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ADVISER'S APPROVAL L. Herbert Bruneau

SOME ASPECTS OF THE PHYSIOLOGICAL ACTIONS OF THYROID HORMONES

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ACTIONS OF THYROID HORMONES

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PREFACE

Through the years the focus of attention has been more and more on the whole life cycle of the thyroid hormone, which has thus become a major preoccupation. Much progress has been made in the elucidation of the hormonal life cycle and how abberrations in it can cause clinical sydromes. It is only recently that workers in this field have recognized that minute amounts of the thyroid hormones are secreted by the gland and will produce responses when administered to humans and experimental animals. For this reason, emphasis will be laid on work which deals with physiological rather than pharmacological effects.

The list of organs, organs systems, and metabolic processes affected by thyroid hormones is longer by far than that for any other hormone. If one seeks to find some unifying pattern or principle among these diverse functions of thyroxine, in the present state of our knowledge this proves impossible. What common factor could there be between: (a) guanine deposition in the fish scale; (b) melanin deposition in bird feathers; (c) threshold stimulus sensitivity in nervous receptors; (d) closure of epiphyses in bones; (3) schooling behavior in fishes; (f) creatine-

creatinine conversion; and (g) water diuresis?

It has been argued, because of this variety of actions, that thyroid hormones must influence cellular metabolism at some elementary level. Yet, if thyroid hormones influenced general cellular metabolism at such an elementary level, why are its effects not even more widespread? How can we explain what specificity of action thyroxine does have? These are some of the attitudes and questions which should be borne in mind in considering the numerous phenomena which can be classified as physiologic effects of thyroid hormones.

To gain perspective on the physiological actions of the thyroid hormones, I have interpreted results from observations on growth in mammals, alterations in physiological activities due to insufficient and excess amounts of the thyroid hormones, effects on metabolic rate or oxygen consumption in mammals and on the function of other glands or organs.

Indebtedness is acknowledged to Drs. W. S. Newcomer and L. H. Bruneau for their critical reading and valuable suggestions of this study. My thanks go to Mrs. Rose F. Buschman for assistance in proof reading.

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CHAPTER I

INTRODUCTION

The relatively simple structure of thyroxine makes it an inviting molecule for attempts at understanding hormone action. This promise of simplicity, however, is not apparently borne out by the multiplicity of thyroid actions. Variations of thyroid hormone concentration alter respiration, temperature regulation, growth, development, response to other hormones, nerve function, and the metabolism of proteins, fats, carbohydrates, vitamins, anions and cations.

If it is accepted that hormones act by reacting chemically at a locus on their target molecules, the structure of thyroxine suggests that the variety of physiological, chemical and physical manifestations can be attributed to a few types of interactions at the molecular level. Alternatively, the analogues of thyroxine may each have a different and specific reactivity that produces a different physiological result, and the conversion of one analogue to another accounts for the variety of hormone effects.

The chemical characteristics of the thyroid hormones

are of interest in respect to a number of problems. Some knowledge of these processes is available, but many other fundamental problems are scarcely elucidated. The chemically active parts within the molecule of the thyroid hormone which permit an effect upon the cells, and the nature of the receptor mechanisms which must exist within the cell to bind the hormone before it can accomplish its purpose, are poorly understood. However, a forward step seems to have been taken with the discovery of a series of thyroxine analogues which function as inhibitors of thyroxine within the cells, possibly in some instances, if not all, by the principle of specific metabolic or competitive inhibition.

Secretion and Transport

Thyroxine is formed in the thyroid gland. Only a small part of the thyroxine in the gland is in the free form (less than 1 per cent) and represents the immediate source of serum thyroxine. The secretion of hormone from the gland to the blood involves an enzymatic proteolysis of thyroglobulin in the gland, with liberation of free thyroxine and triiodothyronine. The rate of release of hormone from the thyroid is very largely regulated directly or indirectly by pituitary thyrotrophin, genetic factors, dietary iodide, adrenal gland and antithyroid drugs. The normal rate of secretion of thyroid hormones in man

is 0.2 to 5.2 ug. per 100 grams of body weight per day.[1]

The concentration of thyroid hormone in the blood is maintained at a more constant level than is the rate of secretion of hormone from the gland. This is because the blood level represents a balance between the rate of secretion and the rate of metabolism or excretion of the hormone.

The blood is not merely a passive vehicle for the transmission of hormonal products to the periphery, but contains specific constituents which interact with the thyroid hormones. The thyroid hormones are affixed to some plasma proteins. The alpha-globulin type of 'thyroxine binding globulin' (TBG) has the highest binding affinity for thyroxine. Thyroxine binding prealbumin (TBPA) has the next highest affinity for thyroxine. Serum albumin binding capacity is not known but it has very low affinity for thyroid hormones.

The binding of thyroxine by serum and tissue proteins is determined by a reversible equilibrium between bound and free thyroxine. The level of free thyroxine in human serum is 4×10^{-11}M. Triiodothyronine is bound more loosely than is thyroxine to thyroxine binding globulin and not at all to thyroxine binding prealbumin, its relative free concentration is higher than that of thyroxine. The importance of considering the free hormone level stems

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[1]Werner, Sidney C., The Thyroid: A Fundamental and Clinical Text (New York, 1962), p. 49.

from the fact that only the non-protein bound thyroxine or triiodothyronine can diffuse into the tissues and be made available for their metabolism or perhaps even for their actions.

Thyroxine binding globulin and thyroxine binding prealbumin exhibit very marked differences in their relative binding affinities for derivatives of thyroxine. Even slight modifications in the thyroxine molecule can dramatically increase, decrease or even abolish the interaction. TBG binds 3, 5, 3'-triiodothyronine one-third or one-fourth as firmly as thyroxine, TBPA does not interact at all with triiodothyronine; on the other hand, 3, 5, 3',5'-tetraiodothyroacetic acid is bound to TBPA about a thousand times as firmly as thyroxine is but hardly at all to TBG. The different binding sites in serum are involved in the interaction with different derivatives. These differences in relative binding affinities if reflected in the rates at which these compounds are distributed to tissues are due to excretion and metabolic use.

Active Forms and Penetrability

A number of congeners and analogues of thyroxine have been studied with a view towards delineating the specific contributions of the various portions of the intriguingly complex molecule. Reports in the literature show remarkable qualitative differences of certain analogues, such as

immediate calorigenic responses to 3, 5, 3'-triiodothyronine or to 3, 5, 3'-triiodothyroacetic acid and 3, 5, 3', 5'-tetraiodothyroacetic acid. None of these has received consistent confirmation and it is considered that compounds such as the pyruvic and acetic acid derivatives are metabolic products of 3, 5, 3'-triiodothyroacetic acid and 3, 5, 3', 5'-tetraiodothyroacetic acid rather than "activation" materials. The muscle tissue in general carries out not deamination or decarboxylation, but only deiodinatum of 3, 5, 3'-triiodothyronine and thyroxine.

The hormone 3, 5, 3'-triiodothyronine stimulates the basal metabolic rate more rapidly and intensely than thyroxine. It has been suggested that the conversion of thyroxine to 3, 5, 3'-triodothyronine is a homeostatic mechanism evoked by body need for increased hormonal action. The more rapid onset of response to 3, 5, 3'-triiodothyronine seen in the human is not as apparent as in lower mammals.

When the alanine side chain is replaced by a fatty acid of one to four carbon in length, metabolic activity is decreased, being only a few per cent of thyroxine with formic, 17 per cent with acetic, 8 per cent with propionic, and 4 per cent with butyric. The alanine side-chain is deaminated and decarboxylated by some tissues of the body and the pyruvate, lactate, and acetate derivates of thyroxine and 3, 5, 3'-triiodothyronine are encountered

physiologically, as well as the acetate, such as being the "activated" form of the thyroid hormones. Substitution of bromine, chlorine or methyl for all four iodines drastically lower the activity of thyroxine.

Actually, the preponderance of data indicates that the relative effectiveness of thyroid hormones depends upon their different distributions.[2] D-thyroxine and L-thyroxine are equally active on tissues. Although the L-isomers of either thyroxine or triiodothyronine are 10-20 times more effective in lowering serum cholesterol than D-isomers. Similar differences exist between the time courses of action of thyroxine and its analogues which vary both with the compounds chosen and the organ examined. Such differences in physiological response to thyroxine analogues arise from different abilities to reach the target sites rather than different affinities for those sites. The binding affinities of thyroxine and triiodothyronine are identical; the rate-limiting step is said to be a diffusion process, with triiodothyronine reaching the binding sites twice as fast as thyroxine whether differences in charge account for a 2-fold difference in diffusion constants or whether active selective transport occurs, is not certain.

In evaluating the effects of large amounts of thyroid hormone one must consider how much hormone penetrates to

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[2]Gross, J., "The Distribution of Radioactive Thyroid Hormones in Tissues," Brookhaven Symposia in Biology, No. 7 (1954), pp. 102-111.

the target sites on the molecular level. The actions of large amounts of thyroid hormones are sometimes thought to bear little relation to the effects of the minute quantities effective in the natural state; it is assumed that the administered hormone reaches its targets, and that the hormone acting in the normal situation is not actively concentrated at its locus of action.

The actual distribution of either naturally present thyroid hormone or administered doses is not yet entirely clear. Protein-bound stable iodine has been measured as an index of thyroxine concentration; on this basis, liver normally contains significantly higher concentration than serum or other tissues.

The binding of the thyroid hormones to proteins affects hormonal action.[3] Binding to serum proteins compete with the uptake of the hormone by tissues; on the other hand, some protein-thyroxine complexes are more active than the free hormone. Early studies indicate that desiccated thyroid has more physiological action than accounted for by its thyroxine content.

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[3]Farer, L. S. et al., "Thyroxine-Serum Protein Complexes in Various Animals," Endocrinology, 70 (1962), pp. 686-691.

CHAPTER II

UTILIZATION OF ENERGY

Calorigenic Action of Thyroid Hormones

The calorigenic action or effect on cellular oxidation of the thyroid hormones is their most fundamental action in adult mammals and is used as one of the indices of thyroid activity in man. The calorigenic action is generally represented in terms of the basal metabolic rate (BMR); this is a measure of heat production in a fasting subject who (ideally) is mentally and physically relaxed. Since calometry is not usually feasible, oxygen consumption is measured and heat production is then calculated. The basal metabolic activity since only the former is influenced directly by the thyroid hormones.

Large amounts of desiccated thyroid greatly elevate respiratory exchange. With the use of a smaller amount of isolated thyroid hormones, it is certain that the calorigenic action is of physiological significance. This calorigenic action is restricted to homeothermic vertebrates and invertebrates since the effect of thyroid hormones on the metabolic activity of poikilothermic vertebrates and

invertebrates is debatable.[4] It has been shown that every milligram of thyroxine produced an extra 1008 calories when given to man.

Evidence proving that the basal metabolic rate under steady-state conditions is in fact directly related to the level of circulating thyroid hormones has been obtained relatively recently. It had to await the microchemical measurement of blood iodine as a reliable indicator of circulating hormone. Salter[5] proposed the relationship,

$$BMR = \log (\text{blood I} - 3)$$

blood I being expressed as micrograms per 100 ml.

The measurement of basal metabolic rate is a valuable clinical test for diagnosis of thyroid disorders. Its value has, however, declined in recent years with the development of direct and indirect tests of thyroid function, such as radioiodine uptake and secretion, serum protein-bound and butanol-extractable iodine, and blood cholesterol.

Among the several hundred non-endocrine factors affecting basal metabolism that have been described, age, sex, environmental temperature, activity of skeletal muscles, activity of smooth muscles and the various organs, and

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[4]Lynn, W. G. and Wachowski, H. E., "Thyroid Gland and its Functions in Cold-Blooded Vertebrates," Quarterly Review of Biology, 26 (1951), pp. 123-129.

[5]Salter, W. T., "Fluctuations in Body Iodine," Physiological Review, 20 (1940), pp. 345-376.

activity of the central nervous system are important. Under basal conditions, 80 per cent of the oxygen consumption is accounted for by the activities of the brain, heart, splanchnic area, and kidneys, with an additional 5 per cent by the functioning of respiratory muscles. Females have a 3 to 5 per cent lower caloric output than males at all ages. Both the sexes, after the age of 20, show a slightly irregular, progressive decrease in oxygen consumption with advancing age; the rate of decrease is more abrupt from infancy to the age of 20.

Chemical Structure and Relative Potencies

Much interest has been focused on the relationship between chemical structure and hormonal activity; and with the discovery that triiodothyronine exhibited a relatively higher potency than thyroxine, research has been prompted in this field. It has been recently suggested that the foci of multiple biological activities of thyroid hormone reside in different parts of the molecule.[6] The concept of "dissociation" of biological functions according to chemical modifications has often been implicated as the basis for clinical application derivatives such as D-thyroxine and acetic, propionic, and formic acid derivatives of the iodothyronines in lowering blood cholesterol with the

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[6]Selenkow, H. A. and Asper, S. P. Jr., "Biological Activity of Compounds Structurally Related to Thyroxine," Physiological Review, 35 (1955), p. 426.

minimum calorigenic action.

Table I summarizes the influence of chemical modifications of the hormone molecule on its relative calorigenic potency. The relative values are only approximate since they were obtained from studies carried out under very different conditions. The diphenyl ether grouping is essential for calorigenic action since the iodotyrosines are inactive. The position of the substituents is important. As a rule, the 3, 5, 3'-triiodinated derivatives have a higher relative activity than the corresponding 3, 5, 3', 5'-tetraiodinated compounds, although a few exceptions are known. An interesting exception is 3', 5'-dimethyl-3, 5-diiodothyropropionic acid which is 30-40 per cent more active in stimulating basal metabolic rate than the 3, 5 3', 5'-tetraiodo analog.[7] There should be at least one substituent in each benzene ring; iodine as a substituent yields compounds with higher activity than those with bromine, chlorine, or other groups such as methyl and butyl. Modifications of the alanine side-chain of the thyroxine molecule, as in the formic, acetic, and propionic acid analogs result in a marked reduction in calorigenic potency.

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[7]Pittman, C. S., Shida, H., and Barker, S. B., "Effects of Methyl Group Substitution for Iodine on Metabolic Activity of Thyroxine, Triiodothyronine and Tetraiodothyropropionic Acid," Endocrinology, 68 (1961), pp. 248-252.

TABLE I

RELATIVE CALORIGENIC POTENCIES OF THYROID HORMONES AND SOME OF THEIR DERIVATIVES

Compound	Relative Potency
L-Thyroxine	100
D-Thyroxine	5-8
	8-12
3, 5, 3'-Triiodo-L-thyronine	150-350
	100-250
	90-100
3, 5, 3'-Triiodo-D-thyronine	10-15
3, 5-Diiodo-L-thyronine	0-5
3, 3', 5'-Triiodo-DL-thyronine	0-5
	0-3
2', 6'-Diiodo-DL thyronine	0
3-Iodo-L-thyronine	0-3
3'-Iodo-L-thyronine	0
3, 5-Diiodo-L-thyronine	0
3', 5'-Diiodo-DL thyronine	5
3, 3'-Diiodo-L-thyronine	5
3, 5, 3', 5'-Tetramethyl-DL-thyronine	0-3
3, 5-Diiodo-3', 5'-dimethyl-DL thyronine	0
3, 5-Diiodo-3'-methyl-DL-thyronine	17
3, 5, 3', 5'-Tetraiodothyropropionic acid	150
3, 5, 3'-Triiodothyropropionic acid	5-15
3, 5, 3', 5'-Tetraiodo thyroacetic acid	5-15
3, 5-Diiodo-3', 5'-dimethyl thyropropionic acid	5-15
3, 5, 3'-Triiodothyroacetic acid, Methyl ether	10
3, 5-Diiodothyroacetic acid	0-1
Thyroxamine	0-5
3, 5-Diiodo-thyronamine	0

Lipid Metabolism

Among the lipids, cholesterol shows the greatest regularity in response to the circulating level of thyroid hormone but other lipid components are affected similarly. The levels of neutral fat, phospholipid, B-lipoproteins, some fatty acids, total free tocopherols and the electrophoretically immobile chylomicron fractions have been shown to vary inversely with thyroid activity or circulating hormone level.

Thyroid hormone stimulates the removal of cholesterol from the plasma, which has been shown by the increase in the rate of turnover of labeled plasma cholesterol in thyrotoxic humans. Both the main pathways for the disposal of the plasma cholesterol - its excretion as sterol and its conversion to bile acids - are affected, but it is not known how the thyroid hormone brings about these two effects. The increase in the rate of removal of cholesterol is accompanied by an increase in the rate of synthesis, the net result being a fall in the plasma cholesterol level. The increased rate of synthesis is a response to the increase in the rate of removal, since cholesterol synthesis is related inversely to the cholesterol concentration in the liver. However, a combination of factors, one of which may be a fall in the concentration of adenine triphosphate in the liver may cause the rise in the rate of synthesis.[8]

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[8]Fletcher, K. and Myant, N. B., "Partial Reversal of the Effects of Thyroxine on Lipid Synthesis in Rat Liver by the Addition of Cofactors in Vitro, Journal of Physiology, 157 (1961), pp. 542-564.

The thyroid hormones influence the tissue distribution of neutral fat and fatty acids by modifying the rate of release of free fatty acids from the glyceride fat of the adipose tissue. Thyroid hormone acts in conjunction with other hormones, by potentiating the "tonic" stimulation of the adipose tissue cells brought about by the circulating epinephrine and the local sympathetic nerves.[9]

Cholesterol is an integral part of cell membranes and sub-cellular particle membranes and so many of the oxidative reactions in cholesterol degradation are associated with mitochondria which are rich in fatty acids of the poly-unsaturated-methylene-interrupted type. The turnover of cholesterol can be influenced by dietary factors such as the fatty acid composition and especially the linoleic acid content of the diet. Linoleic acid is one of the acids selectively esterified to cholesterol, as in most tissues and body fluids under normal dietary conditions cholesteryl linoleate is present in high concentration.

A number of thyroxine analogues capable of influencing cholesterol metabolism, after the manner of thyroxine, but with minimal effects on "metabolic" stimulation are shown in Table II. With the analogues being tested in various systems, various derivatives of thyroxine behave in different ways.

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[9]Kurland, G. S. and Freedberg, A. S., "Hormones, Cholesterol and Coronary Atheroselerosis," Circulation 22 (1960), p. 464.

TABLE II

EFFECTS OF THYROACTIVE COMPOUNDS

Thyroactive Compound	Relative Effect on Cholesterol Metabolism
3, 5, 3', 5'-tetraiodo-L-thyronine	100
3, 5, 3', 5'-tetraiodo-D-thyronine	10
3, 5, 3',5'-tetraiodothyropropionic acid	10.0
3, 5, 3', 5'-tetraiodothyroacetic acid	2.0
3, 5, 3', 5'-tetraiodothyroformic acid	1.0
3, 5, 3'-triiodo-L-thronine	300
3, 5, 3'-triiodo-D-thronine	150
3, 5, 3'-triiodothyropropionic acid	20.0
3, 5, 3'-triiodothyroacetic acid	30.0
3, 5, 3'-triiodothyroformic acid	1.0
3, 5-diiodo-L-thyronine	3.0
3, 5-diiodo-D-thyronine	2.0
3, 5-diiodothyroacetic acid	2.0
3, 5-diiodothyroformic acid	---

Vitamin Metabolism

Since the thyroid can affect nutrition by its influence on the metabolic rate and on metabolic processes, it is not surprising that requirements for certain vitamins are altered. Conflicting results have been obtained for vitamin metabolism because of inadequate control over the diet, variation in the dosages of vitamin supplements, and differences between species, age, or sex of the animals used.

Absorption or digestion of vitamin A, or both, and conversion of vitamin A is influenced by thyroid hormones. The carotenes, as vitamin A precursors, are one of the main sources of this vitamin in man. It was formerly held that the site of transformation of precursors to active vitamin A was in the liver, where vitamin A is stored. There is ample evidence in animals that the reaction takes place in the small intestinal mucosa. There is little storage of vitamin A when there is insufficient amount of thyroid hormones; therefore an increased excretion of carotene appear in the feces.

Thyroid hormones influence the relationship between caloric intake and vitamin B complex requirements. An increased need for vitamin B is necessary with increased thyroxine. There is evidence that this vitamin may decrease the nitrogen loss resulting from the catabolic action of thyroxine.

With excess thyroxine, vitamin D deficiency develops due to an increase fecal calcium.

Muscle Contraction

The thyroid hormones affect muscle contraction. Both excessive and insufficient amount of thyroid hormones cause changes in the skeletal musculature.[10]

If excess thyroid hormones are produced, there is some reduction in the power of muscular contraction, and is generally associated with easy fatigability and various degrees of muscular atrophy. The rapid weakness or myasthenia, as it is often called, is more evident in the large proximal limb muscles than in the distal ones, despite the fact that the muscular involvement is generalized. The small, distal limb muscles are also affected. Facial, laryngeal, pharyngeal, and lingual muscles are seldom sufficiently involved with excess thyroid hormones. The muscle weakness tends to vary from person to person, but rarely if ever progresses to total paralysis.

Muscular atrophy is detected by the intrinsic muscles of the hands and face. Concavity of the thenar and hypothenar muscle masses and deepening of the interosseous space appear, and there are hallows above and below the cheek bone.

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[10]Millikan, C. and Haines, S. F., "The Thyroid Gland in Relation to Neuromuscular Diseases," American Journal of Physiology, 135 (1949), p. 419.

The tendon reflexes tend to be brisk. The presence of tremor creates the appearance of fascicular twitching, but these twitchings of fascicles of muscles usually disappear when relaxation is complete.

Insufficient amounts of thyroid hormones cause stiffness and slowness of movement and may be greatly augmented by cold, a phenomenon which has been called paramyotonia. Speech is deliberate and slow, reflecting the retarded thought and action. The tongue is large and awkward. Aching pains in muscles are not infrequent, and muscular action itself may be painful. The strength of muscle contraction is not reduced, and in some instances is said to be increased. Muscle contraction is slow, but this depends, in part at least, on the retarded mental activity. The tendon reflexes are slow.[11]

Thyroid hormones cause single defects in the contractile mechanism of the muscle fiber. There is at present no evidence of interference with the transmission of nerve impulses along the spinal or peripheral neural pathways or across the myoneural junction. The disorder must be a functional one in the strict sense, for it has been unaccompanied by any structural change demonstrable by the histologic techniques in current use.

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[11]Chaney, G. W., "Tendon Reflexes in Myxedema," Journal of Clinical Endocrinology, 11 (1951), p. 1186.

Central Nervous System

No tissue suffers more severely than the brain from a lack of thyroid hormone during foetal development and in early life. The changes that occur in the central nervous system as a result of thyroid hormone deficiency vary according to the time of onset of the disease. The growth and differentiation of the brain is hindered. Thyroid hormone deficiencies often result in psychotic behavior with hallucination, confusion and stupor. Nervous function at all levels is influenced by thyroid hormone: exchange of water and salts between cells and body fluids, spontaneous electrical activity, threshold of sensitivity to a variety of stimuli, reflex time, motor behavior, and mental activity.

A deficiency of thyroid hormone is known to hinder the action of a number of important cerebral enzyme systems.[12] The central nervous system is dependent on these enzymes for normal metabolic activity, a deficiency will interfere with cerebral function and is a factor in the pathogenesis of the mental retardation, psychosis and coma. Most available evidence indicates that with decreased thyroid hormone there are decreased rates of cerebral blood flow and of cerebral oxygen consumption.

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[12]Thompson, R. H. S. and King, E. J., "Biochemical Disorders in Human Disease," (New York, 1957) pp. 338-342.

The total oxygen consumption of the brain is reduced 37 per cent and the cerebral oxygen utilization by 27 per cent; the cerebral blood flow is lowered 38 per cent and cerebral glucose consumption 26 per cent.[13]

There are changes in the Purkinje cells of the spinal cord, medulla, cerebellum and cortex due to insufficient amount of thyroid hormones. There are vacuolizations of nerve cells, eccentricity of nuclei as well as slight changes in the fibrils of the small pyramidal cells. There is generalized chromatolysis of the entire nervous system.

The cranial nerves are also affected by insufficient thyroid hormones. Vision is blurred due to primary optic atrophy, retrobulbar neuritis and retinitis with central scotomas. Hearing is disturbed due to deafness in the nerve and middle ear either separately or in combinations. There is depression of taste and smell. The tenth and twelfth crainal nerves are impaired. Slurred speech due to infiltration of the vocal cords and tongue is detected. Disturbance in the sensory portion of the fifth cranial nerve causes facial neuralgia.

Insufficient thyroid hormones effect changes in the peripheral nerves. There are subjective sensory complaints such as numbness of the hands and feet, and lancinating extremity pain and burning pareathesia. Sluggishness, fatigue, and psychomotor retardation also involve the nervous system with insufficient thyroid hormones.

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[13]Scheinberg, P. et al., "Correlative Observation on Cerebral Metabolism and Cardiac Output in Myxedema," Journal of Clinical Investigation, 29 (1950), 1139-1145.

The increased secretions of thyroid hormones cause emotional instability. Tremor, sweating, labile tachycardia, and loose bowels are experienced by anxiety. Tears are precipitated by trivialities. Speech is rapid and excitable, with frequent change in topic. Cerebral dysfunction is largely the result of heightened metabolic rate, with unknown factors possibly playing a role.

Skeletal System

The thyroid hormone has an important role in osseous development. With the decrease in the thyroid hormone there is marked retardation of ossification and the body retains infantile characteristic of bone structure not encountered to the same degree in other types of dwarfism with regarded bone age. The maturing skeleton in childhood is more sensitive than are other systems to thyroid hormone deficiency. In thyroid deficiency in children the upper and lower skeletal segments remains infantile in relation to chronologic age and there is marked retardation of the ossification of the epiphysis and appearance of bone nuclei together with a lack of maturation of the naso-orbital configuration.[14] The locus of damage to both growth and maturation patterns of skeleton is in the diaphysio-

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[14]Wilkins, L., The Diagnosis and Treatment of Endocrine Disorder in Childhood and Adolescence, Springfield, (1957), pp. 85-105.

epiphyseal plane without any modification of bone texture and weight or prolongation of the growth period to compensate for diminished velocity.

The action of various hormones on the sequence of browth and maturation is very complex, for one hormone may effect the production of another and the interrelationships in their attack on end organs may be confusing. Furthermore, hormones apparently do not initiate unique sequences of events but only modify the pattern of growth and development within limits determined by genetic constitution.

Excess thyroid hormone produce profound changes in calcium and phosphorus metabolism, but rarely does it cause severe disease of the skeleton. The most frequent is a collapsed vertebra. Periarthritis of the shoulder (subacromial bursitis) is frequently associated with excess thyroid hormone. Linear bone growth is accelerated in children. The time of epipyseal closure is accelerated. In children, bone age may exceed chronoligic age.

There is no direct evidence of increased parathyroid activity with excess thyroid hormone. There is an accelerated turnover of calcium. The serum calcium level is usually elevated sufficiently to produce nausea and vomitting, and renal damage.[15] Phosphorus administration lowers the concentration of calcium in serum and urine to normal levels.

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[15]Walter, D. G., "An Assay of the Skeletogenic Effect of L-triiodothyronine and its Acetic Acid Analogue." Bulletin John Hopkins Hospital, 101 (1957), p. 101.

The bones affected by bone demineralization are the spine, ribs, pelvis and long bones. Spontaneous compression fractures of the neck and supracondylar area of the femur also occur.

The effect of thyroid hormone upon the acceleration of maturation is very striking. Doses of L-triiodothyronine as low as 2×10^{-9} moles per 10 pounds body weight double the rate of skeletal differentiation.[16] Triiodothyroacetic acid produces qualitatively similar effects but in higher doses. Both thyrosine and triiodothyronine in physiologic concentrations hasten maturation of isolated limb buds in tissue culture.

Cardiovascular System and Blood

Marked increases in oxidative metabolism of essentially all tissues with excess thyroid hormones create an enormous demand for oxygen which must be satisfied by the heart and circulation. Consequent to this demand, there is an increase in circulating erythrocyte mass, in blood volume and velocity. Blood flow to selected areas such as skin, muscle, and kidneys is increased, but is normal in the cerebral and splanchnic circulations.[17]

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[16]Follis, R. H., Jr., "Skeletal Changes Associated with Hyperthyroidism," Endocrinology, 29 (1941), p. 258.

[17]Andrus, E. C., "The Thyroid and the Circulation," Circulation, 7 (1953), pp. 437-442.

The splanchnic arteriovenous oxygen difference is increased despite the normal rate of flow. The oxygen requirements are only determinants of flow. The greater flow through skin and lungs than through the splanchnic bed depends upon the necessity to dissipate excissive heat in order to maintain thermal homeostasis. The increase in pulse pressure results from increased cardiac output in association with reduced peripheral resistance. The pulse on palpitation is rapid and bounding. The systolic blood pressure is frequently elevated. The diastolic blood pressure is characteristically decreased. The heart beats with extreme violence.

To propel an increased blood volume at the velocity necessary to maintain a normal or slightly decreased arterio-venous oxygen difference, the minute volume output of the heart must increase to double that of normal subjects at rest. The principal physiologic mechanism for maintenance of this high cardiac output is an accelerated heart rate without significant increase in stroke output.

With insufficient amount of thyroid hormone being produced there is a reduction in both minute output and stroke output and these alterations are parallel to the fall in oxygen consumption. The ratio of cardiac output to oxygen consumption does not differ from normal and it is not uncommon to have reduction of 50 percent in cardiac output. The peripheral venous pressures and right atrial pressures are not elevated except in the pressure of cardiac failure or large pericardical effusions. Blood velocity

and flow are diminished and peripheral resistance is increased. The blood volume is reduced as is the circulatory erythrocyte mass. Some organs such as the brain and kidney show a fall in blood flow paralleling the reduction in oxygen consumption. Because of diminished flow, the skin may show an increase in arteriovenous oxygen difference disproportionate to oxygen consumption and this accounts for the overall increase in A-V difference of mixed venous blood. There is a diminished vital capacity of the lungs in the absence of congestive heart failure caused by obesity and alveolar hypoventilation.

Cerebral blood flow and oxygen consumption are both decreased to the same extent so that cerebral A-V oxygen difference remains unaltered.

Besides its action on the cardiovascular apparatus, the thyroid hormone effect changes in the composition of the blood.[18] The red blood cell and hemoglobin values are in the low normal range and the red cell diameter, shape, and hemoglobin concentration, as well as serum iron and bilirubin levels, differ slightly from normal.

Total blood volume is increased with respect to both plasma and total red cell mass. However, this increase does not exceed 10 per cent. This results from peripheral

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[18]Kunde, M. M., Green, M. F., and Burns, G., "Blood Changes in Experimental Hypo-and Hyperthyroidism," American Journal of Physiology, 99 (1952), pp. 469-475.

vasodilatation, with arteriovenous shunts and increased cardiac output.

The peripheral white blood cell count is normal or slightly low. Lymphocytosis, absolute or relative, is by no means always present. Although lymphocytosis is often slight, lymphocytes occasionally exceed 50 per cent of the total leukocytes and include abnormal types.

With excess or insufficient amounts of thyroid hormones there is no deviation in the number of platelets. Coagulation is also normal in spite of mild prolongation of prothrombin time. The low prothrombin level is thought to be related to liver damage, as a result of depletion of glycogen and other substances.

The iron-binding capacity of the serum is lowered resulting in a greater need for iron in the tissues. Pernicious anaemia is thought to be associated with insufficient thyroid hormones.

Water Metabolism

The effect of thyroid hormone on water metabolism is due to the general disturbance in cellular metabolism. The filtration of water through capillary walls is decreased and insensible water loss via the lungs is diminished in proportion to the decrease in basal metabolic rate while such loss through the skin is decreased to an even greater degree with insufficient thyroid hormone. Decrease in thyroid hormones causes diminished maximal renal tubular

secretory and reabsorptive capacity, in association with depression in renal blood flow and glomerular filtration. Intrarenal vasoconstriction approximately commensurate with that elsewhere in the body is responsible for change in renal blood flow, but it is uncertain whether this is a response to systemic circulatory inadequacy or to chronic anemia.

Excess thyroid hormones have an effect on total body water but in general the volume of extracellular fluid and of plasma are raised. In general, the blood sugar, the blood urea and nonprotein nitrogen and the serum electrolytes remain within normal limits. Renal function in man is altered. Renal hemodynamic changes, consisting of increased renal blood flow and glomerular filtration rate, are attributable to intrarenal vasodilation mirroring vasodilation elsewhere in the body.[19]

Reproduction

Thyroid hormone has some influence on almost every phase of reproduction.[20] The thyroid hormone is essential for the maintenance of fertility, pregnancy, ovulation

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[19]Mokler, C. M., "Influence of Thyroid Hormone on Body Water Compartments in Dogs," Federation Proceedings, 18 (1959), pp. 106-111.

[20]Pitt-Rivers, Rosalind and Trotter, W. R., ed., The Thyroid and Reproduction in Mammals, by N. B. Myant (Washington, 1964), I, pp. 283-298.

and mammary function. This hormone plays a synergistic, auxiliary or complementary role particularly in the female, at periods of sexual and reproductive activity. Thyroid hormone in physiological amounts has effect on reproduction in the adult male in most species.

With excess thyroxine being produced, sexual maturation is retarded in both sexes. In males, excess thyroxine or desiccated thyroid causes a decrease in sperm production and in the weight of the testis and the accessory sexual organs. In females, excess thyroxine causes changes in the menstrual cycle, usually taking the form of an amenorrhea or lengthening of the interval between periods and in a decreased flow.

Insufficient amount of thyroxine may have its origin at the time of puberty. It is characterized by retardation of bone growth, obestity, delayed development of the generative organs, a postponed menarche, and, later, a tendency to menorrhagia. In adult females, abnormal uterine bleeding is frequently due to defects in the follicle-corpus lutem cycle. Psychogenic factors may be responsible in many cases, acting by way of the autonomic nervous system upon the vessels or musculature of the uterus. With small amounts of thyroid hormone fertility is impaired due to menstruation or ovulation being abnormal, so there is a definite degree of sterility. Early abortion due to defect in the mechanism responsible for the physiologic lowering in the protein-bound iodine during the pregnant state and decrease in the milk yield in the mammary glands

are caused by thyroid deficiency. In males marked testicular atrophy is present and a loss of axillary and pubic hair, as well as hair on the face and body. The rate of hair growth, especially of the beard, is noticeably decreased.

The reproductive capacity of some individuals within a species is unaffected by a wide range between excess and insufficient thyroid hormone, whereas other individuals tolerate only a narrower range before reproduction is impaired.

Anions and Cations

The alterations in magnesium metabolism under the influence of the thyroid hormones have been investigated but are still not well defined. But in recent findings the "free" and the "bound" magnesium is below normal with decreased thyroid hormone.

Phosphorus metabolism is altered markedly under the influence of thyroid hormones. With excess thyroxine a negative phosphorus balance exists and is lost both in the urine and feces. The phosphate loss is not correlated with the basal metabolic rate. The excretion is higher than expected from nitrogen and calcium excretion and this suggests that increased phosphocreatine breakdown is the source for the extra phosphate. The rate of incorporation of phosphorus into organic linkage is decreased in the muscle, liver and kidney. The turnover rate of phosphorus is increased in the bones and the disturbance in phosphate metabolism affects mobilizable bone phosphate.

With insufficient thyroid hormone there is a decrease in the rate of accumulation of serum phosphate and increased cellular phosphatase activity in the long bones.

The metabolism of calcium is occasionally altered with chief alterations observed in bones; they are also found in other tissues. Calcium is reduced in fecal and urinary excretion with reduced thyroid hormone. A positive balance of this constituent can be expected provided an equivalent decrease in the intake of calcium has not occurred.

Increased thyroid hormone causes increased turnover rate of calcium in the bones but with slight decrease in the long bones and skeletal muscles.

Sodium and potassium exchange is decreased with excess thyroxine. The uptake of potassium is decreased in erythrocytes although the total erythrocyte potassium is unchanged. The alteration in potassium metabolism depends upon the calcium and magnesium concentration in the body. Thyroxine decreases the ratio of intra-to extracellular potassium in the brain.

CHAPTER III

SUMMARY AND CONCLUSIONS

From the numerous phenomena which can be classified as physiologic effects of thyroid hormones, thyroxine is obviously an essential part of the body's homeokinetic mechanisms. It's most clearely definable single function is the establishment of the fundamental rate of energy turnover for muscle, heart, liver and kidney. In achieving this, the hormone is probably bound to some specific protein site with especial affinity for 3, 5 and 3' positions on the diphenyl ether portion of the molecule. The process by which thyroxine affects energy turnover is not thoroughly understood, but may well involve special aspects of amino acid and protein metabolism, possibly including formation of new enzymatically active protein.

Besides this metabolic function, thyroxine is also intimately concerned in such specialized body processes as growth and development, nervous system activity, response to catechol amines, and reproduction. The evidence is not in favor of these being controlled through energy turnover, but they may well be a result of the same basic alterations (in specific proteins, for instance) which result in metabolic control. Despite the increasing depth of our

knowledge concerning thyroid hormone action, one cannot at the present time be more definite.

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