Action of Muscular Work on Transfer of Sugars Across Cell Barriers: Comparison With Action of Insulin

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It has been known clinically for many years that intense muscular work increases the uptake of sugar from the blood, even in the untreated diabetic patient (1, 2). This has recently been studied in the diabetic animal by Ingle (3, 4) who showed that severe work can cause a drop in blood sugar to extremely low levels in diabetic animals receiving no insulin. He has also demonstrated that at the work intensities which he used, the effect of insulin and of work were additive.

On the basis of recent work on the action of insulin, we have postulated that this hormone effects a system which serves to transfer sugars of a definite chemical configuration from the extracellular fluid compartment into certain cells (muscle) (5, 6). Some of the sugars responsive to the action of insulin are not utilizable by muscle. Under the influence of the hormone, they acquire a wider volume of distribution. Because of the similarity of the action of work to that of insulin in respect to blood glucose, we were led to investigate whether, like insulin, it would affect the entry of sugars on the basis of chemical configuration irrespective of utilization. In other words, does work, as well as insulin, act upon some 'cell surface barrier' which is the specific determining factor for the entry of sugars.

METHODS

Both eviscerated-nephrectomized dogs and rats were used. Pancreatectomy was performed on some of the dogs and the animals were allowed to recover for 7 days prior to use in an experiment. During this interval 5-10 U of a slow-acting insulin was administered daily for control of the diabetes. Insulin was withheld for 48 hours before evisceration of the animal. Spinal cord section was performed in some of the rats by cutting the entire spinal column just below the ribs and controlling hemorrhage with pressure from a cotton pledget clipped into place. Work performance consisted of the direct electrical stimulation of one or both hind legs, at the rate of 3 stimuli/sec, which were just supra-maximal. The limbs were made to work against a suspended weight, 2 kg in the case of the dogs and 50 gm in the case of rats. An approximate estimate of the work performed was 150-200 gm-cm/sec, per rat of 200 gm body weight; and 15-20 kg-cm/sec, per dog of 15 kg body weight. In all experiments, sufficient glucose was administered to maintain near normal blood levels. The curve of distribution of the test sugars was determined by administering 1 gm/kg body weight of the substance intravenously. In the experiments with dogs, arterial blood samples were drawn at intervals for 3 hours. In the rats, the blood level of the test sugar was determined at the end of 2-3 hours from the beginning of work performance. Previous experiments had indicated that this was a sufficiently long period for distribution of galactose in total body water under the action of insulin. Sugars which were not responsive to insulin showed a level corresponding to a distribution in about 40-45% of body weight at that time interval.

Methods used for the determination of the various sugars employed are detailed in a previous publication (5) and are summarized in table 1 of the preceding paper (6). d-sorbitol was determined by the method of Todd, et al. (7).

RESULTS

Muscular work exerted an effect on the distribution of three of the sugars tested in rats. This 'responsive' group (fig. 1) included d-galactose, l-arabinose and d-xylose. As we have previously reported in dogs (5), the final blood level achieved in eviscerated-nephrectomized rats by these three sugars corresponded to a distribution in some 40-45% of body weight. Intense muscular work was accompanied by a wider area of distribution and these same sugars exhibited lower blood levels with work, corresponding to a final distribution in 65-70% of body weight, i.e., total body water.

By contrast, the blood levels of the remainder of the sugars tested failed to be influenced by simultaneous intense muscular contraction (fig. 2). Thus, d-arabinose and l-rhamnose achieved final distributions of 40-
"RESPONSIVE" SUGARS

(BLOOD LEVELS 2-3 HOURS AFTER INJECTING 1 Gm./Kg., i.v.)

![Graph showing blood levels of "responsive" sugars during work and rest.]

"NON-RESPONSIVE" SUGARS

(Blood levels 2-3 hours after injecting 1 Gm./Kg. i.v.)

![Graph showing blood levels of "non-responsive" sugars during work and rest.]

Fig. 1. Effect of muscular work on distribution of sugars in eviscerated-nephrectomized rats. Final blood levels of the test sugars are indicated. These substances are nonutilizable in these preparations and 2-3 hours is ample time for complete distribution (6) to occur. For these sugars it can be readily seen that muscular work is accompanied by a wider body area of distribution and hence a lower blood level. Individual experiments are designated by open and closed circles while the columns are average results.

Fig. 2. Distribution of sugars in eviscerated-nephrectomized rats. These sugars are again nonutilizable and the final blood levels at 2-3 hours represent complete distribution of the test sugar. By contrast with the results illustrated in fig. 1, the distribution of these substances is unaffected by muscular work. The various "nonresponsive" sugars achieve different body distributions or "spaces" but in each instance they are the same at work as at rest.

45% in the peripheral tissues of the rat (as previously found in the dog) not only at rest but in the face of severe muscular work. d-Sorbitol remained essentially extracellular in a space of some 30% of body weight irrespective of work. d-Fructose and, to a lesser extent, L-sorbose differ from the other sugars tested in that they were shown to be utilized...
in the eviscerated-nephrectomized dog (6) and presumably in the peripheral tissues of the rat in these experiments. Nevertheless, there is no greater rate of disappearance of these ketohexoses with work.

The effect of work on increasing the rate of glucose uptake by tissues has been shown to be independent of insulin by its demonstration in an insulin-free depancreatized animal. Accordingly, this 'distributing' action of work on nonutilizable sugars was examined in eviscerated-nephrectomized dogs which had been depancreatized a week previously and deprived of insulin for 48 hours. Muscular work effected the same wider distribution of d-galactose into total body water in the diabetic preparation as in the eviscerated normal dog. The same distinction between 'responsive' and 'nonresponsive' sugars as found in the eviscerated-nephrectomized rat with work was demonstrated in the dog. The distribution of d-arabinose was unaffected by work while d-xylose behaved, as did d-galactose, by entering total body water (65–70% body weight) with intense muscular contraction (fig. 3).

Since the contraction of the hind legs, themselves only a fraction of body weight, was promoting the entrance of appropriate sugars into

**Fig. 3.** The distributions of sugars found to be 'responsive' and 'nonresponsive' in peripheral rat tissues are tested here in the dog and compared with the previously reported action of insulin on the distribution of d-galactose (5). Muscular work promotes wider distribution of d-xylose and d-galactose just as insulin does, but fails to influence the behavior of d-arabinose which is nonresponsive to insulin. This insulin-like action of muscular work is just as effective in the chronically depancreatized preparation and is thus independent of insulin.
general systemic as well as local influence of work persisted despite the neurological isolation of the contracting muscles.

**DISCUSSION**

The postulation by this laboratory that insulin acts primarily to promote the faster entry of 'responsive' sugars, independent of any secondary utilization of such substances (5, 6) has led us to question the generally accepted notion that muscular work promotes increased uptake of glucose by virtue of increased rates of utilization of the sugar by the working muscles. The data in this report constitute a parallel phenomenon to that found for insulin, namely that muscular work promotes the entry into certain cells of appropriate sugars which have little, if any, access to these intracellular spaces at rest. Such sugars are not utilisable by the tissues of this preparation and this is a cellular entry phenomenon, independent of the known enzyme systems of metabolic utilization. Muscular work appears to be overcoming some cell surface barrier for certain sugars. These 'responsive' sugars are the same substances previously found to require insulin for transport across the presumed cell surface barrier. Indeed, the chart of sugars 'responsive' to insulin, as previously reported (6), is equally applicable to the description of sugars 'responsive' to muscular work (see fig. 4 of preceding paper, 6). Those sugars which obtain access to the intracellular space of certain cells as a result of muscular contraction, exhibit a common chemical configuration about carbons 1, 2 and 3, the same configuration seen in the structure of d-glucose. It is thus reasonable to postulate that the observed effect of work on increased glucose uptake is identical to the cellular entry phenomenon described here, even though the utilisable nature of glucose does not allow for the distinction between cell entry and intracellular utilization.

Despite the close parallel between the action of insulin and the action of muscular work outlined here, the same effect on glucose uptake, the same 'distributing' action on nonutilized sugars, and the same selective specificity of sugars with a d-glucose carbons 1, 2 and 3 configuration for transport across cell surface barriers, muscular work is independent of the presence of insulin and is operative in the depancreatized, insulin-free animal. Since a local and neurologically isolated vigorously working muscle group can influence sugar uptake by the rest of the body, it can be assumed that the influence is humoral.

![Fig. 4. Effect of hind-leg muscular work on distribution of d-galactose in eviscerated nephrectomized rats. Conditions for d-galactose are the same here as in fig. 1 but with the hind limbs stimulated after section of the lumbar spinal cord. The effect of muscular work in facilitating a wider distribution of the sugar is equally great as in the intact preparation. The final blood level represents a distribution in 68%, i.e. total body water, the locally contracting muscles are exerting an effect throughout the entire animal despite cutting of the nerve connections to the working area, suggesting the involvement of a humoral factor.](http://ajplegacy.physiology.org/)

We are, therefore, postulating that certain cells of the body (muscle primarily) exhibit a barrier of some sort at their surfaces to the entry of many sugars, and that a transport system, activated both by insulin and by a humoral agent of working skeletal muscle, operates to afford cellular entry to sugars possessing a particular chemical configuration. The actual independence or convergence of the insulin and work mechanisms, the limits of specificity of chemical configuration of sugars involved, and the relation of these phenomena to the behavior of the liver in relation to carbohydrates remain to be investigated.

**SUMMARY**

Muscular work is known to increase the rate of uptake of glucose by tissues. In the
eviscerated-nephrectomized animal, the tissues are unable to utilize various sugars including isomers of glucose. Under such experimental conditions, muscular work promotes cellular entry of some of these sugars despite the absence of utilization. This constitutes a phenomenon parallel to that proposed by this laboratory for the action of insulin, i.e., a primary action on facilitating transfer of certain sugars across cell surface barriers. Just as in the case of insulin, work promotes cellular entry of sugars possessing the same chemical configuration as d-glucose at carbons 1, 2 and 3. This action of muscular work is independent of insulin and is exhibited in the depancreatized preparation. Local muscular contraction acts to facilitate sugar entry into total body water and appears to be operating by a humoral mechanism.

It is thus postulated that both insulin and a humoral product of contracting skeletal muscle can activate a transfer mechanism for certain types of sugars across cell surface barriers.

REFERENCES