Thyroid Function in Developmental Disorders

by J. Gerald Young and Donald J. Cohen

Abstract

The relationships between catecholamines and thyroid state are considered from clinical and molecular perspectives. The effects of thyroid hormone on adrenergic systems are mediated by altered receptor and post-receptor function. Clinical symptoms of major childhood neuropsychiatric disorders, as well as related biological measures, may be influenced by thyroid hormone regulation.

Interactions between the thyroid and catecholamine systems are clinically evident in the close resemblance of symptomatology of the hyperthyroid state to \( \beta \)-adrenergic effects (tachycardia, increased systolic blood pressure, increased myocardial contractility, and tremor are common) (DeGroot and Stanbury 1975) and the clinical response of hyperthyroid patients to \( \beta \)-adrenergic antagonists (e.g., propranolol) (Mazzaferri et al. 1976; Lancet editorial 1980). On the other hand, newly admitted psychiatric patients may have transient thyroid dysfunction in which hyperthyroidism is associated with mania, severe anxiety, agitation, and thought disorder, while hypothyroidism is related to alcohol, hypnotic substance abuse, and weight gain (Kolakowska and Swigar 1977; Cohen and Swigar 1979; Swigar et al. 1982).

Experimental observations at the molecular level give further evidence of a thyroid-catecholamine interaction (e.g., the negative relation between thyroid function and indices of catecholamine function, such as catecholamines and their metabolites and related enzymes) (Ho-Van-Hap, Babineau, and Berlinguet 1967; Klawans and Shenker 1972; Christensen 1973; Stoffer et al. 1973; Cohen et al. 1974; Nishizawa et al. 1974; Noth and Spaulding 1974). Nevertheless, several factors complicate the interpretation of these data. First, the relations described at the clinical and molecular levels differ. At the organ or systemic level, as manifest in observable symptoms, the catecholamine and thyroid effects act in the same direction, that is, a component of hypothyroidism is a hypoadrenergic state. On the other hand, at the molecular level, the data document an inverse relation in which abnormally high thyroid hormone levels are accompanied by indices suggesting reduced catecholamine function. This apparent contradiction is theoretically resolved by hypothesizing changes in receptor state, ultimately leading to congruent effects at cellular and systemic levels.

Second, relations between the thyroid and catecholamine systems differ across species and in different tissues of the same species (Tong and D'Iorio 1976; Ho-Van-Hap, Babineau, and Berlinguet 1967). Generalizations from one tissue to another are precarious; this is especially important in clinical studies in which lack of access to brain tissue requires indirect measures of catecholamine function to infer similar effects in brain.

Third, a clear negative relation between thyroid function and indices of catecholamine function

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may be evident for some indices only when thyroid function is outside the normal range. Inclusion of subjects with normal thyroid function may obscure an otherwise observable relation.

Fourth, thyroid functional effects at the cellular level are consequent to the action of at least two hormones, triiodothyronine (T₃) and thyroxine (T₄) (Sterling 1979a, 1979b). In addition, a substantial portion of T₃ active at cellular sites is derived from peripheral conversion of T₄. Use of a single measure (such as serum T₄) to indicate metabolic effects of the thyroid must be cautious (Ingbar and Braverman 1975).

Strong evidence for thyroid hormone effects on receptor function comes from several sources. Electrophysiological studies at the neural level have indicated postsynaptic changes in altered thyroid states. For example, Purkinje cells of the rat cerebellum, the discharge rate of which is largely determined by tonic inhibitory noradrenergic afferents from the locus ceruleus, fire at a faster rate in hypothyroid rats; Purkinje cells are also less sensitive to iontophoretically applied norepinephrine. The subsensitivity of the Purkinje cells to norepinephrine is reversed by administration of T₃ (Marwaha and Prasad 1981).

Second, binding studies of adrenergic receptors have demonstrated a decrease in the number of β-receptors in hypothyroid states (Banerjee and Kung 1977; Ciaraldi and Marinetti 1977; Williams et al. 1977; Hoffman and Lefkowitz 1980; Bilezikian and Loeb 1982), which fits well with the subsensitive response of the cell to norepinephrine in the hypothyroid animal.

Third, diminished adenylate cyclase activity in peripheral tissues has been observed in hypothyroidism (Levey, Skelton, and Epstein 1969). Thus, the sum of the evidence to date converges to indicate thyroid modulation of cellular response to noradrenergic neurotransmission by enhancing postsynaptic receptor response and increasing overall noradrenergic effects at organ and systemic levels (Whybrow and Prange 1981).

There is another viewpoint from which thyroid–catecholamine interactions are critically important to researchers. Given the strong evidence of these interactions, thyroid function stands as an important source of variance to be considered in studies of catecholamine metabolism. The nature of the thyroid–catecholamine interactions must be specified, so that there is less likelihood that they will act as confounding factors in experimental procedures not targeted on thyroid effects.

The implication of thyroid effects as contributors to the regulation of activity level and sympathetic function, each an important focus of research in major neuropsychiatric disorders of childhood, led to research designed to clarify thyroid actions in these disorders (Cohen et al. 1974, 1980; Young et al. 1982b).

In a series of studies of normal subjects and patients with psychiatric or endocrine disorders (Young et al. 1982a, 1982c; Young, Kypri, and Cohen 1982) described in this issue of the Schizophrenia Bulletin, the interaction between thyroid regulation and catecholamine-related enzymes was investigated. These studies exemplify approaches to dissecting the relation between the neuroendocrine system and neuronal function in clinical research.

References
Ho-Van-Hap, A.; Babineau, L.M.; and Berlinguet, L. Hormonal action on monoamine oxidase activi-


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