Stimulation in Vitro of Pathways of Glucose Oxidation in Thyroid by Thyroid-stimulating Hormone

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Despite many observations on morphologic and biochemical changes in the thyroid after the administration of thyroid-stimulating hormone, its exact mechanism of action is still obscure (1, 2). The earliest in vitro effect previously reported was a small increase in oxygen consumption 10 minutes after the addition of TSH to thyroid slices (3). TSH has also been found to increase phospholipid synthesis and iodide trapping, organification of iodide, and thyroid hormone release, but these effects have been somewhat delayed (4, 5).

In a preliminary note we reported evidence for the existence of the hexose monophosphate pathway for glucose metabolism in thyroid slices and the ability of TSH to increase glucose oxidation (6). Stimulation of glucose oxidation was evident 5 minutes after the addition of TSH. Although not as dramatic as its effect on glucose-l-Cl4 oxidation, there was also some increase in glucose-6-C14 oxidation to C14O2 when TSH was present. This effect of TSH was not elicited when ACTH, prolactin or growth hormone were tested. The purpose of this communication is to elaborate on this observation as well as to present some information regarding possible mechanism of action.

EXPERIMENTAL PROCEDURE

Calf thyroids were obtained at the abattoir and kept on ice until sliced. Within an hour after the animals were killed, slices varying between 100 and 200 mg were made with a Stadie-Riggs slicer, lightly blotted on filter paper and weighed on a torsion balance. Each slice was placed in a 25-ml Erlenmeyer flask containing 2 ml of Krebs-Ringer bicarbonate buffer (pH 7.4), 0.5 \( \mu \)e of either glucose-1-C14 or glucose-6-C14 (purchased from the National Bureau of Standards), and either 2 or 5 mg of glucose. All substrates tested were dissolved in buffer. The flasks were gassed with 95% O2 and 5% CO2 and incubated in a Dubnoff metabolic shaker at 37° for 45 minutes. At the end of the incubation period there is still evidence of a stimulating effect of TSH, although by this time the difference between the control and stimulated slices is not as great as at earlier times. Previously we noted a small effect from one preparation of FSH which could be explained on the basis of its known contamination with a small amount of TSH (8). Another preparation of FSH which contained very little TSH gave no stimulation (Table I).

Table III indicates that other drugs which are known to interfere with thyroidal iodine metabolism do not appear to effect the conversion of glucose-C14 to C14O2. Although propylthiouracil by itself had no effect on glucose-1-C14 oxidation to C14O2 in thyroid slices, it did appear to inhibit partially the stimulating effect of TSH. Other antithyroid drugs did not modify the TSH effect (Table III).

Glucose oxidation was not altered by the addition of 10 \( \mu \)e of either thyroxine or triiodothyronine to the medium. The response of glucose oxidation to C14O2 to

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1 The abbreviations used are: TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropin; FSH, follicle stimulating hormone.
various amounts of TSH is indicated in Table IV. This effect of TSH is not limited to calf thyroid slices, since the same result has been obtained with slices from normal human thyroid. In this latter case it was also possible to observe stimulation within 5 minutes of the addition of TSH. It is most unlikely that the effect of TSH is a nonspecific protein effect, since other proteins such as albumin, insulin, and plasma proteins produced no stimulation of glucose oxidation to \( \text{CO}_2 \) and in some cases there was a suggestion of an inhibitory action (Table IV).

In an attempt to delineate the mechanism of this TSH effect, the action of the hormone was measured on glucose uptake by thyroid slices. In these studies the period of incubation was 4 hours. Experiments of shorter duration led to inconclusive results. Table V demonstrates that TSH does increase glucose uptake by thyroid slices. Although this same effect can be produced by insulin, it is not a nonspecific protein effect, since albumin and ACTH were inactive. There was no increase in the combined activity of glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase of thyroid slices incubated with TSH as compared with control activity. Slices in the control slices averaged 105 units per g (99 to 109) as compared to 103 units per g (91 to 114) in the TSH-treated slices.

Thyroid slices obtained from a rabbit treated with propylthiouracil for 2 months converted more glucose-1-\( \text{C}^4 \) and glucose-6-\( \text{C}^4 \) to \( \text{CO}_2 \) than slices obtained from normal rabbits, although glucose-1-\( \text{C}^4 \) oxidation still predominated. In addition, TSH was without effect when added to the slices from the treated rabbit.

**DISCUSSION**

The specificity of the effect of TSH on glucose oxidation to \( \text{CO}_2 \) in thyroid slices is indicated by the fact that none of the other pituitary hormones tested was active, and that TSH produced no changes in either liver or testis. In addition to its specificity, this action of TSH is apparent within 5 minutes after the addition of the hormone. Since this effect occurs earlier than all those previously reported (2), it suggests that the primary action of TSH is on glucose metabolism by the thyroid. In these experiments the most impressive change is oxidation of glucose-1-\( \text{C}^4 \) to \( \text{CO}_2 \), presumably by the hexose monophosphate pathway. The generation of TPNII by this pathway has been emphasized recently in relation to various synthetic reactions, especially fatty acid synthesis (10). Furthermore, Stanford and Morris (11) have reported a deiodinase in thyroid which specifically requires TPNH. It is conceivable that increased production of TPNH and fatty acid synthesis could ac-
primary action on glucose metabolism. Insulin also increases glucose uptake by thyroid slices, yet there is no increased oxidation of glucose to \(^{14}C_2O_2\) (Table IV). The insulin effect is presumably mediated by an increase in glucose transport into the cell (13) and also stimulates glucose oxidation to \(^{14}C_2O_2\). This difference suggests that TSH stimulates glucose oxidation by some other means, and that the increased glucose uptake is secondary. It further suggests that in the thyroid the rate-limiting step for glucose oxidation is not the rate of entry of glucose into the cell. The effect of TSH on glucose uptake appears to be specific, since albumin and ACTH were unable to increase glucose uptake. The failure of TSH to increase the activities of glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase is not surprising, since it is more likely that the level of TPN controls the activity of the hexose monophosphate pathway (13).

**SUMMARY**

Thyroid-stimulating hormone in vitro is capable of stimulating oxidation of glucose-1-\(^{14}C\), and to a lesser extent of glucose-6-\(^{14}C\), to \(^{14}C_2O_2\) in thyroid slices. This effect appears to be specific, since adrenocorticotropic, prolactin, growth hormone, and follicle-stimulating hormone were inactive and thyroid-stimulating hormone had no effect on liver or testis slices. Since an effect was apparent within 5 minutes after the addition of thyroid-stimulating hormone, it is suggested that this might be the primary action of the hormone on the thyroid gland and its effect on phospholipid synthesis and iodine metabolism are secondary. None of the anti-thyroid drugs interfered with glucagon oxidation to \(^{14}CO_2\), although there was some inhibition of the thyroid-stimulating hormone effect when propylthiouracil was present.

Although thyroid-stimulating hormone causes an increased glucose uptake by thyroid slices, this does not appear to be the mode of action of the hormone, since insulin also increases glucose uptake but does not stimulate glucose oxidation. Thyroid-stimulating hormone does not increase the levels of glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase.

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**TABLE IV**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount per flask (mg/l)</th>
<th>Glucose uptake* (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>2 mg</td>
<td>2.95 ± 0.22 (4)</td>
</tr>
<tr>
<td>TSH</td>
<td>1 unit</td>
<td>3.70 ± 0.30 (4)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 unit</td>
<td>3.64 ± 0.26 (4)</td>
</tr>
</tbody>
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*Mean ± standard error.
†Number of determinations.
REFERENCES

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