Glucose and the dextran 'anaphylactoid' inflammation[1]

V. W. ADAMKIEWICZ AND LIDIA M. ADAMKIEWICZ
Laboratoire de Physiologie, Université de Montréal, and Hôpital Hôtel Dieu de Montréal, Montréal, Canada

ADAMKIEWICZ, V. W. AND LIDIA M. ADAMKIEWICZ. *Glucose and the dextran 'anaphylactoid' inflammation.* Am. J. Physiol. 198(1): 51–53. 1960.—Male Sprague-Dawley rats, 120–150 gm in body weight, injected simultaneously with the glucan dextran (1 ml 6% w/v, i.p.) and with an overdose of glucose (3 × 5 ml, 25% w/v, s.c.) which cannot be markedly reduced by excretion in about 24 hours, do not undergo dextran 'anaphylactoid' inflammation. If the amount of glucose is smaller (2 × 5 ml, 25% w/v, s.c.) and can be reduced by excretion within about 10 hours, the inflammation occurs, but is greatly delayed in time and diminished in intensity. The specific inhibitory action glucose exerts on the biological activity of the glucan dextran is discussed.

THE GLUCAN DEXTRAN, a polymerized glucose, when injected into rats induces the 'anaphylactoid' inflammation.

We reported that insulin administration sensitizes to this inflammation (1, 2). Conversely, the lack of insulin, such as it exists during alloxan diabetes, totally inhibits the inflammation (3).

However, in alloxan diabetic rats, the true hypoinsulinism results in a secondary relative glucose overdosage of the animal. The role of such an overdosage in the inhibition of the inflammation has been investigated now. It was found that a true glucose overdosage of normal rats, which induces a secondary relative hypoinsulinism, also totally inhibits the dextran anaphylactoid inflammation.

METHODS

The rats used were males of the Sprague-Dawley strain, 120–150 gm in body weight, maintained on Purina fox chow cubes and water.

The dextran was a 6% w/v solution in physiological saline (Abbott). It was injected intraperitoneally, 1 ml (60 mg)/rat, at the beginning (0 hr.) of each experiment.

The glucose administered was a 25% w/v hypertonic solution in water. It was injected subcutaneously on the back in the amount of 5 ml (1.25 gm) per rat, three times: at 0, 1 and 2½ hours (1st experiment); or two times: at 0 and 1 hours (2nd experiment).

Two other hypertonic solutions were used (1st experiment) as equimolar controls for glucose: an 8.03% w/v solution of urea in water, and an 8.46% w/v solution of sodium chloride in water. Both were injected in the amount of 5 ml/rat, three times, similarly to glucose.

Glucosuria was estimated (2nd experiment) at the 0 hour, and then hourly till the end of the experiment. This was done by collecting some drops of urine from each rat directly into test tubes (rats micturate on handling). The glucose in the urine was measured by the Clinitest procedure, a modification of the Fehling test (Clinitest Reagent Tablets, Ames Co.).

The intensity of the general anaphylactoid inflammation was estimated as follows. At the 0 hour, and then every hour after the injection of dextran until the end of the experiment, the following eight organs were inspected separately in each rat: the snout, the two ears, the four paws and the scrotum. The intensity of inflammation which appeared in each of these organs was evaluated thus: no inflammation = 0 marks; traces of inflammation = 1 mark; well developed inflammation = 2 marks; very well developed inflammation = 3 marks. The sum was obtained of all marks gained by each rat at the time of inspection. For example: if each of the eight organs was inflamed maximally at the time of inspection, gaining each 3 marks, then the rat gained a total sum of 3 × 8 = 24 marks. These sums were used to calculate the mean intensity of inflammation per rat in the experimental group.

Within 5 hours after the injection of dextran, in any experimental group, either all the rats were inflamed to a greater or lesser degree, or none became inflamed.

Autopsies were performed on the animals which died during the experiments.

Received for publication August 24, 1959.
[1] This study was supported by Research Grant No. A-2260 from the U.S. Department of Health, Education and Welfare, and Research Grant No. MA 640 from the National Research Council of Canada.

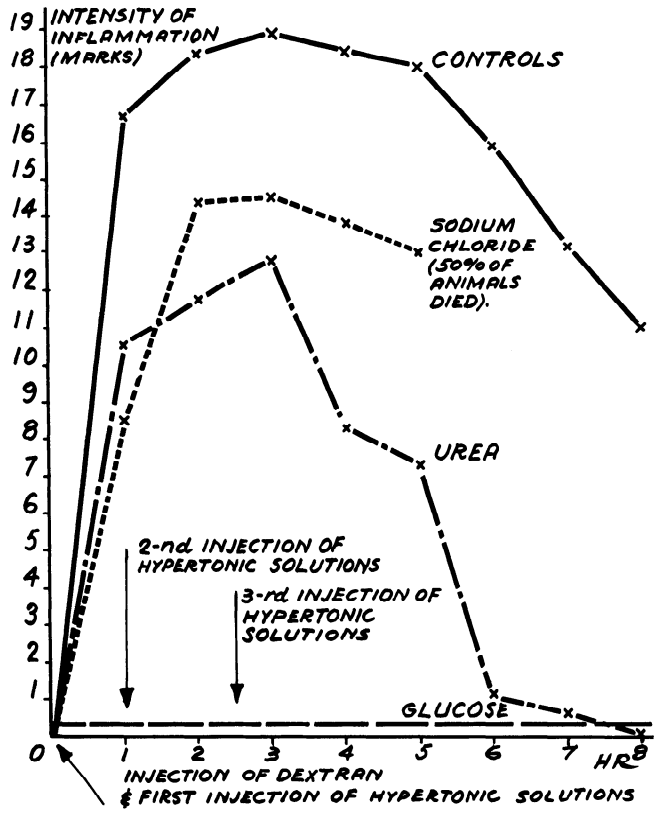

FIG. 1. Inhibition of dextran 'anaphylactoid' inflammation by glucose. *Abscissa:* hours after injection of dextran; *ordinate:* intensity of inflammation (see METHODS). All rats were injected with dextran. In addition 1 group received hypertonic urea, 1 group, hypertonic NaCl, and 1 group, hypertonic glucose. Only the hypertonic glucose inhibited completely the inflammation.

RESULTS

Inhibition of dextran anaphylactoid inflammation by glucose. All the rats of four groups, each of 10 animals, received an injection of dextran. The first of these groups (controls) had no other treatment and showed an intense anaphylactoid inflammation, which started half an hour after the injection, and reached its peak (19 marks/rat) at the 3rd hour. The second and third groups received three consecutive injections of urea or of sodium chloride, respectively. They reacted by a conspicuous anaphylactoid inflammation which started also half an hour after the injection of dextran. The peaks in the urea group (13 marks/rat) and in the sodium chloride group (15 marks/rat) were reached equally on the 3rd hour. Both these peaks were lower than that of the control group. The fourth experimental group of rats received three consecutive injections of the glucose solution. These animals did not develop the anaphylactoid inflammation (fig. 1).

Five rats from the sodium chloride group died at the 4th hour. Before death they underwent the anaphylactoid inflammation. Two rats from the glucose group died on the 6th hour. They did not undergo the anaphylactoid inflammation. All the dead rats displayed, at autopsy, massive hemorrhages in the subdural region of the brain. Such hemorrhages, and the ensuing death, are a constant finding in rats overdosed with various hypertonic solutions, (4).

Relationship between reduction of a glucose load and the dextran anaphylactoid inflammation. Two groups were used, again each of 10 rats. All the animals were injected with dextran. The first group (controls) had no other treatment and reacted by an intense inflammation which started within half an hour after the injection and reached its peak (22 marks/rat) at the 3rd hour. The second experimental group received two consecutive injections of glucose. Their urine was collected hourly for glucosuria determination. The peak of glucosuria (1.75 gm%) occurred at the 3rd hour, and glucosuria disappeared on the 10th hour. The flooding of the organism of these rats with glucose delayed the onset of the anaphylactoid inflammation to the 5th hour. The peak of inflammation (12 marks/rat) was reached only at the 10th hour. It corresponded to the time when glucosuria disappeared, and it was half lower than in the control group (fig. 2). None of the animals died.

DISCUSSION

Rats overdosed with glucose, and displaying a lasting glucosuria do not undergo the anaphylactoid inflammation when injected with the glucan dextran.

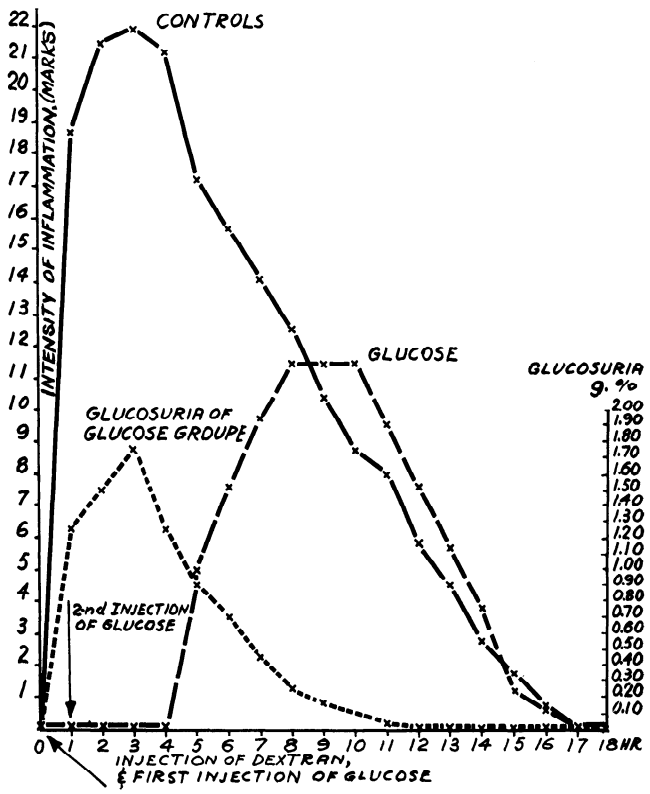

FIG. 2. Relationship between reduction of a glucose load and dextran 'anaphylactoid' inflammation. All rats were injected with dextran. In addition, 1 group received hypertonic glucose in an amount which was eliminated within 10 hr. as seen from its glucosuria curve. The inflammation in this group was delayed in time and diminished in intensity. Its peak corresponded to the time of disappearance of the glucosuria.

This inhibition of the inflammation is not related to the hypertonicity of the injected glucose, since the injection of hypertonic solutions of urea or sodium chloride, equimolar with the glucose, does not abolish the inflammation.

But the hypertonicity of the injected solutions induces in the animals a state of stress. Stress, in general, exerts an anti-inflammatory effect (5). This may account for the lesser intensity of inflammation in the urea- and sodium chloride-treated animals in the first experiment, and in the glucose-treated animals in the second experiment, as compared to the control groups.

Rats overdosed with hypertonic solutions of urea or sodium chloride die displaying a characteristic syndrome, but before death they undergo the anaphylactoid inflammation. On the other hand, hypertonic glucose, besides being able to induce the same characteristic syndrome, also abolished the anaphylactoid inflammation. Therefore, glucose exerts a specific inhibitory action on the biological activity of the glucan dextran.

Nevertheless, rats injected simultaneously with dextran and with an overdose of glucose will undergo the anaphylactoid inflammation provided they can reduce the surplus glucose in about 10 hours. Under these circumstances, no inflammation occurs during the first few hours, while the transport mechanisms carry glucose. It is only when the load of glucose has been partly eliminated that the transport mechanisms can carry the dextran to those structures which undergo the anaphylactoid inflammation. It appears, therefore, that a competition exists for the transport mechanisms between glucose and the glucan dextran.

When the load of glucose is so large that it requires about 24 hours for reduction, no anaphylactoid inflammation occurs at all, probably because by then dextran may have lost its anaphylactoid properties. Even if it eventually should reach the structures which undergo the anaphylactoid inflammation, it is apparently unable to trigger it.

It is known that various monosaccharides are carried at different rates by transport mechanisms across the cell barriers of the intestine (6). The present experiment suggests that the same sugar is transported across cell barriers at different rates, depending on whether it is present in a monomolecular form (glucose) or a polymerized form (the glucan dextran). Apparently, the monomolecular form is carried first, and has precedence over the polymerized form.

On the basis of these observations, the mechanism of insulin sensitization to the dextran anaphylactoid inflammation (1, 2) could be explained partly as follows. Insulin diminishes in various ways the amount of 'free' monomolecular glucose in the organism of the rat, leaving the transport mechanisms freer to carry the glucan dextran across cell barriers, in larger amounts, to the sites of the anaphylactoid inflammation. The over-all effect of insulin is therefore a potentiation of the inflammation.

During alloxan diabetes (3), on the other hand, the transport mechanisms are flooded with free monomolecular glucose. This impairs the transport of the glucan dextran to the sites of the anaphylactoid inflammation. The over-all effect of the diabetes is therefore an inhibition of the inflammation.

The authors express thanks to Mr. Edo J. Pertici for his help during these experiments.

REFERENCES

1. ADAMKIEWICZ, V. W. AND Y. L. LANGLOIS. *Canad. J. Biochem. Physiol.* 35: 251, 1957.
2. ADAMKIEWICZ, LIDIA M. AND V. W. ADAMKIEWICZ. *J. Physiol.* 145: 667, 1959.
3. ADAMKIEWICZ, V. W. AND LIDIA M. ADAMKIEWICZ. *Am. J. Physiol.* 197: 377, 1959.
4. SELYE, H. *Acta anat.* 16: 108, 1952.
5. SELYE, H. *The Physiology and Pathology of Exposure to Stress.* Montreal: Acta, Inc., 1950.
6. CORI, C. F. *J. Biol. Chem.*, 66: 691, 1925.