by hexamethonium(11) but was not reduced by trimethaphan(13).

Using threatening(17) and tilting(20) as plasma FFA elevating factors, it has been observed that ganglionic or adrenergic blocking agents counteract the rise in FFA.

The rise in blood glucose was not depressed by guanethidine. The elevation evoked by epinephrine was 28.4 mg/100 ml before administration of guanethidine, and under its influence, 25.1 mg/100 ml. Corresponding values in respect to norepinephrine were 6.4 and 1.4 mg/100 ml.

On the basis of this experiment it seems probable that the sympathetic blocking agent, guanethidine, has a depressing effect on plasma FFA level and that mobilization of FFA caused by the autonomic nervous system may also be counteracted by quanethidine.

Summary. 1) Plasma FFA concentration under the influence of a sympathetic blocking agent, guanethidine, and the effect of this blocking agent on the rise in FFA evoked by administration of epinephrine and norepinephrine in rabbits were studied. 2) Plasma FFA declined under the influence of guanethidine. 3) The rise of plasma FFA evoked by administered epinephrine was somewhat counteracted by the blocking agent. The effect of the agent on the rise evoked by norepinephrine was inconsistent.

1. Bogdonoff, M. D., Estes, E. H., Jr., Trout, D. L., PROC. SOC. EXP. BIOL. AND MED., 1959, v100, 503.

2. Cardon, P. V., Jr., Gordon, R. S., Jr., *J. Psychosom. Res.*, 1959, v4, 5.

3. Laurell, S., *Acta physiol. Scand.*, 1957, v41, 158.

4. Friedberg, S. J., Harlan, W. R., Jr., Trout, D. L., Estes, E. H., Jr., *J. Clin. Invest.*, 1960, v39, 215.

5. Fredrickson, D. S., Gordon, R. S., Jr., *ibid.*, 1958, v37, 1504.

6. Fritz, I. B., Davis, D. G., Holtrop, R. H., Dundee, H., *Am. J. Physiol.*, 1958, v194, 379.

7. Issekutz, B., Jr., Spitzer, J. J., PROC. SOC. EXP. BIOL. AND MED., 1960, v105, 21.

8. Bogdonoff, M. D., Estes, E. H., Jr., Friedberg, S. J., Klein, R. F., *Ann. Int. Med.*, 1961, v55, 328.

9. Dole, V. P., *J. Clin. Invest.*, 1956, v35, 150.

10. Gordon, R. S., Jr., Cherkes, A., *ibid.*, 1956, v35, 206.

11. Havel, R. J., Goldfien, A., *J. Lipid Res.*, 1959, v1, 102.

12. Shafrir, E., Steinberg, D., *J. Clin. Invest.*, 1960, v39, 310.

13. McElroy, W. T., Spitzer, J. J., *Am. J. Physiol.*, 1961, v200, 318.

14. Cass, R., Kuntzman, R., Brodie, B. B., PROC. SOC. EXP. BIOL. AND MED., 1960, v103, 871.

15. Butterfield, J. L., Richardson, J. A., *ibid.*, 1961, v106, 259.

16. Trout, D. L., Estes, E. H., Jr., Friedberg, S. J., *J. Lipid Res.*, 1960, v1, 199.

17. Bogdonoff, M. D., Weissler, A. M., Merritt, F. L., *J. Clin. Invest.*, 1960, v39, 959.

18. Klein, R. F., Bogdonoff, M. D., PROC. SOC. EXP. BIOL. AND MED., 1960, v103, 544.

19. Benfey, B. G., Ledoux, G., Melville, K. I., *Fed. Proc.*, 1958, v17, 349.

20. Hamlin, J. T., Hicker, R. B., Hoskins, R. G., *J. Clin. Invest.*, 1960, v39, 606.

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Studies with Mouse Pituitary Thyrotropic Tumors. VI. Monodeiodination of Tetrac. (28151)

EUGENE M. VOLPERT, JOAN TIERNEY AND SIDNEY C. WERNER*

Departments of Medicine and Biochemistry, Columbia University College of Physicians and Surgeons, New York

Mouse pituitary thyrotropic tumors *in vivo* monodeiodinate I-131 labeled L-thyroxine (T_4*) to labeled 3,5,3'triiodothyronine (T_3*)(1,2), whereas a mouse adrenotropic tumor and several other tumors and control tissues tested completely deiodinate the T_4* to iodide-131. The presence of T_3* after T_4* injection peripherally also can be demonstrated in mouse and human pituitaries(3).

The present study was undertaken to de-

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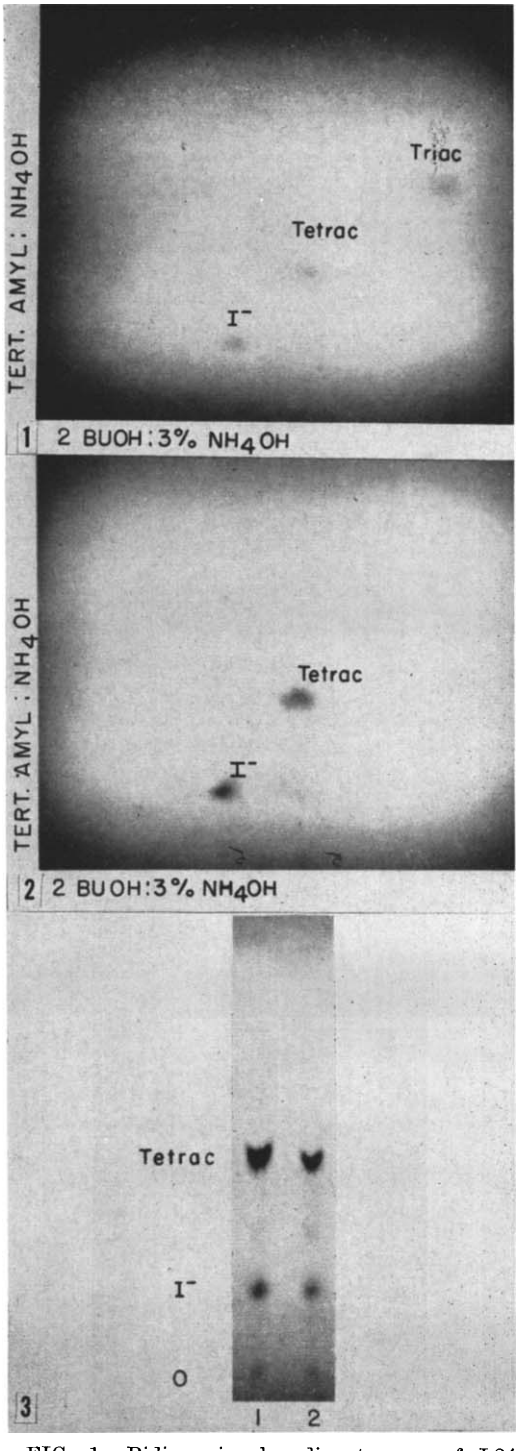

FIG. 1. Bidimensional radioautogram of L24 tumor extract, 24 hr after Tetrac* injection.

FIG. 2. Bidimensional radioautogram of adrenotropic tumor extract, 24 hr after Tetrac* injection.

FIG. 3. Radioautogram made from extracts of sera of tumor bearing mice, 24 hr after injection of labeled Tetrac*. 1. L24 thyrotropic tumor in adrenalectomized mice. 2. Adrenotropic tumor in adrenalectomized mice. Solvent: tert. amyl alcohol-NH_4OH-water 5-1-4.

termine whether the labeled acetic acid analogue of T_4, 3,5,3′,5′tetraiodothyroacetic acid (Tetrac*) was similarly metabolized to 3,5,3′ triiodothyroacetic acid (Triac*). This was planned to study further the possibility that monodeiodination of T_4* might have occurred peripherally rather than in the thyrotropic tumor with subsequent localization of T_3* in the tumor.

Methods. Three strains of mouse pituitary thyrotropic tumors were implanted intramuscularly in female LAF_1 mice about 21 g in weight. One strain, 4183, was dependent responsive to thyroid hormone, and the second, L24, was autonomous semi-responsive, that is, growth was inhibited by thyroid hormones only when the tumor was small. The third, L23, was autonomous non-responsive. Two other tumors were used, an adrenotropic pituitary tumor and a fibrosarcoma that originated spontaneously in an LAF_1 mouse of our own. These were similarly transplanted. Details concerning these tumors as well as the biological and chemical procedures used have been described(2).

The L23 tumor and the fibrosarcoma were implanted in normal mice and normal muscle was obtained from intact mice. The L24 and 4183 tumors were implanted in radiothyroidectomized mice, and the adrenotropic tumor into surgically adrenalectomized animals.

The tumors were used at an estimated size between 0.3 g and 2 g two weeks to 3 months after implantation, depending on the tumor. Tetrac* (Abbott) labeled in position 3′ with I-131 was injected intraperitoneally in amounts varying between 0.5-0.8 μg (11-13 μc) and the tumors or control tissues removed 24 hours later, after exsanguination. Groups of 3 animals were autopsied for each tumor or control tissue and the experiment then repeated. The consistent behavior of the tumors makes this limited number permissible.

Both mono- and bi-dimensional paper chromatography were conducted and gave distinct separation of Tetrac* from Triac.*

Results. Radioactivity was demonstrated (Fig. 1) in the area of Triac* on the chromatograms of extracts of each of the 3 thyrotropic pituitary tumors as well as in the Iodide* and Tetrac* areas (Fig. 1). In contrast, radioactivity could be identified only in the Iodide* and Tetrac* areas in the chromatograms of extracts from the adrenotropic tumor (Fig. 2), the fibrosarcoma, or healthy kidney tissues. Triac* was not detected in any of the chromatograms from the sera obtained at the same time as the tissues above (Fig. 3).

Discussion. The fact that Triac* was present only in the 3 thyrotropic tumors after peripheral injection of Tetrac* tends again to suggest that monodeiodination is conducted by thyrotropic tumor cells(1,2) and presumably by normal thyrotropes(3). The fact that T_3* is not found in adrenotropic or other tumors tested or in kidney tissue tends to suggest that monodeiodination is unique for thyrotropic cells. Most other studies with various healthy tissues have shown only traces of(4, 5,6,7,8) or no(9,10) T_3* formation, whereas such a pathway has never been established for Tetrac*(9,11,12,13). Recently, cardiac muscle has been shown to conduct monodeiodination of thyroxine*(14).

The possibility has been considered that monodeiodination may have been conducted elsewhere in the body and the product then localized preferentially in the thyrotropic tumor cells(1,2). The absence of Triac* from the serum in the present experiments, like the absence of T_3* from the serum in the T_4* experiments, and the known failure of most tissues to conduct monodeiodination except possibly the heart favors the concept proposed above, that monodeiodination actually occurs within the thyrotropic cell.

Summary. I-131 labeled 3,5,3′,5′ tetraiodothyroacetic acid was injected into healthy mice and into mice bearing 3 different strains of pituitary thyrotropic tumors, a pituitary adrenotropic tumor, and a fibrosarcoma. I-131 labeled 3,5,3′ triiodothyroacetic acid was detected as a metabolite in the 3 thyrotropic tumors but in no other tissue. It is suggested that thyrotrope cells conduct monodeiodination of tetraiodothyroacetic acid as well as of thyroxine, and that such monodeiodination is conducted uniquely by the thyrotropes.

1. Werner, S. C., Volpert, E. M., Grinberg, R., *Nature,* 1961, v192, 1193.

2. Volpert, E. M., Grinberg, R., Werner, S. C., *Endocrinology,* 1962, v71, 361.

3. Grinberg, R., Volpert, E. M., Werner, S. C., *J. Clin. Endocrinol. and Metab.,* 1963, v23, 140.

4. Ford, D. H., Corey, K. R., Gross, J., *Endocrinology,* 1957, v61, 426.

5. Ford, D. H., Gross, J., *ibid.,* 1958, v62, 416.

6. Roche, J., Michel, R., Gruson, M., *C. R. Soc. Biol.,* 1958, v152, 1324.

7. Roche, J., Michel, R., Sonntag-Nussenzweig, R., Meldolesi, M. F., *ibid.,* 1960, v154, 1732.

8. Albright, E. C., Larson, F. C., *J. Clin. Invest.,* 1959, v38, 1899.

9. Etling, N., Barker, S. B., *Endocrinology,* 1959, v65, 95.

10. Lissitzky, S., Benevent, M. T., Roques, M., *Bull. Soc. Chim. Biol.,* 1961, v43, 743.

11. Yamazaki, E., Slingerland, D. W., *Endocrinology,* 1959, v64, 126.

12. Green, W. L., Ingbar, S. H., *J. Clin. Endocrinol. and Metab.,* 1961, v21, 1548.

13. Galton, V. A., Ingbar, S. H., *Endocrinology,* 1962, v71, 369.

14. Heninger, R. W., Larson, F. C., Albright, E. C., Endocrine Soc. 44th Meet. Abst., 1962, p27.

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