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INFLUENCE OF THE THYROID GLAND ON THE ACCUMULATION OF SUGARS IN RAT INTESTINAL MUCOSA DURING ABSORPTION

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An impairment of sugar tolerance is a common finding in subjects suffering from hyperthyroidism (Althausen & Weaver, 1937; Abt, 1962) and according to Althausen & Stockholm (1938) the thyroid gland exerts a marked influence on the absorption of sugars by the small intestine of the rat. Although Althausen (1949) has concluded that sugar absorption is increased in hyperthyroidism and decreased in hypothyroidism other workers have been unable to agree that the thyroid hormones exert a stimulating effect on the intestinal transport of sugars, either *in vivo* or *in vitro* (Moseley & Chornock, 1947; Pfleger, Rummel & Jacobi, 1958; Wiseman, 1964). Many differing factors, all of which are difficult to control, are liable to influence the findings in absorption investigations on animals *in vivo* (Althausen & Stockholm, 1938; Fenton, 1945). Since there is now evidence that the processes underlying sugar transport in the mammalian small intestine are associated with the accumulation of sugar in the mucosal tissue and, in particular, in the epithelial cells (McDougall, Little & Crane, 1960; Wilson, 1962; Kinter & Wilson, 1962) we have accordingly examined the effects of the thyroid gland on the capacity of rat intestinal mucosa to accumulate sugars during absorption *in vitro*. A preliminary account of some of our findings has been given (Bronk & Parsons, 1964).

METHODS

At the age of 25–35 days (75–115 g body weight) groups of male albino rats of local stock were surgically thyroidectomized and then maintained on *ad libitum* supplies of a commercial diet (small animal diet, Spillers Ltd., Gainsborough) for a further 40–55 days before intestinal sugar accumulation was examined; at this time the body weights were in the range 160–190 g. The success of the operation of thyroidectomy was deduced from changes in body weight observed post-operatively; only those animals in which the weight gain became restricted to less than 20 % of the normal rate were selected for investigation (Bronk & Bronk, 1962). With this criterion, complete ablation of the thyroid gland was achieved in rather more than 80 % of the operated animals. Forty-five days after operation, one group of thyroidecto-

mized animals was treated with a single dose of 30 μg 3,5,3′:-triiodo-L-thyronine (T_3) injected subcutaneously 2 days before the studies of intestinal accumulation were undertaken.

Sugar accumulation by the mucosa was measured after absorption by cannulated everted sacs of jejunum. A segment of jejunum (10–15 cm, oral end *ca.* 3 cm below ligament of Treitz) was rapidly removed from the decapitated animal and rinsed through with ice-cold 150 mM-Nc Cl solution. The entire segment was gently pushed on to a polythene cannula (3 mm o.d.) and the lower end tied onto a groove in the cannula; the segment was then everted by stripping the wall over the ligated end. The lower end of the everted segment was then tied off with a second ligature. From a syringe attached to fine (1 mm o.d.) polyethylene tubing the sac was filled with about 1·5–2·0 ml. warm, oxygenated incubation medium and it was then immersed in 15 ml. incubation medium which was recirculated with a gas lift. One sac was thus prepared from each animal, an interval of some 45 sec elapsing from the death of the animal to the immersion of the everted sac in the incubation medium. After absorption (usually 20 min), the sac was withdrawn from the incubation medium, the mucosal surface gently blotted and the epithelial layer removed by pulling a microscope slide along the length of the intestinal segment. The mucosal tissue thus collected (300–400 mg wet weight) was divided into two lots; one lot was rapidly weighed, homogenized, and the content of reducing substances determined; on the other lot, the water content and fat-free dry weight were measured so that it was possible to deduce the fat-free dry weight of the sample which was homogenized. The tissue was homogenized with a stainless-steel pestle rotating at 250 rev/min in the presence of 4 ml. zinc sulphate-barium hydroxide contained in a viridia precision-bore glass tube 11 mm i.d. (Chance Bros., Ltd., Smethwick). Fat-free dry weight (FFDW) was determined as described for liver slices by Parsons & van Rossum (1961).

Total reducing substances were estimated by the method of Nelson (1944). Inulin was determined as 'fructose' by the method of Bacon & Bell (1948).

Oxygen consumption of the whole intestinal wall was measured polarographically as follows. Rings of jejunum (1–2 mm thick) were incubated in 2·5 ml. of medium in a cylindrical glass vessel provided with a water jacket. The medium was previously gassed (air 95% v/v CO_2 5% v/v). The contents of the vessel were maintained at 38 ± 0·1° C. Changes in O_2 tension in the medium were followed with a Clark O_2-electrode (Yellow Springs Instrument Co.) as described for mitochondria by Kielley & Bronk (1958). Changes in O_2 tension were followed over periods of up to 3 min. There was negligible tissue disintegration during the period of measurement.

The incubation medium contained (m-mole/litre) NaCl, 113; $NaHCO_3$, 25; KCl, 4·5; $MgSO_4$, 1·0; $CaCl_2$, 1·25; NaH_2PO_4, 0·2; Na_2HPO_4, 1·8. Equilibrating gas mixture, O_2 95% v/v, CO_2 5% v/v. Other substances were added to the incubation fluids where necessary at concentrations indicated below.

RESULTS

As a test of the utility of the method for the study of sugar transport in the intestinal mucosa, the capacity of the tissue to accumulate sugars was examined. Preliminary experiments indicated that an absorption period of 20 min was sufficient for optimum sugar accumulation in the mucosal tissue and that the accumulation of sugar in the intestinal tissue remaining after the mucosa had been removed (i.e. the muscle coats) was always less than in the mucosa. Accordingly measurements were made of the tissue accumulation after 20 min absorption of some sugars which are classically described as being either 'actively absorbed' or 'passively absorbed' by the intestine. In addition the effects of certain inhibitors were examined.

The results are given in Tables 1 and 2. The age of the animals at the time of these experiments was in the range 60–90 days. The findings are expressed in two different ways. The tissue accumulation represents the amount of reducing substance expressed as sugar referred to unit fat-free dry weight of mucosa. The tissue-medium concentration ratio (T/M) represents the final concentration of sugar in the tissue water divided by the sugar concentration present in the mucosal fluid at the end of the absorption period. The value of T/M is equivalent to the fraction of the tissue water which is penetrated by the substance under study. Thus for a value of T/M which is less than unity, the substance in question behaves as if it does not penetrate the whole of the mucosal-tissue water and a value which is greater than unity implies that the substance is concentrated in the tissue water of the mucosa, i.e. is subjected to active transport.

TABLE 1. Accumulation of sugars measured as reducing substance in rat jejunal mucosa after 20 min absorption. Initial sugar concentration mucosal and serosal fluids 5·5 mM, except where indicated. Values are of means ± S.E. of mean (no. of observations)

Sugar	Tissue accumulation (mg/g FFDW)	Concentration in tissue fluid / Concentration in mucosal fluid
D(−)-Arabinose	2·9 ± 0·1 (7)	0·66 ± 0·03 (7)
L(+)-Arabinose	3·3 ± 0·2 (7)	0·76 ± 0·03 (7)
D(+)-Xylose	6·3 ± 0·3 (11)	1·01 ± 0·03 (11)
Galactose	13·9 ± 0·6 (14)	2·28 ± 0·13 (14)
3-O-Methyl glucose	13·5 ± 0·1 (8)	2·42 ± 0·06 (8)
Galactose (28 mM)	38·1 ± 1·6 (6)	1·49 ± 0·05 (6)

It is seen from Table 1 that under our experimental conditions galactose and 3-O-methyl glucose are accumulated in the mucosal tissues during 20 min absorption, that D-xylose appears to be distributed uniformly throughout the mucosal tissue, i.e. penetrates the tissue, but is not accumulated and that arabinose appears not to penetrate the whole tissue water (T/M < 1). In control experiments with normal 80-day-old rats, the residual substances found in the intestinal mucosal layers after incubation for 20 min with no added sugar amounted to 0·72 ± 0·16 (8) mg g^{-1} fat-free dry weight (expressed as galactose). We have also determined the fraction of the mucosal-tissue water (α, Parsons & van Rossum, 1961) which is derived from the mucosal fluid by measuring the penetration of inulin present in the mucosal incubation fluid (1 g/100 ml.) during 20 min absorption with galactose present. Under these circumstances α_{inulin} = 0·063 ± 0·01 (6). We have not corrected the data given in Table 1 for the sugar present in this mucosal fluid fraction of the extracellular fluids of the tissue. From the data in Table 2 it is seen that the tissue accumulated is abolished when lithium is substituted for the sodium in the incubation medium, but that the substitution does not prevent the penetration of the sugar into the tissue water (T/M = 1). Phlorrhizin at concentrations of 10^{-4} M in the

mucosal fluid not only abolishes the ability of the tissue to accumulate galactose, but also inhibits the penetration of the sugar to the whole of the tissue fluid (T/M < 1). At 10^{-7} M concentration, there is still some inhibition of the tissue accumulation of sugar. In our preparation the presence of strophanthin G (10^{-4}M) in the mucosal fluid does not inhibit the sugar accumulation by the mucosal tissue. In the absence of Ca^{2+} and Mg^{2+}, 2 mM EDTA

TABLE 2. Effects of inhibitors in mucosal fluid on accumulation of galactose in rat jejunal mucosa after 20 min absorption. Initial galactose concentration in mucosal and serosal fluids 5·5 mM. Values given are of means ± S.E. of mean (no. of observations)

Addition	Concentration (M)	Tissue accumulation (mg/g FFDW)	Concentration in tissue fluid / Concentration in mucosal fluid
None	—	13·8 ± 0·6 (14)	2·28 ± 0·3 (14)
Lithium substituted for sodium	138×10^{-3}	4·0 ± 0·2 (6)	0·91 ± 0·04 (6)
Strophanthin G	$1·3 \times 10^{-4}$	12·2 ± 1·1 (6)	2·84 ± 0·39 (6)
$-Ca^{2+}-Mg^{2+}$+EDTA*	$2·0 \times 10^{-3}$	7·0 ± 0·8 (6)	1·27 ± 0·10 (6)
Phlorrhizin	10^{-7}	10·8 ± 0·2 (4)	1·87 ± 0·12 (4)
	10^{-6}	7·7 ± 0·6 (7)	1·39 ± 0·2 (7)
	10^{-5}	5·8 ± 0·2 (6)	1·01 ± 0·02 (6)
	10^{-4}	4·2 ± 0·2 (10)	0·74 ± 0·02 (8)

* EDTA = diamino-ethane-tetraacetic acid.

in the mucosal fluids inhibits, but does not abolish, sugar accumulation. From our results we conclude that the measurement of the ability of the mucosal tissue to accumulate sugars during absorption appears to be a suitable quantitative method for investigating the properties of the intestinal translocative system for sugars.

Effects of thyroidectomy on sugar accumulation

One consequence of thyroidectomy in the young rat is a considerable reduction in the average rate of growth of the operated animals. The growth rates of the thyroidectomized animals used in our experiments are given in Table 3. It is seen that during the first post-operative week the growth

TABLE 3. Growth rates of thyroidectomized rats. Normal rate of linear growth over body weight range (116·8–215·5 g) 7·05 ± 0·32 (11) g day^{-1}

Days post-thyroidectomy	Gain in body wt. (g day^{-1}) A. 0–7	B. 21–42	% $B/A \times 100$
Animal group ...			
Galactose accumulation	4·92 ± 0·42 (8)	0·836 ± 0·093 (8)	17
Xylose accumulation	4·26 ± 0·51 (6)	1·05 ± 0·24 (6)	25
Physical characteristics	4·20 ± 0·34 (5)	0·362 ± 0·049 (5)	9
Oxygen uptake	4·24 ± 0·40 (6)	0·646 ± 0·151 (6)	15
Treated with T_3			
Galactose accumulation	4·29 ± 0·47 (8)	0·818 ± 0·098 (8)	19
Oxygen uptake	4·40 ± 0·28 (8)	0·702 ± 0·223 (8)	16

of the animals continues at a substantial rate which falls by the fourth week to a low level. We therefore undertook two main sorts of control measurements for the investigations of the effects of thyroidectomy on the mucosal-sugar accumulation during absorption. In one set ('age controls') the accumulation was measured in the intestinal mucosa of normal unoperated rats of the same age as the thyroidectomized animals (65–90 days, body weights 300–340 g). In the other set ('weight controls') the accumulation was measured in the intestinal mucosa of normal unoperated rats of the same body weight as the thyroidectomized animals (160–190 g). The ages of these control animals were from 40 to 50 days. In these animals and in the thyroidectomized animals the accumulation of galactose and

TABLE 4. Accumulation of galactose in mucosal tissue of rat jejunum after 20 min absorption. Initial concentration of sugar in mucosal and serosal fluids 5·5 m-mole/l. Values are means ± S.E. mean (no. of observations)

Animals	Mucosal tissue accumulation (mg/g FFDW)	Concentration in tissue fluid / Concentration in mucosal fluid
Thyroidectomized	14·51 ± 0·56 (8)	2·58 ± 0·13 (8)
Thyroidectomized injected with T_3	18·86 ± 0·97 (8)	3·07 ± 0·19 (8)
Age controls	13·88 ± 0·62 (14)	2·28 ± 0·13 (14)
Weight controls	12·14 ± 0·41 (14)	2·14 ± 0·09 (14)

TABLE 5. Accumulation of xylose in mucosal tissue of rat jejunum after 20 min absorption. Initial concentration of sugar in mucosal and serosal fluids 5·5 m-model/l. Values are means ± S.E. of mean (number of observations)

Animals	Mucosal tissue accumulation (mg/g FFDW)	Concentration in tissue fluid / Concentration in mucosal fluid
Thyroidectomized	5·41 ± 0·16 (6)	0·93 ± 0·02 (6)
Age controls	6·30 ± 0·27 (11)	1·01 ± 0·03 (11)
Weight controls	5·77 ± 0·34 (15)	0·96 ± 0·04 (15)

D(+)-xylose was examined. The findings, which are presented in Tables 4 and 5 indicate that removal of the thyroid gland does not impair the ability of the intestinal mucosa to accumulate galactose and does not affect the penetration of xylose into the mucosal tissue. It would thus appear that in the absence of the thyroid gland there is no major deficiency in the processes underlying the 'active transport' of galactose by the intestinal mucosa of the rat.

After treatment with 3,5,3′:-triiodo-L-thyromine (T_3) there is an increase in the capacity of the mucosal layers of the thyroidectomized rats to accumulate galactose measured as reducing substances referred to as unit fat-free dry weight ($P < 0·01$). For the ratio (galactose concentration in tissue fluid)/(galactose concentration in medium), the mean value found in the mucosae of the thyroidectomized animals which had been

treated with T_3 was significantly higher than the ratio found with either group of controls ($P < 0{\cdot}01$), although it was not significantly higher than the mean for the thyroidectomized animals ($P > 0{\cdot}05$).

Effects of thyroidectomy on respiration of rat intestinal wall

We have measured the respiration rates of rings of rat jejunum whole wall suspended in incubation medium at 38° C. The measurements were made on rings cut from three sorts of animals, namely, from normal 80-day-old control animals, from thyroidectomized animals and from thyroidectomized animals which had been treated with T_3. Taking the mean value of the respiration rate per unit fat-free dry weight for the normal animals as 100, our findings were as follows, normal animals, $100 \pm 3{\cdot}60$ (11), thyroidectomized, $104{\cdot}0 \pm 6{\cdot}25$ (6), thyroidectomized treated with T_3, $126 \pm 7{\cdot}17$ (8). We conclude that thyroidectomy does not affect the respiration rate of the whole wall of rat jejunum but that treatment of thyroidectomized rats with T_3 increases the respiration rate above the value found for both normal ($P < 0{\cdot}01$) and thyroidectomized ($P < 0{\cdot}05$) animals.

Effects of thyroidectomy on the physical characteristics of rat small intestine

Although thyroidectomy is without marked effect on the ability of the rat small intestinal mucosa to accumulate galactose when this accumulation is referred to unit dry weight, the capacity of the whole intestine to absorb *in vivo* might be influenced by the thyroid if the gland produced effects, for example, on the total length of the small intestine or on the dry weight per unit of intestinal length. We have therefore measured some of these physical parameters of the small intestine of 80-day-old rats and the findings are given in Table 6. We find that thyroidectomy at the age of 25 days produces no marked effect on the total length of the small intestine but that the total dry weight, the fat-free dry weight and the tissue water per cm of jejunum are markedly reduced.

TABLE 6. Physical characteristics of small intestine of male albino rats. Animals 80 days old (normal body weight approx. 300 g unless as indicated). Values are means ± S.E. of mean

	Normal	Thyroidectomized	Normal / Thyroidectomized
Length of whole small intestine (cm)			
180 g body wt.	$107{\cdot}8 \pm 1{\cdot}9$ (11)	$105{\cdot}9 \pm 1{\cdot}75$ (15)	1·02
330 g body wt.	$112{\cdot}9 \pm 2{\cdot}1$ (12)		1·07
Jejunal dry wt. (mg cm^{-1})	$17{\cdot}4 \pm 1{\cdot}7$ (8)	$11{\cdot}9 \pm 0{\cdot}8$ (5)	1·46
Jejunal FFDW (mg cm^{-1})	$14{\cdot}5 \pm 1{\cdot}0$ (8)	$9{\cdot}2 \pm 0{\cdot}5$ (5)	1·58
Jejunal tissue water (mg cm^{-1})	$63{\cdot}6 \pm 5{\cdot}1$ (8)	$42{\cdot}4 \pm 2{\cdot}9$ (5)	1·50

DISCUSSION

Our findings indicate that there is no major impairment of the processes underlying the 'active transport' of sugar by the jejunum of the thyroidectomized rat. Our evidence for this view derives from the fact that in both normal and thyroidectomized animals the mucosal layers possess the capacity to accumulate galactose and that the concentration of galactose achieved in the tissue fluids after 20 min absorption is still between 2 and 3 times that in the fluid bathing the mucosal surface in the thyroidectomized animals. It will be seen that in the case of sugars such as galactose which are accumulated in the tissue, correction of the experimental findings for the sugar contained in the fraction of the tissue water which is mucosal fluid (α) will give an increased value for the average concentration in the mucosal cellular and submucosal extracellular fluids. In the case of sugars such as arabinose which appear to be excluded from part of the intestinal mucosal tissue water, correction of the experimental findings for the sugar contained in the mucosal fraction of the tissue fluids (α) will give a lower value for the average concentration in the mucosal cellular and submucosal extracellular fluids.

The finding that thyroidectomy does not produce a major deficiency of sugar transporting mechanisms in rat jejunum may be related to the fact that in the thyroidectomized animals there is no impairment of the mucosal tissue respiration although such animals exhibit a marked depression of the respiration of, for example, liver mitochondria (Bronk & Bronk, 1962; Bronk, 1963).

Our findings for sugar accumulation and for the respiration of the intestinal mucosa have been expressed in terms of unit fat-free dry weight of the tissue. The question arises as to what is a satisfactory reference framework to which sugar accumulation or respiration can be related. Similar difficulties have arisen in connexion with the description of the composition of other tissues, e.g. liver (Parsons & van Rossum, 1963). It would appear from the data presented in Table 6 that hypothyroidism has a relatively small effect on the total length of the small intestine but does markedly reduce the solid and the fluid content of unit length of the jejunum. If in the animals *in vivo* the mesenteric vascular circulation clears most of the sugar which we have found to accumulate in the mucosal layers *in vitro*, it is of interest to calculate the extent to which thyroidectomy is likely to affect the sugar clearance from a 10 cm segment of jejunum. On the basis that the mucosal dry weight in both normal and hypothyroid animals constitutes one half of the intestinal dry weight, then the clearance from a 10 cm segment over a 20 min period of the galactose absorbed from a 5·5 mM solution would be 1·01 mg for the 80-day-old

control animals and 0·67 mg for the thyroidectomized animals. A similar sort of calculation shows that the oxygen consumption of a length of jejunum of a thyroidectomized animal would also be expected to be about 66 % of that found for the same length of jejunum of an 80-day-old control animal. Thus, although we find that in the thyroidectomized animals there is no fundamental impairment of the processes underlying sugar transport or depression of the rate of oxygen consumption of the rat jejunum, the results do in fact suggest that both the total absorptive capacity and the total rate of oxygen consumption of the intestine will be depressed in the thyroidectomized animals. Our findings are therefore not at variance with the conclusions of Althausen (1949) that sugar absorption is decreased in hypothyroidism *in vivo*.

Our data show that the removal of the thyroid has a profound effect on the water content and on the dry weight of the small intestine. In addition, removal of the thyroid gland produces marked changes in the growth rate of young animals (e.g. Table 3). The intestinal mucosa is a tissue with a high rate of growth and of cellular turnover (Leblond & Walker, 1956). Further, Leblond & Carriere (1955) have found that in the duodenum of surgically thyroidectomized rats, the number of dividing cells in the crypts of Lieberkühn is reduced to about 60 % of the control value. All these facts lead us to conclude that the secretions of the thyroid gland may promote the growth of the intestinal wall and in particular the growth of the intestinal mucosa. Clearly the influence of the thyroid gland on intestinal mucosal growth warrants further investigation, although a comparison of histological sections and examination of the villus architecture with the stereoscopic dissecting microscope does not reveal any striking differences in the gross morphological appearances of tissues taken from normal control and hypothyroid animals. It is of interest in this connexion that recently Levin & Smyth (1963) have reported that in rats injected with 0·3 mg thyroxine daily over a period of 21–28 days, the wet weight of the small intestine is increased. However, no data are available in this instance to determine to what extent the weight increase is due to changes in either the water content or the dry weight per unit length of the hyperthyroid intestine.

The fact that the administration of T_3 to the hypothyroid animals increases the capacity of unit fat-free dry weight of the intestine to accumulate galactose implies that the sugar accumulation per unit length of the intestine will be increased as the result of the administration of T_3. We therefore conclude that the administration of T_3 increases the absorptive capacity of the intestine for galactose, again in general accord with the conclusions of Althausen (1949).

Finally, we must point out that our observations on the effects of

thyroidectomy on the ability of the intestinal mucosa to accumulate sugars during absorption have been undertaken on animals which have been subjected to surgical thyroidectomy some 7–8 weeks previously. Thus our finding that after a lapse of this time there is no impairment of the processes underlying the accumulation of sugar in unit dry weight of jejunal mucosa does not necessarily mean that the secretions of the thyroid are without effect on these processes. Administration of T_3 to thyroidectomized animals certainly increases after two days the accumulative capacity of the intestinal mucosa towards galactose, and long standing removal of the thyroid gland may lead to the production of compensatory effects by some other organ. In this case the effects of the administration of T_3 to chronically thyroidectomized animals may also involve responses mediated through another organ.

SUMMARY

1. A method is described for measuring the accumulation of sugars by rat intestinal mucosa during absorption *in vitro*.

2. In surgically thyroidectomized animals there is no impairment of the ability of unit fat-free dry weight of the intestinal mucosa to accumulate galactose and the penetration of D(+)-xylose into the mucosal tissue is unaffected. After treatment of thyroidectomized animals with 3,5,3′:-triiodo-L-thyronine (T_3) there is an increase in the capacity of unit fat-free dry weight of the mucosal layers to accumulate galactose during absorption.

3. The respiration of unit fat-free dry weight of the whole wall of the jejunum is not different from that of normal animals. The administration of T_3 to thyroidectomized animals increases the respiration rate to above the value found for normal and thyroidectomized animals.

4. The total dry weight, the fat-free dry weight and the tissue water per cm of jejunum are markedly reduced in thyroidectomized animals, but the total length of the small intestine is but little affected.

5. Reasons are given for supposing that the thyroid gland may influence the growth of the small intestinal mucosa. It is concluded that although there is no fundamental impairment of the processes underlying sugar transport or respiration in rat jejunum, the absorptive capacity for sugar and the rate of oxygen consumption of the intestine are depressed in thyroidectomized animals.

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