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ENDOCRINE RESPONSE TO TRAINING PROGRAMS
IN THE MIDLIFE

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SUMMARY

It has been proposed that regular physical exercise training could delay the normal process of aging and protect against the metabolic disorders of midlife. In order to relate the hormonal response to training and its protective effects, the recent theory on aging are firstly exposed. The role of hormonal changes on aging process is evoked. In the second part, the normal hormonal response to physical exercise and training, are exposed. In the last part, the specificity of hormonal response to training in midlife is used to explain some protective effect of training. The principal effect seem the improvement in insulin sensitivity but the role of training on growth hormone and androgen could be involved in the effect of training on muscle mass and bone density.

Key words : Hormonal response to training - Ageing process - Midlife - Insulin sensitivity - Growth hormone - Androgens.

INTRODUCTION

Continuation of physical training in midlife is of major epidemiological interest. The question is to know how far physical training is able to prevent ageing processes which start at midlife. To provide some answers to this question we will successively review the ageing theories and consequences of ageing on the energy metabolism and supporting tissues, and the influence of hormones on this process. Using this data, we will compare the hormonal response to training of young and older subjects; we will try and define relationships between the hormonal response to physical training and protection against the ageing process.

1. AGEING PROCESS

Current knowledge on the ageing mechanism has been comprehensively reviewed by Treton and Courtois (24). While we are totally unaware of it, a continuous biological process, senescence, takes place as soon as we are born and constantly changes the structure and operating process of our organism. This process takes place at a rate and according to patterns which are different for various categories of cells, tissues and organs. It concerns all strata of living matter, from the simplest molecules to the most sophisticated control systems.

Two families of theories, not necessarily contradictory, have attracted the attention of gerontologists over these past twenty years, one implying that ageing is an unpredictable (stochastic) phenomenon, the other defending the idea that ageing is programmed. These theories rely on the general concept that each organism has its own quota of life to live and will age and die as a function of the use made of this quota. Numerous experiments have been run to
try and modify this quota by various factors: temperature, caloric restriction, physical training. In cold-blooded animals it is possible to shorten or prolong life-span by modifying temperature as this factor has a direct effect on their metabolism. In mammals, we observe that small species (rats, mice) which have a high metabolism, live a short time whereas larger species (cows, horses) with a lower metabolism live longer.

Numerous experiments on diet restriction in mice and rats showed longer life-span, and reduced decline in the immune system associated with ageing. In certain cases it reduced the incidence of certain diseases including cancer.

Physical training has recently been recommended as a cure to improve health and prolong life (11). Life expectancy of laboratory rats is increased if regular moderate physical training (equivalent to jogging in man) is started in early life and always continued. However, too few long term investigations have been performed in man to give such results a general value. Regular exercise improves performance of the heart and lungs, reinforces bone strength, and prevents cardiovascular diseases. But the effects of physical training on life-span are still unknown. Several factors influenced by physical exercise may act upon ageing. Free radicals, generated by muscular effort can react with many biological molecules (fatty acids, DNA, proteins). Modified lipids (peroxide) alter the structure of biological membranes, causing a rupture of lysosomes, releasing the peroxidized or undegradable polymerized elements which can ultimately promote ageing.

Hormonal and immune phenomena resulting from physical exercise could act upon an internal clock or pace maker controlling ageing. There are two major categories of pace maker: in one, the pace maker is connected to the brain, more specifically to neuro-endocrine control on the anterior hypophysis; in the other the pace maker is connected to the thymus or immune system.

1.1. Pace maker hypothesis

Pacemaker connected to the hypophysis

The hypophysis is a gland which plays a key role in the life cycle of vertebrates (growth, sexual maturity) by its neuro-hormonal control. It has been shown that underfeeding depresses the anterior function of the hypophysis, delays maturation and prolongs life-span. A substantial increase in life-span is thus observed in rats which were hypophysectomized in early life and administered a treatment of corticoids. The ageing rate of collagen, kidneys and immune system of these animals is lower, and the incidence of vascular diseases is also reduced.

Pace maker connected to the thymus and immune system

This system changes during maturation and ageing and could play the role of ageing pace maker. This would result in a decline in T immune control and growing self-immunity. There is no doubt that changes in the T immune system take place during ageing and play a role in certain age related diseases (rheumatisms). However, the question is to know how far this immune phenomenon acts as causal agent of ageing. We will see later how it is possible to relate the hormonal response to physical exercise with its influences on the thymic and immune systems.

1.2. Metabolic and degenerative diseases associated with ageing

Aside from unavoidable programmed cell death, a number of diseases occurring at midlife may accelerate the ageing process. The high epidemiological prevalence of cardiovascular and metabolic diseases placed them at the forefront of investigations. It has been unequivocally shown that the normal ageing process is associated with enhanced resistance to insulin, partly considered as the cause of increased concentrations of circulating lipids and, particularly, very low density lipids (VLDL). This increase is associated with a gradual elevation of insulin concentrations in rats fed ad libitum (1). In rats restricted feeding increases life-span, this increase being associated with depressed insulinemia and circulating lipid concentrations (14). This data supports the idea that initial variations in sensitivity to insulin are the cause of changes in circulating lipid concentrations. The effect of physical training on prevention of metabolic diseases mostly results from the effects of physical exercise on the mechanism of insulin.

A decrease in the levels of insulin and an increase in the consumption of glucose are observed during physical exercise. Considering the role of insulin in the penetration of glucose into the muscle, this phenomenon may appear to be a paradox. However, this apparent contradiction disappears if we take into consideration the fact that exercise enhances glucose transportation into muscles. This phenomenon occurs at low insulinemia, but not if it is null. It is partly associated with a significant increase in sensitivity to insulin during physical exercise. Physical training makes this effect durable and permanently increases sensitivity to insulin. This plays a key role in metabolic changes induced by physical exercise. The study of animal models shows enhanced glucose transfer under the effect of the same concentration of insulin on rat muscles after three weeks of training (6)(Fig. 2). The mechanism of this enhanced sensitivity to insulin is associated with a reinforced insulin-
receptor binding, and also with an increase in the tyrosine kinase activity at the post-receptor stage. These studies on animals explain the effects of physical training observed on healthy man. Recent research by Sato et al. (21) using the insulin clamp showed a substantial increase in sensitivity to insulin in trained subjects compared to sedentary subjects.

However, another hormonal factor could be suggested to explain the effects of physical training on metabolism. Recent results by Rivière et al. (19) show that lipolysis induced by increasing concentrations of adrenaline is higher in preparations of adipocytes sampled from trained women, which shows that sensitivity to catecholamines increases under the effect of physical training. Several results indicate enhanced metabolism of lipids depending on the activation of enzymatic systems such as muscle lipoprotein lipase activity. This system is activated by plasma catecholamines. Such actions, combined with the various levels of lipid metabolism explain the difference in lipid concentrations in sedentary and trained subjects. The comparative study by Martin et al. (13) on changes in lipid concentrations as a function of three levels of physical activity indicates a decrease in cholesterol and triglycerides and a higher HDL fraction. Such results can be associated with the enhanced sensitivity to insulin and catecholamines resulting from physical training.

1.3. Effect of ageing on support tissues

The involution of support tissues, bone and muscle, which gradually takes place with ageing is a real problem as it influences the motor activity of the aged. In this review we will use data obtained from immobilization protocols as the reduction in activity is one of the main factors causing a shrinkage of muscle mass in ageing subjects. Ageing processes reduce muscle mass and contractility (12). This muscular atrophy is associated with a preferential decrement in the number of fast twitch fibers. Physical training is capable of reducing muscular atrophy caused by ageing (2)(Fig. 3). We will use current knowledge of the role of hormones on the trophicity of muscle tissue to suggest hypotheses on the protective role of physical training through hormonal responses. The main hormones which can act upon muscles are androgens, glucocorticoids, thyroid hormones, and growth hormone (GH).

1.4. Hormonal changes with ageing

Androgens

Numerous studies have shown that androgenous steroids have an anabolic effect. The histological analysis of this phenomenon shows that the increase in muscle mass results from an increase in the number of non contractile proteins. Administration of testosterone to immobilized rats prevents weight loss in postural muscles but not changes affecting contractile proteins (25). Immobilization also reduces the affinity of muscle testosterone receptors (7, 8).

Role of glucocorticoids

Numerous investigations (reviewed in ref. 7) have shown that hypercorticism is associated with a reduction in muscle mass. This muscular atrophy results from a negative nitrogen balance impairing protein synthesis and enhancing protein degradation. This response is selective of the type of muscle fiber: protein catabolism is clearly greater for fast twitch fibers than slow twitch fibers being more resistant to the atrophying effect of glucocorticoids. Physical training refrains this catabolic action of glucocorticoids on the skeletal muscle. This protective effect is much more efficient for type I slow twitch fibers.

Role of thyroid hormones

The skeletal muscle is a priority target for thyroid hormones whose main role is to regulate the synthesis of the various types of contractile proteins. The elevated concentrations of thyroid hormones increase the synthesis of fast contractile proteins and the formation of fast twitch fibers. Inversely, hypothyroidia reduces the number of fast twitch fibers (7).

Role of growth hormone (GH)

The Role of growth hormone (GH) on growth and protein synthesis of the skeletal muscle is well documented. The study of animals bearing pituitary tumors secreting GH shows an increase in the weight of muscles and in the surface of type I slow twitch fibers, the surface of type II fast twitch fibers being little influenced by GH. This enlargement of muscle volume is the result of an increase in protein synthesis. There is an increase in the number of satellite cells in young animals but not in adult animals. Such structural modifications in the skeletal muscle do not induce typological changes. GH can act either in direct interaction with a muscle receptor, or by increasing somatomedine concentrations in the muscle.

2. EFFECT OF TRAINING ON AGEING PROCESS

Effect of ageing and physical training on bone tissue

The decrease in bone density associated with age is a well known phenomenon. As other tissues, bone is a dynamic system which maintains its condition by constant renewal. Bone remodeling diminishes with age (15). It has been shown that physical exercise is capable of counteracting osteoporosis associated with ageing. It seems that this is a long term effect The
increase in bone capital at midlife resulting from intense physical activity could be the main factor of protection against ageing. The increase in bone density is mainly due to mechanical factors acting on the bone (16). However, the role of hormonal factors should also be mentioned. The metabolism of bone cells is influenced by the parathormone-calcitonine couple, but also by androgens, GH and thyroid hormones. Bone demineralization is observed during overtraining, due to hypogonadism which develops under such circumstances. We can therefore hypothesize that the hormonal response to physical training can affect bone.

Concerning support tissues, bone and muscle, it can be hypothetized that the increased concentrations in anabolizing hormones under the effect of well conducted physical training can explain muscle and bone anabolism.

**Effect of physical training on the immune system**

The effects of physical exercise on the immune system have recently been reviewed (3). Isolated physical exercise increases practically all classes of leukocytes and lymphocytes. The appearance of leukocytes in blood probably results from the various shifts of immunocompetent cells among the various pools of the body. This mobilization of leukocyte classes is selective and does not exceed 24 hours. Chronic physical exercise seems to diminish the number of certain immunocompetent cells although this has not often been demonstrated. The meaning of changes in the numbers of cells induced by isolated physical exercise can be discussed. In the case of chronic exercise they could be interpreted as a sign of immune deficiency in the sportsman. They could also explain changes in the activities of immunocompetent cells.

The mechanisms of this immune deficiency observed in sportsmen remain to be unequivocally confirmed by clinical observation and the many immune changes associated with physical exercise are, so far, mostly unknown. However, two mechanisms could be involved: changes in number and activity of immunocompetent cells. Thus, changes in the activity of "natural killer" cells induced by exercise could be partly explained by changes in the numbers of these cells whereas other activities could be affected by hormonal changes. The increased concentrations of glucocorticoids and catecholamines and the depressed concentrations of circulating androgens could induce a hormonal syndrome causing immune deficiency in the endurance athlete.

**3. HORMONAL RESPONSE TO TRAINING IN YOUNG AND AGED SUBJECT**

**Hormonal responses to physical exercise in young subjects**

A synthesis of hormonal responses to physical exercise in young subjects has been derived from several reviews on this topic (4, 23).

Short intense physical exercise induces a very rapid increase in catecholamine concentrations resulting in a decrease in insulin and an increase in glucagon. This type of exercise also induces an increase in the levels of GH, testosterone and glucocorticoids. During prolonged exercise these hormonal changes tend to amplify, except for plasma testosterone which decreases:

- physical training modifies resting concentrations of several hormones
- insulinemia decreases in young trained subjects
- a high testosterone/cortisol ratio is observed in well trained subjects

Inversely, overtraining depresses testosterone concentrations and hypophyseal reactivity to such stimuli as hypoglycemia.

Several hypotheses can be derived from these observations:

1) the effects of physical exercise on pancreatic hormones (insulin-glucagon) and catecholamines could be the cause of the enhanced tolerance to glucose and lipid metabolism.

2) the effects of physical exercise on anabolizing hormones (GH, androgens) could enhance bone and muscle protein metabolism.

3) the effects of very long and exhausting exercises, such as depressed anabolizing hormones and prolonged increase in glucocorticoids, could result in bone demineralization and depressed immune defences.

We will verify whether such hormonal effects are also observed in aged subjects performing physical exercise.

**3.2. Effect of physical training on the metabolic and hormonal response of middle-aged subjects**

Insulin, glucagon, catecholamines and metabolism

The tolerance to glucose of endurance trained subjects (mean age 46) has been compared with that of young athletic and sedentary subjects (mean age 19) (6). The middle-aged sportsmen ran 60 km a week and had a VO2 max of 63 ml.min⁻¹.kg⁻¹. Glucose and insulin responses were identical in both populations of sportsmen (young and middle-aged) and substantially lower than in the two sedentary groups. Two investigations have been performed on older trained
subjects (60-70 years old) in order to compare their resting insulinemia with that of sedentary subjects of the same age or younger (10, 17). Improved sensitivity to insulin under the effect of training seems constant at all ages. This effect seems affected by a short period of inactivity so that one could conclude that regular exercise protect against the development of insulin resistance and normalize glucose tolerance in aged subject by means of a short term effect of exercise (20).

The response to prolonged sub-maximal exercise shows differences in the regulation of glycemia between trained and sedentary subjects. During a 60 minute exercise at 70% VO2 max glycemia increased in aged and young physically trained subjects whereas it decreased in sedentary subjects of both age groups. This phenomenon can be due to a better ability of trained subjects to tap glycogen stores. The response to glucagon is much lower in both trained groups. A more substantial rise in catecholamines concentrations is observed in both trained groups, indicating that training enhances sympathetic stimulation.

A direct study using labelled noradrenalin perfusion confirmed the fact that physical training significantly increases the production of catecholamines in aged trained subjects but does not affect clearance (18). The authors correlate this increase in sympathetic stimulation with the increase in resting metabolism (Fig. 4).

In 40-70 year old subjects physical training thus significantly increases sensitivity to insulin and sympathetic tone. These two hormonal factors play a direct role in the improvement of lipid metabolism and reduction in fatty mass of aged trained subjects compared to their sedentary counterparts (22). The first hypothesis regarding the role of hormones on energetic metabolism is confirmed: in middle-aged subjects physical training increases the efficiency of insulin and circulating catecholamines on target tissues controlling the regulation of the energetic metabolism.

3.3. Hormones affecting bone and muscle condition

Androgens

The gradual decrease in androgen concentrations with the progression of age has been extensively described. During an investigation on responses to stress assays were made on middle-aged sportsmen competing in a modern pentathlon (8). The mean age of the group was 44. At the time of this investigation subjects were training one hour a day on the average; three subjects had trained for three hours a day during the three weeks prior to the investigation. Resting plasma testosterone concentration in this population was 2.96 ± 0.28 mg ml⁻¹. It was lower than that of younger athletes (mean age 23) participating in the same contest (4.88 mg.ml⁻¹) and that of 45 year old sedentary subjects (4.25 ± 0.18 mg.ml⁻¹).

Under the effect of the stress associated with a rifle shooting contest testosterone concentration respectively increased by 63% and 56% in populations of older and younger athletes. These results show that intense physical training at a sport with several events such as the modern pentathlon decreases the plasma testosterone concentration both in younger and older athletes. Concentrations measured in the younger athletes were lower than those measured in a population of athletes practising strength sports (4.88 ± 1.30 mg.ml⁻¹ vs 6.22 ± 0.12 mg.ml⁻¹). This data confirms Hackney's results (9) which showed a drop in plasma testosterone under the effect of intense endurance training. Older athletes react the same way as younger ones. The decrease takes place from a mean resting level lowered by age-related changes. The concurrence of these two factors reduces testosterone levels in older athletes to very low absolute values. The case by case examination shows the lowest values in the three older athletes who intensely prepared for this contest. Their performance was good: one ranked second for all tests, the other two ranked among the first five winners. This underlines the fact that depressed testosterone levels resulting from intense physical training does not preclude good performance.

The resting levels and the response of glucocorticoids to stress is identical in both populations of athletes. If we consider as valid the fact that the ratio Testosterone/cortisol reflects the anabolic condition, we could believe that older athletes are in a catabolic phase. In the absence of clinical signs reflecting muscular or bone intolerance other factors controlling muscular anabolism have to be identified. GH has been considered as playing a possible role. The data of Hagberg et al. (10) show that resting GH concentrations are the same in young and older athletes and in their sedentary counterparts. However, the increase in GH under the effect of physical exercise is lower in aged athletic and sedentary populations. The response of somatomedines to physical exercise is much higher in the younger athletes. These results seem to indicate that the anabolic stimulus resulting from the effect of physical exercise on GH secretion is lower in older subjects.

The tone of the two main hormonal pathways involved in muscle and bone anabolism seems therefore reduced in middle-aged athletes. The good muscle and bone adaptation of these subjects indicates that these pathways probably play a secondary role. Trophic factors resulting from mechanical constraints applying to bones and muscles and the role of innervation on muscles probably compensate for depressed hormonal secretions. A hypothesis could be suggested, correlating
the depressed thyroid secretions with the increasing number of slow twitch fibers under the effect of age but results are controversial.

Poehlman et al. (17) reported that neither physical training nor ageing modify the resting concentrations of thyroid hormones. Inversely, Hagberg et al. (10) showed that physical training reduces concentrations of thyroid hormones in young and older athletes. This could explain the increase in the number of slow twitch fibers under the effect of endurance training.

Data published on the response of anabolizing hormones in middle-aged subjects only concern endurance training. Results are not conclusive of an anabolizing effect of hormonal adaptations and partly discredit our second hypothesis. However, it would be indispensable to study the hormonal response of middle-aged subjects to strength training protocols.

The third hypothesis concerns the effect of a prolonged increase in the concentrations of glucocorticoids associated with a decrease in androgens on immune defences and bone density. Results obtained on middle-aged subjects confirm the decrease in androgens under the effect of intense physical training. Resting glucocorticoid levels do not seem to be modified. The reactivity of glucocorticoids to physical exercise or stress is normal. It may therefore be suggested that overtraining can induce a catabolic condition in middle-aged subjects as it does in younger ones. However, no result has so far evidenced a reduction in bone density or immune defences in intensively training aged subjects. The only point that we can discuss is indirect: the number of cancers in physically trained populations. Although cancer genesis involves a variety of factors, results suggest that the incidence of this disease tends to diminish in physically active populations. If physical exercise really depresses immune defences, it is possible that the total number of neoplasms tends to increase.

However, the relationship between the ratio testosterone/cortisol, the type of training and the immune system should be investigated.

In conclusion, the study of the hormonal response of middle-aged subjects to physical exercise indicates a very strong relationship between the increased sensitivity to insulin, the increase in sympathetic tone, and the improvement of the lipid balance and body composition.

Changes in the secretion of hormones acting on bone and muscle tissues, such as androgens, GH, and thyroid hormones are not sufficient to completely explain the beneficial effects of physical training on the bone/muscle system.

The negative effect of intense physical training on the immune system or bone density should be further studied, with reference to the hormonal response of middle-aged subjects to physical exercise.

REFERENCES


FIGURE 1:
Survival curves for rats submitted to physical training (wheel runners) or food restricted (pair weight sedentary) compared to sedentary rats (from ref. 11)

FIGURE 2:
Effects of 3 weeks of treadmill running training on 2 deoxy glucose transport in soleus muscle of rat (T: trained rats ; C: control sedentary rats)(from ref. 6)

FIGURE 3:
Effect of physical training and food restriction on soleus muscle mass of youngs and 27 month aged rats (from ref. 2)

FIGURE 4:
Norepinephrine metabolism before (pre) and after (post) endurance training at rest in aged subjects (from ref. 18)
Soleus Fiber Number

p < 0.001

(N) = (8) (8) (5) (9) (7) (8)

12 27

AGE (MONTHS)

Sedentary
Trained
Food Restricted