STUDIES OF THE CONTROL OF THYROID FUNCTION
AS DISCLOSED BY THE EFFECT OF SALICYLATE

by

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An examination has been made of the mechanism by which salicylate and related drugs depress thyroid function. Salicylate and 2,4-dinitrophenol produced a depression in plasma PBI in normal rats, confirming previous reports. Sodium γ-resorcylicte in sufficient dosage also significantly depressed the plasma PBI of normal rats. Sodium p-hydroxybenzoate was without effect. Similar findings were obtained in thyroidectomized rats maintained on thyroxine, indicating a peripheral action of the drugs in depressing plasma PBI.

Bioassay of TSH in the plasmas of normal rats revealed that salicylate, 2,4-dinitrophenol and also γ-resorcylicte significantly depressed circulating TSH; p-hydroxybenzoate was without effect. Previous indirect evidence of a depression in TSH release produced by salicylate, 2,4-dinitrophenol and γ-resorcylicte was therefore confirmed.

This finding of simultaneous depression in circulating thyroid hormone and TSH is contrary to the concept of the negative feedback regulation of the thyroid-pituitary axis. A depression in circulating thyroid hormone would be expected to stimulate pituitary TSH release. It had been postulated previously that the depression in TSH induced by salicylate and 2,4-dinitrophenol was related to their metabolic
stimulating properties, by an action at the hypothalamic sites controlling pituitary TSH release. However, since γ-resorcylicote does not increase metabolic rate, this proposed mechanism for the depression of TSH is excluded.

Using a dialysis procedure, it was shown that the in vitro addition of salicylate and γ-resorcylicote to human or rat serum increased the rate of dialysis of radiothyroxine with which the serum was equilibrated; p-hydroxybenzoate produced a smaller effect. An increased rate of dialysis of radiothyroxine is consistent with an increase in free thyroxine. Circulating free thyroxine was elevated two hours after the administration of salicylate and γ-resorcylicote to man, whereas p-hydroxybenzoate was ineffective. These in vivo findings were confirmed following more prolonged administration of the drugs to rats; 2,4-dinitrophenol also increased circulating free thyroxine in rats.

Using paper electrophoretic separation of human serum proteins, it was demonstrated in vitro and in vivo that salicylate and γ-resorcylicote displaced thyroxine from thyroxine binding prealbumin (TBPA). Although a displacement of thyroxine from TBPA was induced by p-hydroxybenzoate in vitro, this drug was ineffective in vivo. The separation of rat serum proteins was carried out by starch gel electrophoresis. The addition, in vitro, of salicylate and γ-resorcylicote to the electrophoretic buffer produced a
large displacement of thyroxine principally from a fast-moving albumin binding site. There was a small displacement of thyroxine by p-hydroxybenzoate in vitro. In vivo, salicylate and 2,4-dinitrophenol produced a displacement of thyroxine whereas p-hydroxybenzoate and \( \beta \)-resorcylic were ineffective. The increase in free thyroxine produced by salicylate and related drugs therefore resulted from the displacement of thyroxine from specific binding sites in the serum.

The peripheral action of salicylate and related drugs in depressing plasma PBI is compatible with the displacement of thyroxine into the free state, followed by its disappearance from the circulation.

The depression in TSH release induced by these drugs is also correlated with the increase in circulating free thyroxine. It is concluded that the level of circulating free thyroxine serves as the regulator of the negative feedback system controlling thyroid-pituitary interrelations.