l-leucine has an effect very similar to that of the stimuli producing insulin secretion but that it also has a peripheral effect. It cannot be excluded that the rise in plasma insulin effect observed is due to an action of leucine on insulin or on the antagonists, and not on its secretion.

Summary. 1. Intravenous injection of l-leucine produces an increase in insulin activity of the plasma and in glucose uptake by the diaphragm and adipose tissue. This effect is attributed to stimulation of the islets and to greater insulin secretion, or to action on this hormone. 2. l-Leucine added to the incubation buffer increases glucose uptake by the diaphragm and adipose tissue.

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Clarification of the Diverse Actions of Iodide on Antithyroid Effect of Sulfonamides and Thionamides.* (27142)

KATHLEEN MILNE† AND MONTE A. GREER

Division of Endocrinology, Department of Medicine, University of Oregon Medical School, Portland

Since the early reports of MacKenzie(1,2) that the goitrogenic action of the sulfonamides was enhanced by addition of iodide, whereas iodide decreased the goitrogenicity of the thionamides, little has been done to explore this phenomenon further. The thionamides have been studied extensively and considerable knowledge of their effect on thyroidal biosynthetic processes has been acquired. Recent investigations have revealed that increasing doses of propylthiouracil (PTU) inhibit first the formation of iodothyronines (T_3 + T_4), then diiodotyrosine (DIT), and eventually monoiodotyrosine (MIT)(3,4,5). This last step is much more resistant and even relatively huge doses of PTU fail to block completely all MIT formation(5). However, a similar detailed study of the effect of sulfonamides on the thyroid gland has not been made.

The reports that iodide had a converse effect on the goitrogenic action of the sulfonamides and thionamides suggested to us that iodide administration might clarify differences in the mode of action of the two groups. We selected sulfadiazine (SD) and PTU as representatives of each.

Methods and materials. Male Sprague-Dawley rats weighing 100 g were fed a low iodine diet (LID) (≅ 70 μg I/kg) for 14 days containing SD and PTU in the specified amounts. Each group contained 3 rats. Half the animals were injected daily with 1 mg KI intraperitoneally during the course of the experiment. On the 14th day, 100 μC of I^{131} were given intraperitoneally to all animals receiving KI and to those receiving the largest doses of SD and PTU. The others received 20 μC. The animals were sacrificed 24 hours later and weight and I^{131} content of the thyroids determined. The glands from each group were then pooled and homogenized in 4 ml pH 8.6 phosphate buffer containing 1% pancreatin (Viokase 4×) and 1 mg thiouracil. Two drops of toluene were added to prevent putrefaction, and the thyroids were incubated 24 hours at 37°. Aliquots containing 0.025 μC were subjected to

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† Oregon Heart Assn. Summer Research Fellow.

TABLE I. Thyroidal Radioiodine Uptake and Weight with Various Dietary Regimens.

Diet	I^{131}, % uptake	Thyroid wt, mg/100 g
LID	44.0 ± .8*	10.41 ± .83*
" + KI	.3 ± .1	7.96 ± .55
PTU, .0004%	8.1 ± .8	23.30 ± 3.07
" " + KI	.1 ± .01	9.05 ± .07
" .0002%	21.8 ± 4.9	14.68 ± .94
" " + KI	.1 ± 0	7.88 ± .15
" .0001%	35.5 ± 11.9	11.86 ± 1.03
" " + KI	.2 ± 0	8.68 ± .48
SD, 2%	3.3 ± .4	32.89 ± 4.64
" " + KI	.3 ± 0	21.04 ± .1
" 1%	4.1 ± .6	23.57 ± .92
" " + KI	.2 ± .03	21.76 ± 1.17
" .5%	5.1 ± .9	24.46 ± 3.88
" " + KI	.2 ± 0	19.39 ± 1.23

* Mean ± S.E.

ascending chromatography for 16 hours in butanol-acetic acid-water (4:1:5). Appropriate reference compounds were run in the same system. Distribution of radioactivity was determined with a strip scanner and the proportions of radioiodinated compounds quantified by planimetry.

Results. The results in Table I illustrate that PTU and SD produced goiter at all levels tested. Iodide profoundly inhibited thyroidal hypertrophy and vascularity in the PTU group, but had very little effect in this respect in the SD group. I^{131} uptakes of the animals given supplemental iodine were consistently lower than the corresponding non-supplemented groups.

Chromatographic analysis revealed a striking difference in the effect of iodide on the thyroidal biosynthetic mechanisms of the 2 groups. The data in Table II indicate that iodide plus SD completely inhibited all organic binding whereas iodide plus PTU only tended to increase the relative amount of iodide and, to some extent, DIT and T_3 + T_4.

The various biosynthetic steps seemed to have the same relative sensitivity to both SD and PTU, although in these experiments PTU was approximately 1000-fold as potent.

Discussion. The above results clarify why iodide does not significantly inhibit SD-induced goiter. Supplementation of SD with KI blocked all organic binding of iodine, preventing T_3 + T_4 synthesis and presumably thus not inhibiting the augmented TSH release induced by SD alone. Supplementation of PTU with KI, on the other hand, did not appreciably affect the proportions of iodinated compounds in the thyroid. Although I^{131} uptakes were drastically lowered, calculation of expected specific activities indicated that 3 to 4 times as much T_3 + T_4 were produced with PTU plus KI than with PTU alone. This increased thyroid hormone production would be expected to decrease TSH secretion and to produce the observed inhibition of goitrogenesis. Although no iodinated amino acids could be detected in the SD plus KI groups, iodide supplementation did not increase goiter size over that produced with SD alone. It is possible that iodide exerts some direct inhibitory effect on the secretion or action of TSH and that larger goiters are impossible with simultaneous iodide administration.

Doses of PTU and SD chosen for this experiment were not strictly comparable in their effect on I^{131} uptake and thyroid weight. However, preliminary studies with a wider range of both drugs indicate that the diverse effects of iodide reported herein are observed at all comparable levels.

Although large doses of iodide have been found to transiently inhibit the organic binding of I^{131}(6,7), no complete block comparable to that observed in the present experiment has been reported. In our studies there

TABLE II. Percent Composition of I^{131}-Labelled Materials in Thyroid Hydrolysates.

Diet	Origin	Iodide	MIT	DIT	T_3+T_4
LID	8.2	4.1	33.6	24.1	30.0
" + KI	.9	8.3	27.0	45.1	18.6
PTU, .0004%	6.5	20.2	55.2	11.5	6.6
Idem + KI	0	25.0	48.1	12.5	14.4
PTU, .0002%	4.0	7.2	46.3	25.9	16.7
Idem + KI	2.9	17.9	46.1	19.4	13.6
PTU, .0001%	3.0	6.0	43.6	26.7	20.6
Idem + KI	2.6	11.5	39.8	28.8	17.3
SD, 2%	5.4	46.8	43.9	3.9	0
Idem + KI	0	100.0	0	0	0
SD, 1%	5.3	33.7	53.7	7.1	0
Idem + KI	0	100.0	0	0	0
SD, .5%	8.6	29.2	50.5	8.6	3.1
Idem + KI	0	100.0	0	0	0

was no appreciable inhibition of organic binding by iodide alone.

Summary. Rats fed sulfadiazine (SD) or propylthiouracil (PTU) for 14 days developed thyroid hypertrophy. Addition of 1 mg KI daily did not affect the SD-induced goiter but greatly reduced that due to PTU. Neither SD nor PTU alone, in the doses employed, blocked organic binding of iodine completely. Iodide added to SD completely inhibited organic binding of iodine. Iodide added to PTU did not change the degree of inhibition of thyroidal biosynthesis due to PTU alone but increased the absolute amount of thyroxine and triiodothyronine formed.

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Sterol Ester Formation by Rat Liver Homogenates.* (27143)

LEON SWELL, M. D. LAW AND C. R. TREADWELL
Veterans Administration Center, Martinsburg, W. Va., and Dept. of Biochemistry, School of Medicine, George Washington University, Washington, D. C.

It has been variously suggested that cholesterol esters are synthesized in the liver, intestine, or in other tissues in which they occur(1-5). Cholesterol esterase systems which catalyze the synthesis and hydrolysis of long chain cholesterol esters have been shown to occur in pancreas and intestinal mucosa(6,7). It has also been shown that bile salts are a necessary co-factor for enzymatic activity of those systems(6). Several studies(8-10) have presented evidence for the existence of a hydrolytic cholesterol esterase in rat and chicken liver which catalyzes the hydrolysis of short chain fatty acid esters of cholesterol. The physiological significance of this type of hydrolytic system is uncertain since the major proportion of the cholesterol esters in liver contains long chain fatty acids.

Mukherjee and co-workers(11) reported the presence of a cholesterol esterifying system in rat liver which synthesized cholesterol palmitate from added cholesterol-4-C^{14} and palmityl CoA. A 2-step system was suggested involving first, a reaction between palmitic acid and coenzyme A and secondly, a reaction between cholesterol and palmityl CoA. Fredrickson(12) has described a system containing mouse liver mitochondria plus a heat-stable soluble fraction which esterified considerable quantities of added cholesterol-4-C^{14} during incubation. In this system a considerable part of the total material esterified appeared to be intermediate products in conversion of cholesterol to bile acids. As a part of our studies on metabolism of cholesterol esters, we have been investigating the formation of sterol esters in rat liver homogenates. As an initial approach, the formation of sterol esters from acetate-1-C^{14}, mevalonic acid-2-C^{14} and cholesterol-4-C^{14} was determined. Any differences between endogenously formed cholesterol and added cholesterol would be expected to be apparent in such studies.

Methods and materials. Non-fasted male rats weighing 100-125 g were sacrificed by decapitation, their livers removed and chilled on cracked ice. The livers were homogenized in a buffer medium containing 0.1 M phosphate buffer pH 7.2, 0.03 M nicotinamide,

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