ROLE OF INTERMOLECULAR INTERACTIONS IN THE SYNTHESIS AND RECOGNIZTION OF THYROID HORMONES

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Thyroxine (T4), the main secretory hormone of the thyroid gland, is produced on thyroglobulin by thyroid peroxidase (TPO)/hydrogen peroxide/iodide system and converted to its active form (T3) by the selenocysteine-containing enzyme iodothyronine deiodinase (ID). The overactivity of TPO and/or ID leads to "hyperthyroidism", a life-threatening disease, which is treated by antithyroid drugs such as 6-n-propyl-2-thiouracil (PTU) and methimazole (MMI). In view of the current interest in antithyroid drugs and thyroid hormone metabolism, our group is working on the mechanistic aspects of iodination and deiodination reactions.

Recent studies show that intermolecular interactions such as halogen bonds play important roles in the activation and inactivation of thyroid hormones. It has been shown that T4 forms short I···O contacts with its transport protein transthyretin and T4 can bind to RNA sequences through halogen bonds. The flavoprotein iodotyrosine deiodinase (IYD), which salvages iodide from mono- and diiodotyrosine formed during the biosynthesis of T4, may utilize halogen bonds for deiodination reactions. In addition to the recognition of thyroid hormones, intermolecular interactions appear to play major roles in the treatment of hyperthyroidism. Recently, significant research effort has been directed to the understanding of the interaction of antithyroid drugs with iodine. These studies provide insight into the nature of products formed during the inhibition of thyroid hormone synthesis. In this lecture, our recent results on the interaction of methimazole and related antithyroid drugs with iodine will be presented.

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