LITERATURE REVIEW

General Consideration

Thyroid hormones, the principal hormones secreted by the thyroid gland, have the profound stimulating effect on the metabolic rate of the body. Regarding to the mechanism, via wholesale nuclear transcription of a large number of genes, thyroid hormones cause an increased production of several cellular proteins i.e. enzymatic proteins, structural proteins and transport proteins. These consequences lead to a generalized increase in functional activity throughout the body (Larsen and Ingbar, 1992).

It has been well recognized that thyroid hormones are also essential for normal growth and maturation. The growth - promoting effect of thyroid hormones is presumably based on its ability to promote protein synthesis. In the human being, the effect of thyroid hormones on growth is manifested mainly in growing children. During childhood, the thyroid hormones act synergistically with the growth hormone to promote the body growth and normal development (Fisher and Klein, 1981).

Hypothyroidism and Muscular Disorders

Hypothyroidism is the clinical and biochemical syndromes that result from the decreased thyroid hormone production and subnormal serum thyroid hormone concentrations (Utiger, 1989). Hypothyrodism affects most, although not all, bodily organs including the skeletal muscles as a major target organ of thyroid

hormones. The clinical presentations of skeletal muscles vary, depending on the severity of hypothyroidism. The primary manifestations are muscle weakness, fatigue, aching or painful spasms, slow movements and slow reflex responses, and less commonly, muscle cramps and/or muscle enlargement (Ruff, 1986). Lambert, et al. (1951) suggested that the neuromuscular abnormalities occurring in hypothyroid patients were due to an alteration in the contractile mechanism of the muscle itself rather than the defects of motor nerve transmission. This is evidently supported by clinical electromyography. It has been demonstrated that the electromyograms (EMG) in hypothyroid patients are variable , usually , normal EMG or low amplitude polyphasic motor unit potentials are observed (Ruff, 1986). However, so far the mechanisms by which hypothyroidism causes the neuromuscular abnormalities, are poorly understood.

A number of clinical and experimental documents have been demonstrated that hypothyroidism induces a number of morphological, biochemical and functional changes in skeletal muscles (Gold, et al. 1970; McDaniel, et al., 1977; Wiles, et al., 1979; Baldwin, et al., 1980; McAllister, Ogilvie and Terjung, 1991; Caiozzo, Herrick and Baldwin, 1992). Light microscopic and ultrastructural studies in hypothyroid muscles reveal non - specific alterations, including fiber atrophy or enlargements, an increased internal nuclei, the aggregations of mitochondria and glycogen, a dilated sarcoplasmic reticulum and proliferating T - system profiles (Ruff,1986). In addition, experimental results exhibited the reduction of mitochondrial contents in hypothyroid muscle. This has been observed by the study of Bladwin, et al. (1980), who demonstrated that there was a coordinated reduction in mitochondrial components which included cristae elements (e.g., cytochrome c) and related matrix enzymes (e.g., citrate synthase).

The circulating levels of thyroid hormones have been shown to influence the distribution of muscle fiber types. According to the histochemical staining, skeletal muscle fibers have been classified into three fiber types (Gardiner, et al.1980; Hickson, et al., 1984). The slow - twitch red fibers (type I fibers) are characterized by low adenosine triphosphatase (ATPase) activity, high respiratory capacity and low glycolytic capacity. The fast - twitch red fibers (type IIa fibers) contain high ATPase activity, high respiratory capacity and high glycolytic capacity and the fast - twitch white fibers (type IIb fibers) are characterized by high ATPase activity, low respiratory capacity and high glycolytic capacity. Experimental studies on thyroidectomized rats demonstrated the prominent changes in muscle fiber composition. In addition, this effect of thyroid hormones is specific for muscle fiber types. For fast - twitch extensor digitorum longus, hypothyroid state produces a decrease of fast - twitch white fibers (type IIb fibers) and, in contradictory, an increase of slow - twitch fibers (type I fibers). Furthermore, the characteristics of the myofibrillar ATPase, myosin light chains, and lactate dehydrogenase in hypothyroid fast muscle shift to those typical slow muscles (Nihoye and Mommaerts, 1981). Since the increase in slow - twitch fiber complement contributes to the reduction in the energy cost of the muscle contraction, the phenotypic changes in muscle fiber composition may be expected to improve the economy of contraction of hypothyroid muscle (McAllister, Ogilvie and Terjung, 1991). However, it still remains unclear whether hypothyroid status can induce an actual transformation of fast twitch fibers to slow - twitch fibers.

Hypothyroid myopathy has been reported as one of the clinical manifestations. Myopathy varies from mild fatigue to profound weakness and muscle cramps. Halverson, et al. (1979) observed the inflammatory infiltration and fiber necrosis, resembling polymyositis, in the patient with hypothyroidism in addition to myopathy. There has been recently reported the selective atrophy of muscle fibers in hypothyroid state. Clinical studies further extend that the selective atrophy of type II muscle fibers predominates in the adult case of acquired hypothyroidism (McKeran, et al., 1980) while the selective atrophy of type I muscle fibers is characterized in the Kocher - Debre' - Se'me'larigne syndrome of cretinism (Spiro, et al., 1970).

Biochemical changes induced by hypothyroidism result in the reduction in O_2 consumption and basal metabolic rate. These alterations might be occurred as a consequence of mitochondrial impairment (Ruff, 1986). Additionally, clinical and experimental documents have been shown that muscle oxidative enzyme activity as well as mitochondrial oxidative capacity are decreased in hypothyroidism (Gollnick and Ianuzzo, 1972; Hardeveld and Kassenaar, 1978; Baldwin, et al., 1980).

A number of changes in carbohydrate metabolism has been found in hypothyroidism. Experimental results demonstrated that the blood glucose turns over at a significantly lower rate in hypothyroid animals than in euthyroid animals. In addition, the hepatic content of glycogen is much low in hypothyroidism. Collectively, a substantial evidence suggested that hypothyroidism inhibited the hepatic gluconeogenesis, and thus, this inhibition led to suppression of both glucose liberation into the circulation as well as glycogenesis in the liver (Okajima and Ui, 1979). It has been found that glycogen breakdown is also impaired in hypothyroid patient as well. In accordance with this clinical finding, the defect of

glycogen breakdown in the skeletal muscle is associated with the complaint of muscle weakness and the hypothyroid myopathy (McDaniel, et al., 1977).

Thyroid hormones also play the essential role on promoting body growth and normal development. The deficiency of these hormones results in severely short stature which is clinically termed hypothyroid - dwarfism. The growth retardation in hypothyroid state associates with arrests of bone elongation as well as retarded bone maturation (Utiger, 1989). Crispell, et al.(1956) ascribed that one cause of growth retardation in hypothyroidism relates to the decreased protein turnover. They found that both synthesis and degradation of protein were decreased with a net protein catabolism in hypothyroidism. The diminished protein synthesis in hypothyroid state has been suggested to be due to the impairment of transcription. This was clarified by experimental study which showed a reduction in muscle RNA in thyroidectomized rats while the RNA activity was essentially normal (Flaim, Li, and Jefferson, 1978; Burini, et al., 1981). The other possible cause of growth retardation in hypothyroidism is the lack of the effect of growth hormone (GH). It has been reported that thyroid hormone deficiency is accompanied by both a decrease in secretion and a lessened effectiveness of GH (Utiger, 1989). Thus, in conclusion, thyroid hormones in concert with GH play an important role on the body growth and development.

Recently, much attention has focused on the biochemical changes of contractile protein in hypothyroid state. Myosin is recognized as the most abundant contractile protein accounting for about 50 - 60 % of the total muscle myofibril proteins. Structurally, myosin is composed of two heavy chains and pairs of light chains. In the skeletal muscle of rat, myosin exists as a large family of protein isoforms. Experimental studies by using nondenaturing gel

electrophoresis elucidated 5 distinct myosin isoforms within the adult rodent hindlimb musculatures: slow myosin (SM), intermediate myosin (IM) and three fast myosins (FM_1, FM_2, and FM_3). The slow - twitch muscles such as soleus which function primary as antigravity muscles, contain a native isomyosin profile that is predominately SM. On the other hand, IM appears to be expressed in the skeletal muscle composed of a high percentage of fast - twitch red (Type IIa) muscle fibers. In contrast, the three fast myosins are normally expressed in skeletal muscle that possesses a large proportion of fast - twitch white (type IIb) muscle fibers (Tsika, Herrick and Baldwin, 1987). It has been suggested that the diversities of myosin isoforms presenting in the muscle are due to the polymorphic expression of both the light chain (MLC) and heavy chain (MHC) subunits that are encoded by a highly conserved multigene family. By recombinant DNA methodology, 3 MHC genes are predominantly expressed in adult rat skeletal muscle and are designated as fast type IIb (fast - twitch glycolytic, FG), fast type IIa (fast - twitch oxidative - glycolytic, FOG), and slow type I (slow - twitch oxidative, SO) MHC genes.

A number of studies (Fitzsimons, Herrick and Baldwin, 1990; Caiozzo, Herrick and Baldwin, 1992; petrof, et al., 1992), focusing at both the messenger RNA and protein levels, has demonstrated that the expression of the myosin heavy chain (MHC) and myosin light chains (MLC) is influenced by the thyroid state of the animals. Additionally, the mechanism was postulated that thyroid hormones exerted their actions on the phenotypic expression of MHC genes. Experimental studies revealed that the slow muscle was much more responsive than the fast muscle to an altered thyroid state. Alternately, regarding to the native protein level, muscle fibers that express large percentage of slow type I MHC genes will be affected the most, whereas fast muscle fibers expressing

type IIb MHC genes, will be minimally affected. These findings are strongly confirmed by the study of Izumo, et al. (1986). They demonstrated that in the soleus which was classified as the slow muscle, the expression of the intermediate myosion (IM) isoforms and type IIa MHC genes was completely depressed whereas the expression of slow myosion (SM) isoforms and slow type I MHC genes was increased by hypothyroid state. In plantaris which constituted mainly by the fast fibers, hypothyroidism also produced the shift in the distribution of myosin isoforms. However, the altered expression was relatively small with respect to the total myosin pools. Conclusively, the effects of thyroid hormones on the distribution of myosin isoform appear to be muscle specific and these may lead to the alteration of the contractile properties of skeletal muscle.

Hypothyroidism and Contractile Properties of Skeletal Muscle

Alteration in the level of thyroid activities lead to a numbers of clinical features representing the changes in the functional characteristics of skeletal muscle. Clinical findings demonstrate that there are the slow contraction and relaxation of hypothyroid skeletal muscles (Lambert, et al., 1951). In addition, Denys and Hofmann (1972) and Everts, et al. (1981) pointed out that in thyroidectomized rats, the contraction times of single and tetanic twitches were increased. It has been attributed that the prolongation of contraction time might be secondary to the slowness of relaxation of the hypothyroid muscle. Since speed of muscle shortening is markedly correlated with myosin ATPase activity while the sarcoplasmic reticulum apparently plays an important role on excitation - contraction coupling as well as regulating the speeds of contraction and

relaxation of muscle (Ruff, 1986). Thus, it seems that the alteration in myosin ATPase activity (Wiles, et al., 1979; Nihoye and Mommarts, 1981) and the impairment of Ca^{2+} uptake by the sarcoplasmic reticulum (Fangburg, 1968) in hypothyroid state are possible alternative explanation for the sluggish contraction and relaxation of muscle. This is in accordance with the studies of neural conduction time of the deep tendon reflex by Lambert, et al. (1951) who suggested that an alteration in contractile activity in hypothyroid muscles was due to factors which were intrinsic to the muscle rather than those neurals in origin.

Several attempts have been made to study the effects of hypothyroidism on muscle tension. However, the results are still in debate. Grossie (1978) and Everts, et al. (1981) reported that hypothyroidism did not affect both twitch and tetanic tensions. In contrast, Gold and his colleague (1970), provided the experimental evidence demonstrating that isometric twitch tension was decreased in hypothyroid muscles. Based on the greater cross - sectional area of type IIb fibers, the muscle composing of type I and IIa muscle fibers generates substantially lesser tension than the muscle possessing a large proportion of type IIb muscle fibers (Eddinger and Moss, 1987). Petrof, et al. (1992) suggested that the alterations in muscle fiber composition in hypothyroid state might associate with the reduction in force generating capacity. This was correlated with the experiments which were studied by McAllister, et al. (1991). The results exhibited a significant increase over controls in the proportion of type I fibers in hypothyroid - fast twitch - plantaris muscle and consequently, the reduction in isometric force was observed. Furthermore, one possible explanation for the decrement of muscle tension in hypothyroidism seemed to be in part due to the

impaired energy metabolism, thereby, the force generation might be limited (Ruff, 1986).

Endurance Exercise and Skeletal Muscle

The word " exercise " is defined as an active bodily exertion for the sake of restoring the organs and functions to a healthy state or keeping them healthy. The improvement of body organ functions in a number of ways by exercise training varies in their extents according to the type of exercise as well as its intensity, duration and frequency. Two main contrasting types of exercise training are recognized: 1) endurance training involving exercise of relatively low intensity but being maintained for long periods and 2) strength training using the overload principal and progressive resistance technique in which muscles undergo repetitive motion against submaximal resistance (Jones, 1988).

Collectively, results from a comprehensive studies demonstrated that an increase in endurance, as a consequence of regularly performed endurance exercise training, is secondary to the major adaptation in skeletal muscles by increasing their oxidative potential. These adaptations include the changes in structural and metabolic profiles. The prominent structural changes as a result of endurance training are an increase in size and number of mitochondrias including mitochondrial contents (Collnick and King, 1969; Edstrom and Grimby, 1986). Studies in both humans and experimental animals clearly illustrate that capillary density as a local response to endurance training is increased (Andersen, 1975;

Brodal, Ingjer and Hermansen, 1977) whereas the muscle fiber size has been reduced (Housion, Benzen and Larsen, 1979; Edstrom and Grimby, 1986). Thus, when regarded as an adaptive change, the increase vascularization and reduced fiber size both facilitate the transport of substrates, metabolites and O_2 between the fibers and circulation (Edstrom and Grimby, 1986).

Regarding to the metabolic adaptation, endurance training enhances an increased utilization of fat with a proportional decreases in carbohydrate utilization during submaximal exercise. The adaptation is the result of an increase in the intrinsic ability of muscle to oxidize free fatty acid (Holloszy and Coyle, 1984). Moreover, the experimental findings on the enzyme activity illustrate that the activity of mitochondrial respiratory enzymes were, as a result of endurance training, enhanced while the activity of some glycolytic enzymes, particulary, lactate dehydrogenase is depressed (Sjodin, 1976; Chi, et al., 1983). As a whole, the major metabolic consequences of the adaptations of muscle to endurance exercise are a slower utilization of muscle glycogen and blood glucose, a greater reliance on fat oxidation and less lactate production during exercise (Holloszy and Coyle, 1984).

The results obtained from the experimental study in rabbits demonstrated that the long - term stimulations of fast - twitch tibialis anterior and extensor digitorum longus muscles with a frequency pattern resembling that of slow motor neuron activity produced the changes in contractile properties to be the typical slow twitch muscle, for instance, a marked increase in the time to peak and half - relaxation time of the isometric twitch, a decrease in tetanus to twitch ratio and a decrease in the rate of development of tetanic tension (Pette, et al., 1973). In accordance with the study of Jansson and Kaiser (1977) and Chi, et al. (1983), the endurance training induced the selective transformation of muscle

fiber type. Furthermore, an available evidence exhibits that there are a complete conversion of type IIb muscle fibers which normally possess the lowest aerobic capacity to type IIa muscle fibers which have the high oxidative capacity in response to endurance training. These changes were assumed to be another possible way that muscle fibers adapt to increase endurance.

Recently, many investigators have reported the effects of exercise on the expression of skeletal muscle myosin isoform in addition to the transformation of muscle fiber type. In experimental studies on rats subjected to exercise running for 14 week duration, Gregory, Low and Stirewalt (1986) found the dramatic alteration in the myosin isoform expression of the plantaris muscle which normally composes of 53 % fast - red fibers (type IIa muscle fibers), 41 % fast - white fibers (type IIb muscle fibers) and a small proportion (6 %) of slow - twitch fibers (type I muscle fibers). By pyrophosphate / polyacrylamide - gel electrophoresis, a considerable increase in the slow myosin (SM) and intermediate myosin (IM) isoforms has been observed in plantaris muscle obtained from the trained rats. In soleus muscle which contains primarily slow - twitch fibers (type I muscle fibers) as well as a small population (6 - 20 %) of fast twitch fibers (type IIa muscle fibers). The changes of myosin isoform with exercise were characterized by an increase in slow myosin isoform (SM). However, the changes in myosin isoform in the slow soleus are less pronounced than those in the fast plantaris, presumable because the soleus has already well adapted to aerobic exercise (Close, 1972).

Hypothyroidism and Endurance Exercise

Although a normal thyroid state is necessary for maintaining biochemical and functional properties of skeletal muscle, some of the typical exercise-induced responses observed in normal animals have been found in thyroidectomized animals subjected to training. These responses include : resting bradycardia, increased ligamentous strength (Tipton, Tarjung and Barnard, 1968) and cardiac hypertrophy (Song, et al., 1973).

Previous reports have also demonstrated that exercise training in thyroid - deficient animals induced metabolic adaptations in skeletal muscles. Studies in thyroidectomized rats with exercise training, Gollnick and Ianuzzo (1972) noted an increased activity of succinate dehydrogenase in the hindlimb muscles. Later, Terjung and Koerner (1976) noted that the absolute increase in cytochrome c in the skeletal muscles of the trained thyroidectomized animals was essentially the same as that of the normal trained animals. They suggested that these metabolic responses to training of an increased oxidative capacity in skeletal muscle were thyroid - independent responses. Subsequently, the study of Baldwin, et al. (1980), provided the supporting finding which illustrated that both maximal oxygen consumption and oxidative capacity of skeletal muscle of thyroid - deficient rats could be normalized by exercise training .