasma may not be reached when dilute solutions are given intraperitoneally. This could explain the lack of response when 0.5 mg./g. body weight is given in 2.5% solution by this route.

The simplest explanation for the increase in oxygen consumption is to assume that adrenaline is released, possibly by a stimulating effect of the drug on the hypothalamus (George and Way, 1957). This hypothesis agrees with that put forward by Smith (1955) to explain the hyperglycaemia occurring in rats after the administration of salicylates. However, a direct action on tissue metabolism must also be considered as a possibility. Sodium salicylate is known to increase the oxygen uptake of rat cerebral cortex slices (Fishgold, Field, and Hall, 1951) and of liver slices in the presence of citrate (Alwall, 1939).

The view that the increased respiratory rate observed after large doses of salicylates is the result of direct central stimulation by the drug is well established (Smith, 1949). The present experiments do not make it necessary to alter this view. It may well be that the increases in oxygen consumption and in the rate of respiration represent separate effects of salicylates, as seems to be the case in dogs (Tenney and Miller, 1955).

This work was supported by grants from the China Medical Board of New York and the Research Grants Committee of the University of Hong Kong.

References

Alwall, N. (1939). *Acta med. scand.*, **102**, 390.
Cochran, J. B. (1952). *Brit. med. J.*, **2**, 964.
Fishgold, J. T., Field, J., and Hall, V. E. (1951). *Amer. J. Physiol.*, **164**, 727.
George, R., and Way, L. E. (1957). *J. Pharmacol. exp. Ther.*, **119**, 310.
Smith, M. J. H. (1955). *Brit. J. Pharmacol.*, **10**, 110.
Smith, P. K. (1949). *Pharmacol. Rev.*, **1**, 353.
—— Gleason, H. L., Stoll, C. G., and Ogorzalek, S. (1946). *J. Pharmacol. exp. Ther.*, **87**, 237.
Tenney, S. M., and Miller, R. M. (1955). *Amer. J. Med.*, **19**, 498.
Wang, C. F., and Hegsted, D. M. (1949). *Amer. J. Physiol.*, **156**, 218.