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Effect of Thyromimetic Agents on Oxygen Uptake of Rat Heart and Liver.* (24523)

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Barker and Lewis(1) and Barker(2) reported results which indicated that heart slices obtained from thyroidectomized rats treated with L-triiodothyronine or triiodothyroacetic acid elicited an earlier and more dramatic increase in the Q_{O_2} value than did other organ tissue slices. It is conceivable, as Boyd and Oliver(3) pointed out, that although certain thyroidal agents might not elicit a rise in total body oxygen consumption, they might exert a significant effect on the heart. The danger of administering such a compound to patients with past histories of coronary disease is readily apparent. If the results of Barker and Lewis and Barker could be confirmed, the method would serve as a means of ascertaining to what degree a thyroidal agent will stimulate the heart in reference to other organs. With these thoughts in mind, experiments were performed to determine the relationship of the effects of sodium L-3:5:3′-triiodothyronine (triiodo), 3:5:3′-triiodothyroacetic acid (triac) and thyroxamine on total body oxygen consumption and oxygen uptake of heart and liver slices of intact and thyroidectomized rats.

Methods. Total body oxygen consumption of fasted young adult intact rats was determined(4) prior to treatment. With thyroidectomized rats degree of induced hypothyroidism was determined at least one month following surgery. Rats with an oxygen consumption less than 20% of the simultaneously determined intact control values were considered hypothyroid. The intact and hypothyroid rats were then injected subcutaneously 4 days with either triiodo (0.5 mg/kg/day) or triac (2 mg/kg/day). An additional group of hypothyroid rats was injected 4 days with thyroxamine† (4 mg/kg/day). Fasted total body oxygen consumption was again determined on the fourth day prior to receiving the last injection of drug. On the fifth day the animals were sacrificed by stunning and exsanguination. Heart and liver slices were prepared by the use of a Stadie-Riggs tissue slicer. Oxygen uptake was determined in duplicate by direct method of Warburg using Krebs-Ringer phosphate fortified with 100 mg% glucose at 37°C with oxygen as the gas phase.

Results. In intact rats both triiodo and triac significantly ($P<0.01$) increased total body oxygen consumption and Q_{O_2} values for heart and liver (Table I). However, there was no significant difference in degree of response elicited by heart and liver in either the controls or in the triiodo or triac treated group. These data indicated that the heart did not respond more dramatically than the liver as proposed by Barker and Lewis(1) and Barker(2).

Thyroidectomized controls exhibited a significantly lower total body oxygen consump-

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† Obtained from Glaxo Labs., Ltd.

TABLE I. Effect of Various Thyromimetics on Total Body O_2 Consumption and Qo_2 of Heart and Liver Slices.

Group	mg/kg /day	Total body O_2 consumption, L/SqM/hr (Day 4)	Qo_2/mg wet wt (Day 5)	
			Heart	Liver
Intact controls		7.6 ± .6*(9)†	1.11 ± .29 (8)	1.18 ± .08 (9)
" + triiodo‡	.5	10.9 ± .1 (11)	1.83 ± .47 (11)	1.80 ± .31 (11)
" + triac§	2	10.0 ± 1.0 (10)	2.01 ± .65 (10)	1.82 ± .27 (10)
Thyroidectomized controls		5.0 ± .4 (14)	1.12 ± .19 (12)	1.10 ± .14 (14)
" + triiodo	.5	9.0 ± 1.1 (8)	1.95 ± .33 (9)	1.95 ± .31 (9)
" + triac	2	8.4 ± .8 (9)	2.06 ± .41 (9)	1.86 ± .36 (9)
" + thyroxamine	4	5.5 ± .9 (7)	1.65 ± .12 (6)	1.25 ± .14 (8)

* Mean ± S.D. † No. of animals. ‡ L-3:5:3′-triiodothyronine. § 3:5:3′-triiodothyroacetic acid.

tion ($P<.001$); however Qo_2 values of heart and liver were not significantly decreased. These results are in disagreement with those presented by others(5-8).

A significant increase in total body oxygen consumption ($P<.01$) and Qo_2 values of heart and liver ($P<.01$) was obtained in thyroidectomized rats as a result of triiodo and triac treatment. Again there was no significant difference in the degree of response of heart and liver.

Different results were obtained with thyroxamine. Thyroidectomized rats treated with thyroxamine did not show an increase in total body oxygen consumption or Qo_2 of liver. There was, however, a significant increase ($P<.001$) in the Qo_2 value of the heart.

Failure of thyroxamine to elevate the total body oxygen consumption is in agreement with previous reports that it possesses little or no effect in this respect(9-12). Although relatively ineffective in increasing total body oxygen consumption, thyroxamine has been shown to elicit a sensitizing effect on the action of epinephrine on isolated smooth muscle (13,14). It is possible that the increase in the Qo_2 value of the heart as a result of thyroxamine treatment was caused by sensitizing this organ to endogenous epinephrine. It is also possible that the ability of thyroxamine to stimulate the heart while not affecting the liver or total body oxygen consumption may be a reflection of the heart's greater sensitivity to the drug. The effects seen with thyroxamine may be governed by dose and duration of administration. Large doses given over a short period of time may affect only the Qo_2 of the heart; whereas the same dose administered over a longer period may elicit an effect on total body oxygen consumption as well as on the Qo_2 of the heart.

Effects similar to those exhibited by thyroxamine may also be exhibited by other thyroidal agents at doses which do not result in an elevation of total body oxygen consumption. This theory is currently being investigated.

Summary. L-3:5:3′-triiodothyronine and 3:5:3′-triiodothyroacetic acid significantly increased total body oxygen consumption of intact and thyroidectomized rats. L-3:5:3′-triiodothyronine and triiodothyroacetic acid also significantly increased *in vitro* oxygen uptake of heart and liver slices; however, the heart did not respond to a greater degree than the liver. Thyroxamine failed to increase total body oxygen consumption or Qo_2 of liver; however, the Qo_2 value of the heart was significantly increased.

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Thymolytic Activity of 14α-Hydroxycortisol.* (24524)

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This communication reports thymolytic activity of 14α-hydroxycortisol by various methods in rats and mice and demonstrates that relative potency of this steroid compares to cortisol varies significantly with the thymolytic method employed.

Methods and design. Mouse thymolytic test A (Subcut. inj.). C-57 Brown female mice were obtained from Rockland Farms and bilaterally adrenalectomized and ovariectomized under ether anaesthesia at 24 days of age. The steroids were injected subcutaneously in 0.1 ml aqueous suspension in morning and afternoon one day after surgery and mice were autopsied 24 hours after first injection. Body weights and thymus weights were determined and results expressed as ratio of mg of thymus weights to grams of body weights. *Mouse thymolytic test B (Subcut. inj.).* In this test the steroids were injected once on day of operation and again on following day, all other conditions of the assay being the same as test A. *Rat thymolytic test C (Subcut. inj.).* Albino rats 25 days of age were bilaterally adrenalectomized under ether anaesthesia and injected subcutaneously once on day of surgery with 0.1 ml of Tween suspension of the steroid and again the following day. One day after last injection, the rats were autopsied, at which time thymus and body weights were determined. This injection schedule was the same as that of Mouse Test B. *Rat thymolytic test D (oral).* This test consisted in mixing the steroid with ground Purina Chow and feeding the mixture for 48 hours before determining body and thymus weights.

Results. The comparative thymolytic responses to graded doses of cortisol and 14α-hydroxycortisol using the adrenalectomized-ovariectomized mouse are presented in Table I. The statistical calculations (Table IV) demonstrate that tests A and B resulted in similar slopes, but that the index of precision was more favorable for test B and that a significantly lower potency ratio was found for the 14α-hydroxy derivative compared to cortisol. Even lower potency ratios were

TABLE I. Thymolytic Activity of 14α-Hydroxycortisol Compared to Cortisol in Adrenalectomized-Ovariectomized Mice.

Test No.	Steroid	Total dose, mg	No. of mice	Mean thymus ratio ± S.E.
A	0	0	39	3.91 ± .17
	Cortisol	.05	37	3.07 ± .12
		.1	38	3.09 ± .13
		.2	39	2.83 ± .13
		.4	38	1.87 ± .10
	14α-Hydroxy-cortisol	.05	38	3.06 ± .13
		.1	36	3.09 ± .14
		.2	36	2.55 ± .12
		.4	37	1.94 ± .11
B	0	0	18	4.54 ± .26
	Cortisol	.2	19	2.42 ± .13
		.4	20	1.24 ± .09
		.8	21	.81 ± .09
		1.6	21	.58 ± .04
	14α-Hydroxy-cortisol	.2	19	2.57 ± .19
		.4	21	2.05 ± .19
		.8	20	1.39 ± .14
		1.6	18	.75 ± .07

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