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Action of Thyroxin on Tissue Respiration.*

J. A. DYE.

From the Department of Physiology, Cornell University.

Experiments in which thyroxin, or thyroid substance, has been added directly to surviving animal tissues *in vitro* have given, almost without exception, negative results. This might have been expected since the maximum action from a single dose of thyroxin *in vivo* is reached only after several days while the tissue survival is for about an equal number of hours. Respiration experiments on tissues taken from cretin and thyroxinized animals have given variable results. The reports of several workers,[1-7] however, offer rather convincing proof of a direct thermogenic action of thyroxin on the body tissues. The present work was begun to study the nature of this thermogenic action.

The oxygen consumption (QO_2) of muscle fasciculi was measured volumetrically by means of differential microrespirometers (Fenn). The animals were routinely anesthetized with amytal for 30 minutes after which they were bled from the carotid artery. The left semimembranous muscle was quickly removed and the muscle strips carefully prepared according to the method of Richardson,

* This work was aided by a grant from the Heckscher Research Foundation of Cornell University.

1 Rohrer, A., *Biochem. Z.*, 1924, **145**, 154.

2 Hopping, A., PROC. SOC. EXP. BIOL. AND MED., 1930, **28**, 726.

3 Gerard, R. W., and McIntyre, M., *Am. J. Physiol.*, 1933, **103**, 225.

4 Adler, L., and Lipschitz, W., *Arch. f. exp. Path. u. Pharm.*, 1922, **95**, 181, 206, 225, 236.

5 Neuschloss, S. M., *Klin. Wochenschr.*, 1924, **3**, 57.

6 Ahlgren, G., *Skan. arch. f. Phys.*, 1925, **47**, supp. 225.

7 Dye, J. A., and Maughan, G. H., PROC. SOC. EXP. BIOL. AND MED., 1929, **26**, 439, 441.

Shorr, and Loebel.[8] These were suspended in the microrespirometer flasks in buffered saline, pH 7.35, or in the same solution with 0.9 mg. of lactic acid per cc. The air in the flasks was replaced with oxygen. The CO_2 was absorbed by 5 drops of N NaOH solution. The time interval before the microrespirometers were placed in the water bath was 35 minutes. A temperature equilibration of 30 minutes was always allowed (bath T. 38°C.). The tests usually ran for 7 hours. Bacteriological precautions were carefully taken. The tissues were later dried to constant weight at 110°C.

A 36-hour fast in normal pups diminishes the QO_2 of surviving muscle strips by about 21% when compared with that of non-fasting animals. Those of fasting normal animals consumed 2.73 cmm., those of thyroidectomized animals 2.06 cmm. per mg. of dry tissue per hour. Whether fasting or not the QO_2 of muscles from thyroidectomized pups is reduced by about 24.2%. When glucose, but not lactic acid, is added, this reduction in oxygen consumption is only 20%. This might indicate that these tissues handle glucose better than lactic acid. An increase in QO_2 varying from 4 to 9% is obtained by the addition of lactic acid and glucose to the suspension fluid.

The QO_2 values for similar muscle strips taken from pups which had been fed thyroxin tablets (Squibbs, daily; a total of 168 mg. in 35 days) show a comparable oxygen consumption of 4.07 cmm. This represents a 50% increase for thyroxinized animals' muscle strips (first hour) when suspended in saline. When lactic acid was added this increase was only 36.6%. The QO_2 percentages, however, differed in the 2 groups of animals during the succeeding hours. The decline in QO_2 was relatively steeper in the tissues from thyroxinized animals whether or not lactic acid was added. The same gradient decline was steeper in tissues suspended in saline whether the animal was thyroxinized or not, and was greater in thyroxinized than in control animals. The QO_2 of thyroxinized tissue during the seventh hour was only 21.1% greater for saline and only 5.9% greater for lactic acid than in the normal.

These results seem to be explained best by assuming two facts: (1) Thyroxin feeding increases the oxidative capacity of muscle, probably by increasing the tissue oxidases, and (2) due to this increased oxidative capacity the available substrate is exhausted more rapidly. This is shown exceptionally well by the tissues from one thyroxinized animal which gave a QO_2 of 4.28 cm. per mg. of

[8] Richardson, H. B., Shorr, E., and Loebel, R. O., *J. Biol. Chem.*, 1930, **86**, 551.

dry tissue per hour for the first hour, but which fell off 61.7%, 25.5%, and 4.8% during the second, third, and fourth hours, respectively. In the present series of experiments the average rates of decline per hour were 7.5% for normal and 8.8% for thyroxinized animals. When lactic acid was added these declines were somewhat lower, 6% and 7.9% respectively.

The possibility of thyroxin acting as a catalyst is not ruled out, but evidence in agreement with the above expressed point of view is found in the results of Ahlgren,[6] Adler and Lipschitz,[4] Neuschloss,[5] and by previous work from this laboratory.[7, 9]

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Adrenal Cortical Hormone and Tissue Respiration.*

J. A. DYE.

From the Department of Physiology, Cornell University.

Aub, Forman, and Bright[1] reported a 25% decrease in basal metabolism in totally adrenalectomized cats. Injections of extracts at that time available were without effect in increasing this diminished metabolism.[2] Variable results have been reported by others.[3-6] Swingle, Pfiffner, and Webster[7] have shown that the basal metabolism of bilaterally adrenalectomized cats falls progressively from the 6th day postoperative to a level approximately 50% below normal when the animal becomes prostrated. Administrations of adrenal cortical extract to prostrate animals raises the metabolism within 24 to 48 hours, this may reach a point from 10 to 18% above normal in 48 to 72 hours. Upon discontinuing the injections the metabolism returned to normal. These same

[9] Dye, J. A., and Waggener, R. A., *Am. J. Physiol.*, 1928, **85**, 1, 365.

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[1] Aub, J. C., Forman, J., and Bright, E. M., *Am. J. Physiol.*, 1922, **61**, 326.

[2] Aub, J. C., Bright, E. M., and Forman, J., *Am. J. Physiol.*, 1922, **61**, 249.

[3] Golyakowski, Vrach., St. Petersburg, 22, 1017.

[4] Marine, D., and Bauman, E. J., *Am. J. Physiol.*, 1921, **57**, 135.

[5] Scott, W. J. M., *J. Exp. Med.*, 1922, **36**, 199.

[6] Gracinescu, A. V., *Pflüger's Arch.*, 1913, **152**, 187.

[7] Swingle, W. W., Pfiffner, J. J., and Webster, B., PROC. SOC. EXP. BIOL. AND MED., 1930, **28**, 728.