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# STIMULATION OF THYROIDAL RADIOIODINE UPTAKE BY ACTINOMYCIN D AND FLUOROURACIL—AN INDIRECT EFFECT

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**Abstract**—The previously reported stimulation by actinomycin of radiodine uptake in mouse thyroid is mainly due to a decreased food intake.

ACTINOMYCIN D and fluorouracil stimulate the uptake of radioiodide in the thyroids of mice which have been fed successively with an iodine-deficient and an iodine-rich diet.[1] Such a stimulation by inhibitors was interpreted as the reversal of a previous inhibition. It was concluded that in mice submitted to this regime, the thyroid function was depressed.[1] The reversal of this depression by actinomycin and fluorouracil suggested the existence in such thyroids of a "repressing factor", an RNA or a compound whose formation depended on new RNA synthesis. The purpose of this work was to assess if the stimulation by actinomycin and fluorouracil of the radioiodide uptake in the thyroid was due to a direct effect of these inhibitors on thyroid metabolism.

The experimental protocol has been previously described.[2] Homogenous groups of Swiss albino female mice (wt. 15 g) were fed for 7 days with a Remington iodine-free diet (stimulatory pretreatment), then for 3 days with an iodine-rich diet (12mg iodine/kg) enriched with triiodothyronine (7·5 $\mu$g/mouse/day) (suppressive pretreatment). Actinomycin (10 $\mu$g), fluorouracil (10 mg), or a placebo were injected 14 hr and $^{131}$I iodide (4 $\mu$C) was injected 4 hr, before the removal and counting of the thyroids.[1]

The stimulation of radioiodide uptake by the thyroid was observed for various dosages of actinomycin D (from 5 to 25$\mu$ g/mouse) and fluorouracil (from 1 to 25 mg/mouse). The increased radioactivity of the thyroid was precipitable with trichloroacetic acid. No stimulation was observed in the absence of the stimulatory or the suppressive pretreatment, or when the iodine-rich diet was given for more than 4 days. The effect was not modified when no triiodothyronine was given in the suppressive pretreatment; it was observed when the injection of either drug was made from 11 to 28 hr before the removal of the thyroids.

The disappearance rate of radioiodide in the blood, to which the thyroid contributes very slightly (thyroid uptakes of the order of 1 per cent), was similar in actinomycin treated (0·59 per cent/min) and in control animals (0·56 per cent/min). The increased

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thyroidal uptake of radioiodide in treated animals is therefore not due to a decreased iodide excretion.

In mice injected with $^{125}I$ iodide before the suppressive pretreatment, TSH, but not actinomycin, stimulated the release of thyroid radioactivity, as evidenced by the plasma radioactivity 2, 4 and 6 hr after the administration of the drugs. There is therefore no indication that actinomycin induces a secretion of TSH by the pituitary which in turn would cause the stimulation of the thyroidal uptake.

The stimulatory pretreatment brought the radioiodide uptake of mouse thyroids from 3–4 per cent to 20 per cent of the dose; the uptake decreased to 1 per cent of the dose during the 3 days of the suppressive pretreatment. This decrease was stopped by temporary removal of the iodine-rich diet after the injection of the drug or the placebo or by the injection of actinomycin or fluorouracil. In the absence of the iodine-rich diet, the effect of actinomycin was no longer significant (Table 1). A great part of the previously observed stimulation can therefore be explained by reduction of the iodine ingestion.

The stimulation of radioiodine uptake by actinomycin and fluorouracil was less significant when treated and control mice were put in separate cages after the injection of the drug or the placebo (Table 1). This fact is explained by the observation that when separated from control mice, the intoxicated animals still feed themselves to a certain extent, while when they are mixed with the control mice, they are bullied and crowded away from the iodine-rich food.

TABLE 1. EFFECT OF ACTINOMYCIN ON THE UPTAKE OF RADIOIODIDE BY THE THYROIDS OF MICE

| Iodine-rich food after injection of drug or placebo | Separation of actinomycin treated and control mice | Thyroidal uptake (in % of control) | | |
|---|---|---|---|---|
| | | Actinomycin | Control | P |
| | | X $X_1$ $X_2$ | X $X_1$ $X_2$ | |
| − | − | 200 (175–228) | 157 (142–174) | 0·2 |
| + | − | 218 (190–250) | 100 | 0·001 |
| + | + | 160 (141–181) | 123 (105–141) | 0·05 |

− Uptakes of treated mice are expressed as % of the results of control animals.
− Means standard deviations of the mean and P have been calculated on the logarithms of these percentages (2).
X is the antilogarithm of the mean.
$X_1$ and $X_2$ are respectively the antilogarithm of mean $\pm$ S.D.M.

The increased thyroidal uptake of radioiodine in actinomycin and fluorouracil intoxicated mice is therefore mainly due to the diminished ability of intoxicated mice to eat iodine-rich food, the more so, in the presence of healthy competitive mice. These observations do not therefore support our hypothesis on the repression of thyroid function by iodinated peptidic inhibitors.

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