

Table 1. Systemic activity of the juvenile hormone analog, ethyl pivaloyl-L-alanyl-p-amino-benzoate in sunflower plants on *Dysdercus* larvae. The values indicate average scores of hormonal activity as explained in the text.

| Treated part | Tested part | Time to release (days) | Activity at concentrations of (micrograms per plant) | | | | | |
|--------------|--------------|------------------------|--|-----|-----|-----|------|------|
| | | | 1000 | 500 | 250 | 125 | 62.5 | None |
| Stem | Upper leaves | 1 | 5 | 5 | 4.5 | 3.6 | 1.2 | 0 |
| Stem | Upper leaves | 7 | 5 | 4.6 | 3.8 | 1.4 | 0.4 | 0 |
| Stem | Upper leaves | 14 | 3.4 | 1.8 | 0.8 | 0 | 0 | 0 |
| Upper leaves | Stem | 1 | 5 | 4.5 | 4 | 3.4 | 2.3 | 0 |

water were used as the test insects.

The compound was applied on the surface in 100 μ l of water emulsions containing 0.01 percent Tween 80, 1 percent paraffin oil, and graded amounts of the compound from 0 to 1000 μ g per 100 μ l of the emulsion. Immediately after application, the treated parts of the plant were isolated in an inverted plastic cup. Larvae were released on the untreated part of the plant 24 hours after application of the emulsion and were enclosed in a small plastic cup containing a few cotton seeds as food.

The evaluation of juvenile hormone activity was made according to the degree of metamorphosis inhibition determined by morphological criteria after the next molt; the usual 0 to 5 scoring system was used (4). Maximum activity (score 5) requires appearance of perfect supernumerary larvae; score 3 indicates formation of half-larval adultoids; and score 0 indicates formation of morphologically perfect adults. Each experiment was replicated twice with six to ten insect specimens per replication. The values in Table 1 are an average activity score of all insects tested in each concentration.

Initially, excessive amounts of the compound showed systemic activity even when applied in pure acetone or pure mineral oil, but this crystalline compound formed a solid deposit or unabsorbed film of oil on the treated plant surface, which was inconvenient for quantitative measurements. Therefore, in later experiments, water emulsions with Tween 80 were applied on the stem or upper leaves of the sunflower plant. The results presented in Table 1 show that the compound, at about 100 μ g per plant, is able to enter the plant system and exhibit systemic juvenile hormone activity per plant. The data indicate that the compound is transported from the lower part to the upper part of the plant and vice versa, which indicates translocation and distribution throughout the whole plant system. We also found that the com-

pound can enter the plant through the roots for translocation to the stem and leaves. For these experiments we used sunflower plants potted in 50 to 100 g of soil per pot. The soil in the pot was treated once with 5 ml of the above emulsion containing 12.5 to 200 μ g of JHA per milliliter. The insects were released on the untreated parts 24 hours after the soil treatment. The results revealed almost maximum activity at the concentrations of 500 to 1000 μ g per plant. Little activity has been observed in concentrations of 125 to 250 μ g per plant, while no activity was recorded at lower doses.

Thyroid State: Effects on Pre- and Postsynaptic Central Noradrenergic Mechanisms

Abstract. For hypothyroid rats, spontaneous motor activity was less than that in matched normal controls, and the specific activity of tyrosine hydroxylase in the midbrain was significantly greater than that in controls. Rats made hyperthyroid with thyroxine became hyperactive and showed increased sensitivity to the behaviorally activating effects of norepinephrine administered intraventricularly. In hyperthyroid rats, the specific activity of tyrosine hydroxylase in the midbrain remained within the normal range. These results are consonant with studies that suggested both receptor "tuning" and feedback regulation of activity of enzymes involved in biosynthesis of presynaptic neurotransmitter as methods of regulation of the central catecholamine synapse. These results may also help explain the reported potentiation by thyroid hormone of the antidepressant effects of imipramine.

Some of the physiological manifestations of altered thyroid states may be mediated through peripheral and central adrenergic systems (1). For example, thyroxine treatment produces a state resembling hyperthyroidism; this state is characterized by hyperthermia, tachycardia, sweating, and elevated blood pressure. These symptoms are all manifestations of increased adrenergic activity (2). Conversely, hypothyroid animals generally show signs of decreased peripheral adrenergic function (3, 4). In addition, affects of norepinephrine (NE) and epinephrine on basal metabolic rate, glycogenolysis, and lipase activation are markedly increased

Table 1 shows that the compound remains relatively active in the plant system for 1 week after application, although there is a remarkable decrease of systemic JH activity after 14 days, except at the highest concentration tested.

In our preliminary experiments with other chemical types we found lower systemic activity in certain terpenoid compounds. We expect that the observed systemic effect of JHA may enhance the potential utilization of these substances in insect control.

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in thyroxine-treated subjects (4). Finally, in heart and other adrenergically innervated peripheral tissues, turnover of NE is decreased in thyroxine-treated animals, while an accelerated turnover is associated with a hypothyroid state (5).

A similar relationship between thyroxine and catecholamines (CA's) may exist in the central nervous system (CNS). Similarities between the symptomatology of thyroid deficiency and of certain psychiatric illnesses, particularly "endogenous" depressions, are well known (6). Since much evidence supports the notion that central CA's play an important role in the patho-

physiology of depression (7), some of the CNS symptoms of both disorders may result from a common neurochemical mechanism. Consonant with this view is the finding of Prange *et al.* (8) that low doses of L-triiodothyronine (T_3) potentiate the antidepressant effects of imipramine in euthyroid, depressed patients. Other tricyclic antidepressants give similar results (9).

In animals, behavioral arousal, which appears to be influenced by brain CA's (10), also increases in hyperthyroidism and decreases in hypothyroidism (11).

More directly, thyroid state influences the synthesis and metabolism of NE in the CNS. The rate of conversion of isotopically labeled tyrosine to NE is decreased in the brains of hyperthyroid rats and is increased in hypothyroid rats (5). Furthermore, a recent study by Schildkraut *et al.* showed that the turnover of NE in rat brains was increased after long-term treatment with imipramine (12). When thyroxine was administered along with imipramine, the onset of this effect was earlier.

Because of these and other findings it has been suggested that thyroid hormone may exert some of its action by facilitating the action of CA's in both peripheral and central adrenergic pathways. To further explore this relation in the brain, we have examined the effect of thyroid state on (i) spontaneous behavioral activity in the rat; (ii) the specific activity of tyrosine hydroxylase from the midbrain, probably the rate-limiting enzyme in NE biosynthesis (13); and (iii) the magnitude of the behavioral response to intraventricular infusion of NE.

The subjects were adult male Sprague-Dawley rats, weighing between 175 and 225 g. They were housed individually, kept in continuous light, and given food and water as desired. Thyroidectomized rats (14) were used 3 weeks after surgery. Thyroxine-treated rats received daily subcutaneous injections of sodium-L-thyroxine (Sigma), 0.4 mg/kg, for 10 days. Thyroxine-treated rats did not appear toxic, and there were no deaths during the 10 days of treatment. Control and thyroidectomized rats were handled identically and received daily saline injections for 10 days.

After 10 days, the thyroxine-treated rats had gained 2.5 ± 2.8 g, compared with 45.9 ± 2.5 g for control rats and 16.0 ± 4.4 g for thyroidectomized rats. Oxygen consumption (measured manometrically) of thyroxine-treated rats

was approximately 189 percent of normal, and that of thyroidectomized rats was approximately 85 percent of normal. These results are consistent with data on the weight and oxygen consumption of hyper- and hypothyroid rats (15).

On day 9 of injections, each rat was placed in a soundproofed free-field activity chamber (38 by 38 by 30 cm) for a 1-hour period of adaptation. Two

perpendicular light beams and phototransistors divided each cage into equal quadrants. Crossovers were registered when either beam was interrupted. On day 10, 2 to 4 hours after the last thyroxine injection, animals were placed in the chambers for 90 minutes. After the first 15 minutes, animals reached a relatively stable level of activity. Crossovers during the last 75 minutes were used for comparisons between groups.

Thyroxine-treated animals were significantly more active than control animals (Fig. 1, top), while thyroidectomized animals were less active than control animals; however, this difference was not statistically significant. These results agree with those in other studies (11) that showed that activity (in an activity wheel) of thyroxine-treated rats was increased and that of thyroidectomized rats was decreased.

Immediately after completion of the activity trials, the rats were killed by decapitation, and their midbrains were removed and homogenized in 0.005M potassium phosphate buffer, pH 7.0. The homogenates were centrifuged at 50,000g for 20 minutes, and the supernatants were assayed for tyrosine hydroxylase activity by a modification of the method of Nagatsu *et al.* (16). (The supernatants contained over 90 percent of the measurable activity of this enzyme.) Samples of supernatant were used to estimate protein (17). Enzyme activity was calculated as picomoles of tritiated water produced from tritiated tyrosine per milligram of protein per hour.

For thyroidectomized rats, the activity of tyrosine hydroxylase from the midbrain is markedly increased over the control value (142 ± 6 percent); this value is unchanged for thyroxine-treated rats (Fig. 1, bottom). This change is probably not the result of a general increase in protein synthesis, since thyroid deficiency in adult animals does not alter the rate of amino acid incorporation into brain protein; in younger animals, thyroid deficiency decreases synthesis of brain protein (18).

For thyroidectomized rats, the increase in the specific activity of the rate-limiting enzyme for CA biosynthesis may explain the observation that the rate of conversion of isotopic precursor to NE is increased (5). Our results indicate that an increase in the activity of tyrosine hydroxylase may be responsible for this increase in CA synthesis. However, the lack of change in tyrosine hydroxylase activity in hyper-

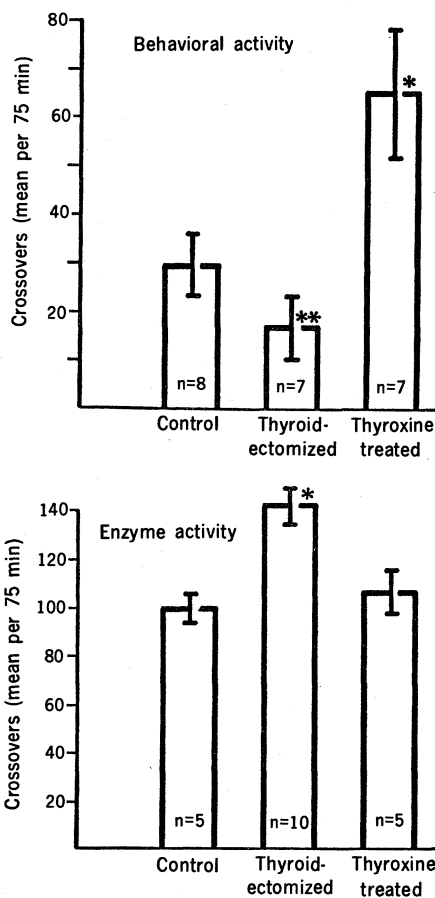


Fig. 1. (Top) The effects of thyroid treatment on motor activity in free-field activity chambers. Crossovers from one quadrant to another were measured during a 75-minute period. Activity of thyroxine-treated rats was significantly increased (*, $P < .02$), and activity of thyroidectomized rats was decreased, although not significantly (**, $.05 < P < .1$). Brackets represent standard error of the mean. (Bottom) The effects of thyroxine treatment and thyroidectomy on the specific activity of tyrosine hydroxylase from the midbrain. Enzyme activity is expressed as percentage of activity in control animals. Thyroxine-treated animals received sodium-L-thyroxine (0.5 mg/kg) for 10 days and were then killed; enzyme activity was unchanged from that of controls. Thyroidectomized animals were killed 3 weeks after thyroidectomy; enzyme activity increased significantly over that of controls ($P < .01$). Brackets represent the standard error of the mean. The number of animals in each group is given by *n*.

thyroid rats is not consistent with Prange's observation of a decrease in NE turnover in thyroxine-treated rats (5). Therefore, the observed decrease in labeled NE may be due to factors other than the activity or amount of the rate-limiting enzyme for NE biosynthesis. For example, if the relevant tyrosine pools were larger or more available in the hyperthyroid state, the labeled amino acid would be diluted more by endogenous substrate, and the decrease in conversion would be more apparent than real. This conversion data would also be found if the hyperthyroid state produced an impairment in storage or uptake of NE and did not affect synthesis at all. Such an interpretation is consistent with the observation by Schildkraut *et al.* (12) that thyroxine treatment augments the rate of disappearance of tritiated NE administered intracister-nally.

Much research has suggested that changes in a relatively small functional pool of NE may correlate well with changes in the amount of spontaneous motor activity (19). And it appears that this functional pool is maintained primarily by de novo synthesis. Therefore, the failure to find an increase in enzyme activity in the midbrain corresponding to the thyroxine-induced increase in motor activity is difficult to explain, as is the association of significantly increased enzyme activity with decreased motor activity in hypothyroid animals. One possible explanation for these disparities is that changes in amount of tyrosine hydroxylase are secondary to the effect of thyroid state on sensitivity of adrenergic receptors (5). Such "tuning" of receptors by hormones has been demonstrated in other systems (20).

However, a "tuning" mechanism by itself does not explain the increase in tyrosine hydroxylase activity in the physically inactive hypothyroid rats. Several recent studies by us and by others are relevant to this increase. For example, Thoenen and his colleagues showed that 6-hydroxydopamine, reserpine, and phenoxybenzamine, drugs that interfere with postganglionic sympathetic transmission, produce an increase in tyrosine hydroxylase activity in adrenal and sympathetic ganglia (21). This increase in enzyme activity appeared to be due to an increased synthesis of new enzyme. The synthesis was mediated by the prolonged, reflexive, compensatory increase in sympathetic nerve activity, since the increase in enzyme activity could be prevented by

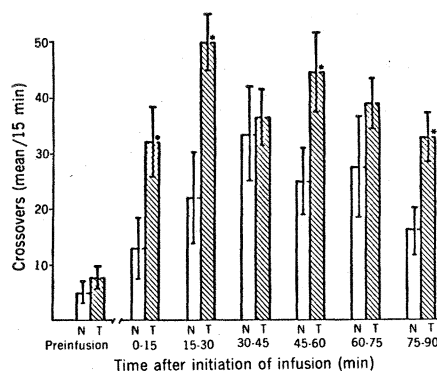


Fig. 2. The effects of infusion with NE (25), 1.0 $\mu\text{g}/\mu\text{l}$, on the behavioral activity of nontreated (N) and thyroxine-treated (T) rats. Crossovers per 15 minutes were measured for 2.5 hours. During hour 1 the animals received no infusion, and data for the last 15 minutes (preinfusion) of this hour are given. The height of each bar shows the mean number of crossovers, and brackets show the standard error of the mean. Thyroxine treatment potentiated the response to NE infusion with respect to the onset, duration, and magnitude of the hyperactivity (*, $P < .01$).

either inhibitors of protein synthesis or by decentralization. In a related study, Segal *et al.* (22) showed that prolonged reserpine treatment produced an increase in tyrosine hydroxylase activity in the midbrain which was paralleled by changes in behavioral arousal.

We found, using a variety of other pharmacological as well as physiological manipulations, that the suppression of central adrenergic activity for relatively long periods of time (4 to 10 days) resulted in an increase in tyrosine hydroxylase activity in the midbrain (23). In view of these results, we suggested that long-term changes in the activity of central adrenergic neurons, produced by a compensatory feedback mechanism, may regulate the amount or activity (or both) of tyrosine hydroxylase activity in the midbrain. Accordingly, in thyroidectomized animals, a decrease in activity of adrenergic receptors may be communicated to the presynaptic cell, with a consequent compensatory increase in tyrosine hydroxylase activity. As judged by the behavioral effects (Fig. 1), the resulting increase in NE synthesis appears to be almost sufficient to overcome the decrease in receptor sensitivity.

To more directly test the receptor sensitization hypothesis, we measured the motor activity of thyroxine-treated and control rats during intraventricular infusion with NE. (Thyroidectomized animals were not included in this study because of the large number of deaths

during or shortly after surgery. For two animals that did survive, response to NE infusion was delayed and decreased compared to that of controls.) For untreated rats, infusion with relatively low doses of NE produces behavioral arousal (10). We reasoned that if thyroxine sensitizes noradrenergic receptors, the behaviorally activating effects of NE would be potentiated by thyroxine treatment.

Rats were injected with thyroxine according to the schedule described earlier except that, on day 3, a cannula was implanted in the lateral ventricle (24). On day 10, the rats were placed in the activity chambers. After 1 hour in the chamber, a 1.5-hour infusion with NE (25) was begun. The concentration of NE was 1 $\mu\text{g}/\mu\text{l}$ and the infusion rate was 20 $\mu\text{l}/\text{hour}$.

Figure 2 shows that in the 15 minutes before the start of infusion, the thyroxine-treated rats were slightly more active than controls. This difference between thyroxine-treated and control rats was significantly increased during the infusion of NE.

In this experiment, NE may act by either displacing endogenous CA's (26) or by directly stimulating adrenergic receptors. The increased response to NE seen in thyroxine-treated rats could be due to an increase in the amount or accessibility of NE available for release, or to an increase in the sensitivity of adrenergic receptors. Since the synthesis of NE in thyroxine-treated animals is either unaltered or reduced, a thyroxine-induced increase in sensitivity of adrenergic receptors appears to be the most reasonable explanation for these findings.

Thus, in the thyroidectomized rat, decreased sensitivity of receptors may result in decreased central adrenergic activity and therefore in decreased behavioral activity. It is hypothesized that decreased postsynaptic activity is communicated (for example, via a feedback loop) to the presynaptic adrenergic neuron and that the resulting neural activity regulates the amount or activity of tyrosine hydroxylase in the midbrain. In thyroxine-treated rats, increased sensitivity to NE results in increased behavioral activity and an increased behavioral response to infusion of NE.

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Prenatal Stress Feminizes and Demasculinizes the Behavior of Males

Abstract. Male rats were exposed to prenatal or postnatal stress, or both. The prenatally stressed males showed low levels of male copulatory behavior and high rates of female lordotic responding. Postnatal stress had no effect. The modifications are attributed to stress-mediated alterations in the ratio of adrenal to gonadal androgens during critical stages of sexual differentiation. Specifically, it appears that stress causes an increase in the weak adrenal androgen, androstenedione, from the maternal or fetal adrenal cortices, or from both, and a concurrent decrease in the potent gonadal androgen, testosterone.

The critical role of androgen during perinatal development on the differentiation of adult sexual behavior potentials has been clearly demonstrated. Male rats deprived of androgen prenatally in injection of the antiandrogenic drug, cyproterone acetate, or neonatally by castrating on the day of birth, display less male copulatory behavior and more female lordotic patterns than normal males (1). Conversely, female rats exposed to exogenous androgen during critical perinatal developmental stages show male-like copulatory and ejaculatory patterns while female receptivity is partially or totally impaired (2).

In the normal male, the differentiating androgen is presumably testosterone secreted by the fetal and neonatal testes. There is, however, an alternate source of androgen, namely, the adrenal cor-

tex. Among other androgenic steroids, the adrenals secrete small quantities of testosterone and large amounts of the less potent androstenedione (3). The possible functional significance of this apparently redundant androgen source has not been investigated. However, since the adrenal cortex under certain pathological conditions releases sufficient androgen to virilize human females (4), its role in the differentiation of healthy individuals may have been underestimated. This possibility is worth consideration in view of the large increases in adrenal 17-ketosteroid output during severe stress. The amount and ratio of androgens measured in plasma and urine of stressed animals differ from those of normal subjects. Exposure to a variety of stressors—including shock avoidance, living in overpopulated colonies, and adreno-

corticotropin (ACTH)—decreases both testicular size and plasma and urine testosterone concentrations but increases the amount of androgen secreted by the adrenal cortex (5). Presumably the increased adrenal androgen is androstenedione since 80 to 85 percent of adrenal androgen is in this form in the normal organism (3). The fetal adrenal cortices also are highly secretory and respond to stress and ACTH (6), and the placenta is permeable to corticosteroids and ACTH (7); thus the fetus is exposed to maternal hormones as well as its own.

Sexual differentiation in male rats stressed during critical prenatal and postnatal developmental stages appears to take place in the presence of large amounts of the weak adrenal androgen, androstenedione, rather than under the primary influence of testosterone. The resulting behavioral potentials would be expected to resemble those obtained by other experimental manipulations which decrease functional testosterone titers. Male behavior should be reduced and female behavior enhanced. In a study designed to test these proposals, 14 time-mated Sprague-Dawley rats were stressed daily during three 45-minute sessions during days 14 to 21 of gestation by being restrained in 7 by 3 inch (18 by 8 cm) semicircular Plexiglas tubes across which 200 foot-candles (2150 lumens per square meter) of light were directed. This treatment produced piloerection and substantial amounts of urination and defecation. Nine control mothers were housed in an adjacent vivarium and were not handled. Half of the prenatally stressed litters and four of the control litters were then given daily postnatal stress from days 1 to 10 of age; stress consisted of three 30-minute sessions during which each male pup of a given litter was placed in a separate compartment of a plastic ice cube tray mounted on a vibrating metal rack. At about 90 days of age, all males were given 30-minute weekly tests with estrous lure females for spontaneous behavior. Each animal continued to be tested until he had either ejaculated or had failed to copulate for 6 weeks. The number of incomplete and complete intromission patterns as well as of ejaculations was recorded.

The results are presented in Table 1. A marked reduction was obtained in the percentage of prenatally stressed animals capable of showing the ejaculatory response. The postnatally stressed group did not differ from the control group, nor did the combination of pre-