

## THE EFFECT OF SALICYLATE ON GLUCOSE TOLERANCE IN THE RAT

by

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### INTRODUCTION

Salicylates cause a number of effects on carbohydrate metabolism such as a depletion of the liver glycogen in normal rats<sup>1</sup> and a reduction of glycosuria and blood glucose in alloxan-diabetic rats<sup>2</sup>. The influence of salicylate on the blood glucose concentrations after the oral and intravenous administration of a solution of glucose to rats has been studied. An increased rate of intestinal absorption of glucose was demonstrated and the implications of this finding are discussed.

### EXPERIMENTAL

Male rats of the Wistar strain, weighing 200–250 g and maintained on cubes (Medical Research Council diet 41) were used. In the first experiment 14 rats were fasted for 24 h and given 2 g of glucose in 10 ml of water by stomach tube. 6 of the animals were given an intraperitoneal injection of 1 ml 0.9 % w/v saline and the remainder an intraperitoneal injection containing 100 mg of sodium salicylate in 1 ml water immediately after the glucose had been given. Blood glucose concentrations were measured on tail-vein samples by the method of NELSON (1944) at 0, ½, 1, 1½, 2, 2½, 3, 6, 12 and 24 h.

In order to assess the influence of the adrenal, the experiment was repeated with 12 rats which had been bilaterally adrenalectomised a week previously and maintained on cubes and 0.45 % w/v saline.

The first experiment was also repeated with 11 rats, 6 injected with saline and 5 with salicylate, except that only 150 mg of glucose in 1 ml of water was administered by stomach tube at 0 h and the blood glucose concentrations measured up to 3 h. This quantity of glucose was chosen because it was approximately equivalent to 50 g of glucose in an adult man. The experiment was repeated with an additional 11 rats, except that all the animals received the 150 mg of glucose in 1 ml of water by injection into a tail vein. The results are expressed as means with the standard deviation.

### RESULTS

The blood glucose concentrations of the saline-treated normal rats and of the salicylate-treated normal rats given 2 g of glucose are shown in Table I.

It is seen that a marked increase in the blood glucose concentrations occurred in the salicylate-treated rats compared with the saline-treated rats, up to 6 h after the injection, but at 12 h and 24 h the results of the two groups were not significantly different ( $P = 0.8$ ) when analysed by Student's test.

TABLE I

EFFECT OF SALICYLATE ON BLOOD GLUCOSE CONCENTRATIONS OF NORMAL RATS AFTER THE ORAL ADMINISTRATION OF 2 g GLUCOSE IN 10 ml OF WATER

Time of estimation (h)	Blood glucose (mg/100 ml)		Comparison of blood glucose results for groups A and B		
	Control A	Salicylate B	n	t	P
0	64.0 $\pm$ 2.1	67.8 $\pm$ 3.0	11	1.6384	0.2
1/2	78.6 $\pm$ 3.2	140.6 $\pm$ 4.8	11	25.5063	0.001
1	85.8 $\pm$ 3.6	162.9 $\pm$ 7.5	11	21.4803	0.001
1 1/2	84.4 $\pm$ 3.6	161.1 $\pm$ 10.7	11	15.4862	0.001
2	83.8 $\pm$ 3.0	160.9 $\pm$ 8.1	11	20.0764	0.001
2 1/2	82.0 $\pm$ 5.3	154.0 $\pm$ 10.2	11	14.8781	0.001
3	74.8 $\pm$ 5.3	158.0 $\pm$ 12.3	11	14.2825	0.001
6	74.0 $\pm$ 4.1	117.0 $\pm$ 10.6	11	3.9826	0.01
12	71.2 $\pm$ 3.7	73.7 $\pm$ 12.6	11	0.8652	0.3
24	69.4 $\pm$ 2.9	71.8 $\pm$ 7.9	11	0.7143	0.5

The results from the adrenalectomised rats are shown in Table II. In these animals a marked reduction in the blood glucose concentrations of the salicylate-treated rats compared with the saline-treated rats, occurred up to 3 h. Three of the salicylate-treated rats died between 3 and 6 h, their blood glucose concentration immediately before death being 25 to 32 mg per 100 ml and the remaining salicylate-treated animals died between 6 and 24 h.

TABLE II

EFFECT OF SALICYLATE ON BLOOD GLUCOSE CONCENTRATIONS OF ADRENALECTOMISED RATS MAINTAINED ON 0.45 % W/V SALINE AFTER THE ORAL ADMINISTRATION OF 2 g OF GLUCOSE IN 10 ml OF WATER

Time of estimation (h)	Blood glucose (mg/100 ml)		Comparison of blood glucose results for groups A and B		
	Control A	Salicylate B	n	t	P
0	54.2 $\pm$ 4.5	51.7 $\pm$ 5.0	10	0.9130	0.4
1/2	101.1 $\pm$ 23.3	61.1 $\pm$ 5.1	10	4.0898	0.01
1	104.0 $\pm$ 27.3	61.7 $\pm$ 7.4	10	3.6330	0.01
1 1/2	107.0 $\pm$ 15.3	52.2 $\pm$ 9.6	10	11.0913	0.001
2	91.2 $\pm$ 19.4	40.0 $\pm$ 8.9	10	9.6841	0.001
3	75.2 $\pm$ 12.5	28.6 $\pm$ 5.0	10	14.5802	0.001
6	63.7 $\pm$ 4.5	29.0 $\pm$ 3.6	7	11.7046	0.001

Table III shows the results of the oral administration of 150 mg of glucose to the normal rats injected with saline or salicylates.

A similar result was found to that obtained in the first experiment, using 2 g of glucose, but when 150 mg of glucose was given intravenously the results shown in Table IV were observed.

There was no significant difference between the values in both control and salicylate-treated groups and it is concluded that the impaired tolerance to orally administered glucose in normal rats is due to increased intestinal absorption of the sugar.

TABLE III

EFFECT OF SALICYLATE ON BLOOD GLUCOSE CONCENTRATIONS OF NORMAL RATS AFTER THE ORAL ADMINISTRATION OF 150 mg OF GLUCOSE IN 1 ml OF WATER

Time of estimation (h)	Blood glucose (mg/100 ml)		Comparison of blood glucose results for groups A and B		
	Control A	Salicylate B	n	t	P
0	67.0 $\pm$ 8.5	71.2 $\pm$ 7.0	9	0.8860	0.3
1/2	90.1 $\pm$ 8.6	101.4 $\pm$ 6.4	9	2.1947	0.05
1	89.0 $\pm$ 5.4	105.6 $\pm$ 12.8	9	2.9161	0.02
1 1/2	83.5 $\pm$ 2.5	101.0 $\pm$ 7.0	9	5.7308	0.001
2	82.5 $\pm$ 9.4	104.0 $\pm$ 11.9	9	4.3076	0.01
3	77.8 $\pm$ 1.5	94.4 $\pm$ 13.4	9	3.0511	0.02

TABLE IV

EFFECT OF SALICYLATE ON BLOOD GLUCOSE CONCENTRATIONS OF NORMAL RATS AFTER THE INTRAVENOUS ADMINISTRATION OF 150 mg OF GLUCOSE IN 1 ml OF WATER

Time of estimation (h)	Blood glucose (mg 100 ml)		Comparison of blood glucose results for groups A and B		
	Control A	Salicylate B	n	t	P
0	66.3 $\pm$ 2.7	68.8 $\pm$ 11.7	9	0.5104	0.6
1/2	104.2 $\pm$ 4.3	98.4 $\pm$ 17.4	9	0.7984	0.5
1	83.3 $\pm$ 2.7	84.0 $\pm$ 8.9	9	0.1836	0.9
1 1/2	79.2 $\pm$ 3.2	78.0 $\pm$ 10.9	9	0.2639	0.7
2	72.0 $\pm$ 2.8	79.0 $\pm$ 10.6	9	1.5755	0.2
3	72.0 $\pm$ 3.0	80.0 $\pm$ 8.5	9	2.1737	0.1

## DISCUSSION

The experiments were made because of a report by COCHRAN, WATSON AND REID<sup>3</sup> that salicylate produced diminished glucose tolerance in a rheumatic fever patient after the oral administration of 50 g of the sugar. These workers interpreted the result as evidence of a similarity in metabolic actions between salicylate and cortisone, an explanation which was difficult to apply to the known effects of salicylate on carbohydrate metabolism in the rat. In this species, at least, salicylate not only produces opposite actions to cortisone on the glycosuria and blood glucose of alloxan-diabetic rats<sup>2</sup> but may even antagonise the effects of the adreno-cortical hormone in producing glycosuria and hyperglycaemia curves after feeding, in normal rats force-fed a high carbohydrate diet<sup>4</sup>.

The results after the oral administration of a large dose of glucose (2 g) showed that salicylate produced increased blood glucose concentrations and this was confirmed when a smaller quantity of the sugar (150 mg), approximately equivalent to 50 g in an adult man, was given. However, when the same amount of glucose was administered intravenously there was no significant difference between the blood glucose concentrations in the control and salicylated animals. Some preliminary results on rheumatoid arthritic patients treated with salicylates have indicated that this finding also applies to man<sup>5</sup>. It is concluded that salicylate causes increased intestinal absorption of glucose in man and the normal rat. If the intestinal absorption of glucose involves an initial

phosphorylation, and HELE<sup>6</sup> has shown that the absorption rate of glucose by rat intestinal mucosa is very similar to its rate of phosphorylation, then the rates of the hexokinase reaction and of the subsequent dephosphorylation of the hexose phosphate will determine the speed of absorption. Salicylate may influence either or both reactions. Another possible effect of salicylate is on gut motility so that the sugar is presented to the intestinal mucosa in an abnormal manner.

Salicylate did not diminish the tolerance to orally administered glucose in the adrenalectomised rats but caused a reduction in the blood glucose concentrations compared with the value observed in control animals. There was no evidence that the absorption of glucose was diminished in the control adrenalectomised animals compared with the control normal animals. The adrenalectomised rats were maintained on saline, and other workers<sup>7</sup> have shown that absorption of glucose in adrenalectomised rats is diminished only when the normal salt balance is upset. The results in Table II indicate that the presence of the adrenals is necessary for salicylate to cause increased blood glucose concentrations after oral administration of glucose and in their absence, salicylate either produced a decreased intestinal absorption of the sugar or reduced the blood glucose concentration by some other mechanism, such as increased tissue utilisation.

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#### SUMMARY

1. The blood glucose concentrations of rats treated with salicylate have been measured after the oral and intravenous administration of glucose and compared with the results obtained from control animals.
2. Salicylate causes increased blood glucose concentrations when glucose is given orally but not when it is injected intravenously.
3. It is concluded that salicylate causes increased intestinal absorption of glucose in the rat.
4. The implications of the results are discussed.

#### RÉSUMÉ

1. La concentration en glucose du sang de rats traités par le salicylate a été mesurée après administration orale ou intraveineuse de glucose et comparée à celle de rats témoins.
2. Le salicylate augmente la concentration en glucose du sang si le glucose est administré par voie orale mais non s'il est injecté par voie intraveineuse.
3. On peut en conclure que le salicylate provoque une augmentation de l'absorption intestinale du glucose chez le rat.
4. Les conséquences de ces résultats sont discutées.

#### ZUSAMMENFASSUNG

1. Die Glucosekonzentration im Blut von mit Salicylat behandelten Ratten wurde nach oraler und intravenöser Verabreichung von Glucose gemessen und mit den Ergebnissen verglichen, welche mit Kontrolltieren erhalten worden waren.

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2. Salicylat verursachte eine Erhöhung der Glucosekonzentration im Blut, wenn die Glucose oral, nicht aber wenn sie intravenös verabreicht worden war.
3. Es wird hieraus geschlossen, dass das Salicylat die Glucoseabsorption durch den Darm bei der Ratte erhöht.
4. Die Resultate und ihre Folgen werden erörtert.

## REFERENCES

- <sup>1</sup> C. LUTWAK-MANN, *Biochem. J.*, 36 (1942) 706.
- <sup>2</sup> M. J. H. SMITH, B. W. MEADE AND J. BORNSTEIN, *Biochem. J.*, 51 (1952) 18
- <sup>3</sup> J. B. COCHRAN, R. D. WATSON AND J. REID, *Brit. Med. J.*, (1950) 1411.
- <sup>4</sup> M. J. H. SMITH, *Biochem. J.*, 52 (1952) 649.
- <sup>5</sup> M. J. H. SMITH, in preparation.
- <sup>6</sup> M. P. HELE, *Biochem. J.*, 55 (1953) 857.
- <sup>7</sup> H. J. DEUEL, *Ann. Rev. Biochem.*, 12 (1943) 135.

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