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New aspects of the hormone and cytokine response to training

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Abstract Exercise training is associated with peripheral-cellular and central-cerebral processes, hormonal-neuronal regulation and transmission mechanisms. During the acute training response, peripheral cellular mechanisms are mainly metabolostatic to achieve energy supply and involve associated cytokine and hormonal reactions. Glycogen deficiency is associated with increased expression of local cytokines (interleukin-6, IL-6), decreased expression of glucose transporters, increased cortisol and decreased insulin secretion and β-adrenergic stimulation. A nutrient-sensing signal of adipose tissue may be represented by leptin which, as for insulin, IL-6 and insulin-like growth-factor I (IGF-I), has profound effects on the hypothalamus and is involved in the metabolic hormonal regulation of exercise and training. Muscle damage and repair processes may involve the expression of inflammatory cytokines (e.g. tumour necrosis factor-α, TNF-α) and of stress proteins (e.g. heat shock protein 72). During overreaching and overtraining, a myopathy-like state is observed in skeletal muscle with depressed turnover of contractile proteins (e.g. in fast-type glycolytic fibres with a concomitant increase in slow type myosins). These alterations are influenced by exercise-induced hypercortisolism, and by decreased somatotropic hormones (e.g. IGF-I). The hypothalamus integrates various error signals (metabolic, hormonal, sensory afferents and central stimuli) and therefore pituitary releasing hormones represent the functional status of an athlete and long-term hypothalamic hormonal and sympathoadrenal downregulation are some of the prominent hormonal signs of prolonged overtraining and performance incompetence syndrome.

Keywords Acute training response · HSP70 · IL-6 · Leptin · Overtraining

This manuscript is dedicated to Manfred Lehmann, who died August 24, 2001. His ideas and spirit influenced much the field of Sports Endocrinology.

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Introduction

Athletic training consists of repetitive phases of normal training, high training load phases, overload training phases and recovery. Overload training phases are characterized by an imbalance between training load and recovery. If such overload is only for a short time and performance, metabolism and homeostasis are restored or improved after recovery, this is referred as "overreaching" or short-term overtraining. If the load-recovery balance is disturbed for longer, a real state of overtraining can be observed with various typical alterations (e.g. molecular, biochemical and regulatory) which may lead consecutively to disturbances of well being, possible illness and underperformance. The balance of training-specific, psychological and other more nonspecific stressors and recovery processes determines the outcome of a given training situation (Lehmann et al. 1997, 1999a; Steinacker et al. 1993, 1999, 2000a, 2002; Weicker and Strobel 1997).

We proposed a model of a biphasic response to overload involving predominantly: (1) peripheral mechanisms in the early phases of overload and (2) more central mechanisms in the more pronounced phases of overload and overtraining. This means that muscular damage and metabolic needs are mainly involved in the acute training response and the chronic training response leads to changes not only in tissue metabolism, somatic growth or differentiation, body composition

and organ function, but also to central regulatory disturbances (Lehmann et al. 1993a, 1997).

The hypothalamus acts as the central integrator of all afferent signals to the brain and has an important role in the regulation of the central responses to stress and training. This integration involves information from autonomic nerve system afferents, direct metabolic effects, hormones and cytokines and also information from higher brain centres. A high information load on the hypothalamus during acute or chronic stress will activate excitatory neurons in the hypothalamic network (Barron et al. 1985; Baskin et al. 1999; Hackney et al. 1990; Heuser et al. 1991; Spinedi and Gaillard 1998; Wittert et al. 1996). This hypothalamic activation may then be related to effects on all efferents – autonomic nervous system, hormonal system, motoneurons – the effects being more stimulating in acute stress and clearly inhibiting in chronic stress, overreaching and overtraining (Lehmann et al. 1992a, 1997, 1998, 1999a, 1999b).

This review deals with new aspects of the hormonal responses to training and tries to integrate new findings regarding the contribution of cytokines and stress proteins to these responses with a particular focus on the messages coming from peripheral tissues to the hypothalamus.

Regulation of the metabolic exercise response

The acute hormonal response to exercise is chiefly concerned with metabolic regulation and is linked to glucose homeostasis in muscle cells and triglyceride balance in adipose tissue (Lehmann et al. 2000).

Hormonal regulation of glucose homeostasis

Glucose homeostasis and the activation of glycogenolysis in muscle and liver as well as upregulation of insulin-dependent and insulin-independent glucose transport are important for the acute exercise response. The intracellular pathways of glucose transport activation involve insulin signalling through the insulin-mediated tyrosine phosphorylation of both the insulin receptor (IR) and insulin receptor substrate-1 (IRS-1), the phosphoinositol 3-kinase (PI3K) pathway and the insulin-independent 5′AMP-activated protein kinase (AMPK) pathway, which both lead to translocation of glucose transporter 4 (GLUT4) from intrasarcolemmal pools/vesicles to the cellular membrane and subsequent glucose uptake by the cell (Kirwan and Jing 2002; Park et al. 2002; Winder 2001). During exercise, glucose transport is mainly regulated by the contraction-stimulated AMPK pathway and this effect will last for 3–6 h post-exercise (Kirwan and Jing 2002; Richter et al. 2001). AMPK expression is dependent on fibre type in the rat (Ai et al. 2002). The insulin-dependent PI3K pathway is important through the subsequent 42 h of recovery (Kirwan and Jing 2002). This means that the need for insulin decreases, insulin sensitivity of the muscle cell increases and plasma insulin levels decrease. With increased glucose uptake by the muscle, hepatic glycogenolysis has to be activated. The subsequent hormonal reactions have been frequently described and involve increases in circulatory plasma cortisol, in growth hormone, and catecholamines and respective changes in the related hormonal regulatory axes. Prolonged exercise results in glycogen depletion which induces further counterregulatory activity of these glucostatic hormones (Jost et al. 1989; Lehmann et al. 1999b; Nehlsen-Cannarella et al. 1997; Stupnicki et al. 1995; Weicker and Strobel 1997). Carbohydrate supplementation during prolonged exercise diminishes these reactions (Lehmann et al. 1992b, 1997). Muscle damage impairs insulin-mediated stimulation of IRS-1 and PI3-kinase in human skeletal muscle (Del Aguila et al. 2000).

When glucose stores are close to full depletion, glycogenolysis and glucose transport have to be downregulated in muscle and liver, as does liver production of insulin-like growth-factor I (IGF-I) because of the insulin-like effect of IGF-I on the blood glucose concentrations. IGF-binding proteins, in particular IGF-binding protein 3 (IGFBP-3), seem to target IGF-I away from insulin-sensitive glucose-consuming tissues (for a review see Ferry et al. 1999). Maintenance of the blood glucose level during exercise is critical for the glucose-dependent brain, otherwise exercising muscles will consume all available glucose with lethal consequences. Therefore, a transient insulin resistance develops during exercise in glycogen-depleted conditions (Kirwan and Jing 2002; Lehmann et al. 2000; Steinacker et al. 2002).

The blood glucose level has been thought to be the main regulatory factor for the metabolic and hormonal control of glucose homeostasis (Borghouts and Keizer 2000). However, as described above, muscle and liver glycogen levels are critical variables for metabolic control during exercise. AMPK is discussed as an intracellular ''masterswitch'' which activates fat oxidation and glucose uptake in relation to the increased rate of ATP utilization during muscle contraction (Ai et al. 2002; Richter et al. 2001; Winder 2001). The changes in blood glucose during exercise cannot truly reflect the glycogen store and that has led to discussion about whether there are messenger molecules acting as metabolic hormones reflecting glycogen levels (Lehmann et al. 1999b, 2000). Among the cytokines, interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) may have a role in glucose homeostasis and will be discussed in more detail.

Cytokines, exercise and glucose homeostasis

Studies of humans reveal that several cytokines, such as TNF-α, the interleukins IL-1β, IL-6, IL-8 and cytokine inhibitors (interleukin-1 receptor-antagonist IL-1ra, TNF-receptors) increase during exercise, as in an acute inflammatory response (Niess et al. 2000; Northoff and

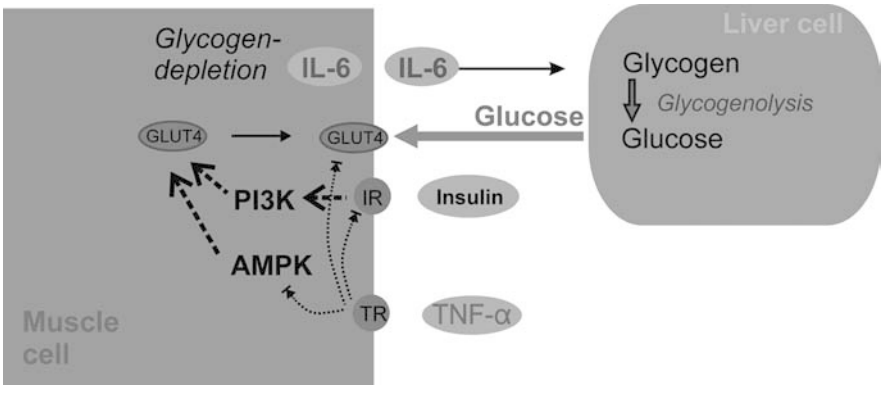
Berg 1991; Northoff et al. 1994; Ostrowski et al. 1998, 1999; Pedersen et al. 1998).

New studies have now highlighted some humoral effects of cytokines. During endurance exercise, pro-inflammatory cytokine production is downregulated and anti-inflammatory cytokines such as IL-1ra and IL-10 are upregulated and there is an increase in IL-6 (Drenth et al. 1995; Nieman and Pedersen 1999; Rohde et al. 1997). Strenuous prolonged exercise induces increases in circulating TNF-α, IL-1β and IL-6 levels. This is counterbalanced by cytokine inhibitors (IL-1ra, sTNF-r1 and sTNF-r2) and the anti-inflammatory cytokine IL-10 (Ostrowski et al. 1999). The magnitude of the changes differs markedly depending on the cytokine being examined, i.e. the plasma concentrations of IL-1 and TNF-α increase one- to twofold, whereas IL-6 has been reported to increase over 100-fold after prolonged exercise (Ostrowski et al. 1999). Local inflammatory reactions may be induced by muscle cell apoptosis or necrosis, by activated macrophages and by inflammatory cytokines (Pedersen et al. 1998; Podhorska-Okolow et al. 1998). Cytokines such as IL-6 or IL-1, which act on peripheral and central organs, may have additional messenger functions (Nieman and Pedersen 1999). The local tissue damage and the resulting inflammation of intensive eccentric exercise have been related to muscle IL-6 levels (Bruunsgaard et al. 1997). However, in later studies no clear relation was found between the IL-6 increase and muscle damage in eccentric exercise (Croisier et al. 1999). During muscle-damaging exercise a source of IL-6 may be macrophages that have invaded the muscle during local muscle inflammation (Pedersen et al. 2001a).

Fig. 1 Interleukin-6 (*IL-6*) is released from working skeletal muscle in relation to glycogen levels. IL-6 induces glycogenolysis in the liver. Muscle glucose uptake is mediated mainly by the glucose transporter 4 (*GLUT4*). GLUT4 activity (expression and translocation from internal pools to cell membrane) is mainly regulated by activity of the insulin receptor- (*IR*-) mediated phosphoinositol 3-kinase (*PI3K*) pathway and independently of insulin by the 5′AMP-activated protein kinase (*AMPK*) pathway. Glucose uptake is inhibited by tumor-necrosis-factor-α (*TNF-α*) released from adipose tissue. TNF-α release may also be activated by inflammation following muscle damage (not shown). See also Kirwan and Jing (2002), Pedersen et al. (2001a) and Steinacker et al. (2002)

After exhaustive exercise with carbohydrate supplementation, cytokine levels are lower post exercise compared with phases without carbohydrates. The lower cytokine level may indicate lower metabolic stress (Nehlsen-Cannarella et al. 1997). These reports led to examinations in which a link between the exercise-induced increase in IL-6 and glucose homeostasis was hypothesized (Gleeson 2000; Steensberg et al. 2000, 2001). In an experiment with one- and two-legged prolonged exercise, the activation of the IL-6 gene was related to muscle glycogen content (Keller et al. 2001). In contrast, during 60 min of exercise at 4 mmol/l lactate, carbohydrate ingestion did attenuate the increase in plasma IL-6, but not that of the already elevated skeletal muscle IL-6 mRNA (Starkie et al. 2001). However, the studies of Steensberg et al. provide evidence that IL-6 is released from the muscle tissue during exercise and that this release is dependent on the pre-exercise glycogen content of the muscle (Steensberg et al. 2000). This release of IL-6 is not related to muscle damage or inflammation as the mode of exercise was kicking leg exercise, which is purely concentric (Steensberg et al. 2000). To summarize current knowledge, it can be concluded that the muscle glycogen content influences the extent of the release of IL-6 during exercise (Gleeson 2000; Pedersen et al. 2001b; Steensberg et al. 2001). There is clear evidence in human and animal models for a stimulatory action of IL-6 on the hypothalamus (Mastorakos et al. 1993; Shizuya et al. 1998). IL-6 stimulates hepatic glucose release (Coppack 2001; Ritchie 1990). In adipocytes, IL-6 stimulates lipolysis (Coppack 2001; Path et al. 2001). IL-6 is released as result of β_2/β_3-adrenoreceptor stimulation (Mohamed-Ali et al. 2001; Path et al. 2001), suggesting an autocrine/paracrine function in adipose tissue. There is a need for further studies on the hormonal functions of IL-6 in the exercise response (see Fig. 1).

The mechanisms of the transient insulin resistance which develops during exercise in glycogen-depleted conditions are only beginning to be understood (Kirwan and Jing 2002; Lehmann et al. 2000). TNF-α modulates insulin-mediated glucose metabolism and it has been shown to inhibit insulin-stimulated tyrosine phosphorylation of both the insulin receptor and IRS-1. Furthermore, in vitro, TNF-α stimulates the downregulation of



GLUT4 in adipocytes, hepatocytes and skeletal muscle (Coppack 2001; Kirwan and Jing 2002; Lehmann et al. 2000; Mantzoros et al. 1997; Uysal et al. 1997). In damaging exercise in humans, a close relation was found between TNF-α production and the decrease in PI3-kinase activity in skeletal muscle (Del Aguila et al. 2000). TNF-α levels in adipose tissue are inversely related to glucose uptake in obese subjects (Katsuki et al. 1998). TNF-α is expressed in skeletal muscle cells of obese and diabetic subjects and muscle TNF-α levels are related to insulin sensitivity (Saghizadeh et al. 1996). Receptors on the plasma membrane bind TNF-α and activate a pathway involving sphingomyelinase and ceramides (Kirwan and Jing 2002). However, the source of TNF-α during exercise is not completely revealed and adipocytes within the muscle may be an additional source of TNF-α (Coppack 2001). TNF-α expression is increased during exercise in adipocytes of the rat (Nara et al. 1999). In addition, damaging exercise will lead to activation of macrophages which release TNF-α (Del Aguila et al. 2000).

Leptin and metabolism

During prolonged training, physical stress and glycogen depletion, the metabolism is maintained by increased utilization of triglycerides by β_3-receptor-related lipolysis and negative triglyceride balance (Lehmann et al. 2000) (see Fig. 2).

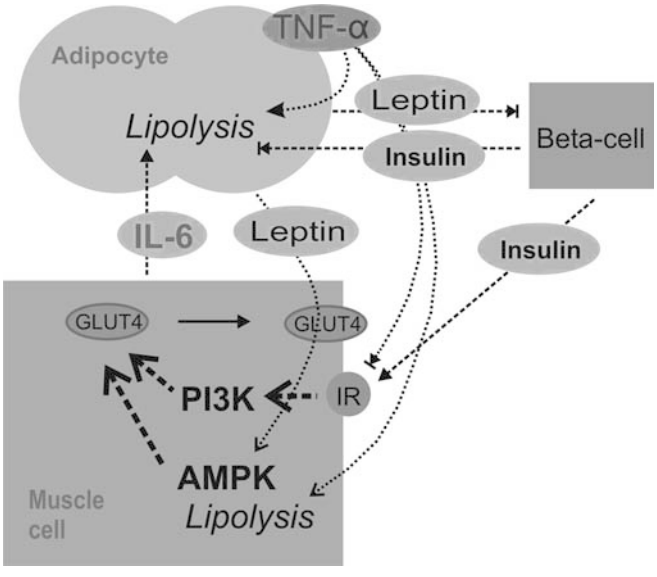


Fig. 2 During exercise-induced glycogen depletion in skeletal muscle, falls in insulin and rises in interleukin-6 (*IL-6*) activate lipolysis in the adipocyte. This leads to a decrease of leptin secretion. Leptin stimulates AMPK-activated lipolysis in skeletal muscle and inhibits insulin secretion from the pancreatic β-cells. Tumor-necrosis-factor-α (*TNF-α*) stimulates lipolysis in adipocytes and skeletal muscle cells and inhibits insulin's action on glucose transport. See text (and Fehmann et al. 1997; Kirwan and Jing 2002; Mizuno et al. 1999; Withers 2001; Steinacker et al. 2002)

The identification of leptin as an adipocyte-derived hormone and its receptor has highlighted the regulation of appetite, thermogenesis and metabolism (Friedman and Halaas 1998). However, it has become evident that leptin does not act only as an "adipostatic hormone". Leptin has profound effects on hypothalamic hormonal regulation (Friedman et al. 1997; Heiman et al. 1997), the hypothalamic neuronal network and neuropeptide Y (NPY) (Carro et al. 1998). There is evidence that exogenous leptin depresses NPY expression in the animal model and that NPY is increased in starvation when leptin is low. Furthermore, NPY-neurons that are activated by fasting express leptin receptors (Baskin et al. 1999; Schwartz et al. 1996). Increased NPY leads to increased neuronal activity and depresses the hypothalamo-pituitary-adrenocorticotropic (HPA) axis. It has also been shown that exogenous leptin is a potent stimulus of growth hormone (GH) secretion and pulsatility (Tannenbaum et al. 1998). Other cellular signals also contribute to the adipocyte hormonal responses, such as TNF-α, which is expressed during exercise in rat adipocytes (Nara et al. 1999). There is increasing evidence that the TNF-α system plays a role in regulating leptin levels in humans (Hotamisligil 1999; Peraldi and Spiegelman 1998).

Therefore, leptin may act as a metabolic hormone and may have effects on hypothalamic regulation during training. We therefore examined six trained athletes who consumed a huge dietary energy intake during 3 weeks of intensive resistance training and low-intensity endurance training and could demonstrate for the first time a decrease in leptin during intensive training although body fat was maintained (Simsch et al. 2002; Steinacker et al. 2000b). With decreasing leptin levels thyroid stimulating hormone (TSH) levels decreased (Simsch et al. 2002). Previous studies had reported conflicting results with no change in leptin (Kraemer et al. 1999) or changes in leptin levels only in relation to changes in body fat content (Hickey et al. 1996; Kohrt et al. 1996; Perusse et al. 1997).

The data presented in our study (Simsch et al. 2002) are consistent with the hypothesis that leptin expression in the adipoctye is related to energy flux and triglyceride loss (Considine 1997a; Flier 1998). This is underlined by a positive relationship between leptin levels and performance in our study. Leptin is considered to be one of the physiological signals designed to prolong survival in hazardous situations such as exhausting exercise or starvation, mainly by reducing basal metabolic rate, increasing food seeking behaviour, increasing the secretion of glucocorticoids and decreasing reproductive function (Considine 1997b; Flier 1998). Plasma leptin decreases with food shortage in animals and humans (Ahima et al. 1999a; Boden et al. 1996). It was demonstrated that exogenous leptin administration during fasting attenuates the reduction in thyroidal and gonadotropic axes, inhibits the rise in corticotrophin-releasing hormone (CRH) and cortisol (Ahima et al. 1999b) and inhibits the fasting-induced suppression of GH secretion (Carro et al. 1997).

Metabolic control mechanisms

There is also evidence that the various hormones and cytokines involved in metabolic control are closely connected in regulatory loops linking the fuel supplying organs (liver, fat tissue), regulatory centres (beta-cell, hypothalamus) and the working muscle cells.

Catecholamines have an important role in modifying hormonal responses during exercise. In human and animal models, β-adrenergic stimulation inhibits leptin expression (Li et al. 1997; Mantzoros et al. 1996), inhibits insulin receptor phosphorylation and decreases insulin signalling pathways (Borghouts and Keizer 2000; Withers 2001) and increases IL-6 release from adipose tissue (Mohamed-Ali et al. 2001; Path et al. 2001).

A feedback regulation has been demonstrated between leptin and insulin (and glucagon) (the adipocyte-pancreatic loop) (Coleman and Merrmann 1999; Fehmann et al. 1997), but there is no evidence of leptin action on the liver (Coppack 2001). There is indication that leptin acts on skeletal muscle by directly activating the β2 subunit of AMPK and by inhibiting acetyl coenzyme A carboxylase, both effects stimulating fat oxidation and glucose uptake (Minokoshi et al. 2002). In contrast, IL-6 stimulates fat oxidation in adipocytes (Coppack 2001; Path et al. 2001).

There is experimental evidence that all metabolic hormones and cytokines have hypothalamic receptors (Haas and Schauenstein 1997). In animal models and in humans, leptin and insulin depress the activity of excitatory neurons in the lateral hypothalamus (Brüning et al. 2000; Withers 2001) and have effects on energy expenditure, body weight control and sympathetic activity. High levels of leptin will inhibit activation of the HPA axis (Ahima et al. 1999a; Gaillard et al. 2000) and inhibit cortisol release (Ahima et al. 1999a; Gaillard et al. 2000). There is some indication that IL-6 increases hypothalamic activity (Lehmann et al. 2000; Pedersen et al. 2001a), and that low plasma levels of leptin, insulin and IGF-I activate the secretion of growth hormone releasing hormone (Wallenius et al. 2001; Withers 2001) and sympathetic activity (Ahima et al. 1999a; Gaillard et al. 2000; Lehmann et al. 2000).

The response to training and overtraining

The training effect starts with exercise-induced metabolic disturbances and cellular damage which initiate metabolic adjustments, transport processes, cellular repair processes and protein synthesis. The acute exercise response has been discussed above and can be roughly described as an activation of many of such processes resulting in adaptation. The repetition of various exercises during a training program should cause increased adaptive responses; however, limited recovery, limited substrate availability and limited protein synthesis and the influence of other stressors will cause fatigue and reduced adaptation or loss of function in the cases of overreaching or overtraining as described in the Introduction.

Tissues react to overload with a decrease in sensitivity to the stimulus. A typical response pattern is downregulation of the β-adrenergic receptors in the state of overtraining but with normal or increased levels of catecholamines, which was one of the first published findings in the endocrinology of overtraining (Jost et al. 1989; Lehmann et al. 1985, 1992b). If the training load is maintained, the adrenal glands become less responsive and there is also a depression of the HPA axis, all resulting in a decrease of circulating levels of catecholamines (Fry and Kraemer 1997; Heuser et al. 1991; Lehmann et al. 1992c; Wittert et al. 1996).

Similar findings can be found for all hypothalamo-pituitary-peripheral hormonal axes with a biphasic response to overload involving predominantly peripheral mechanisms in early phases of overload and of more central mechanisms in more prolonged phases of overload and overtraining (Lehmann et al. 1993b, 1997). In reality, however, there is a more gradual change from the compensated to the decompensated phase of response. This is schematically drawn in Fig. 3 for the HPA axis (Barron et al. 1985; Lehmann et al. 1993b; Urhausen et al. 1998; Wittert et al. 1996).

Hormones, cytokines and the hypothalamus in training and overtraining

How do the peripheral hormones act and are they relevant to the clinical picture of overreaching and overtraining? A few years ago, hormonal feedback to the

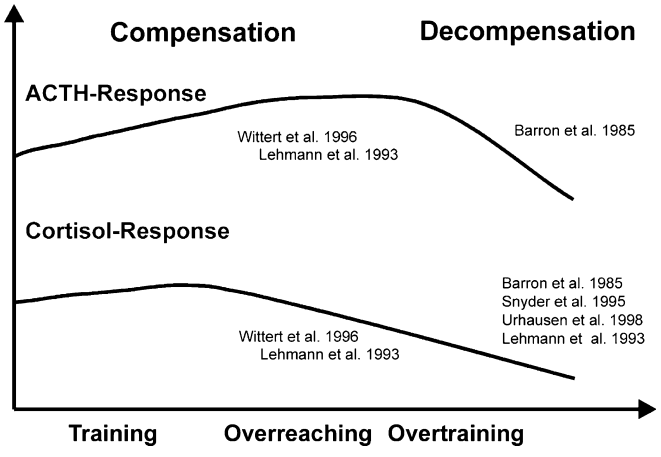


Fig. 3 Schematic representation of the hypothalamo-pituitary-adrenal hormonal axis during training, overreaching and overtraining. In the compensated stage during training, adrenocorticotropic hormone (*ACTH*) and cortisol respond to the metabolic stress with increased levels; in overreaching, the cortisol response is blunted with an augmented ACTH response. Overtraining is characterized by decreased ACTH and cortisol responses. Further explanation see text and Barron et al. 1985; Lehmann et al. 1999b; Snyder et al. 1995; Urhausen et al. 1998; Wittert et al. 1996; redrawn after Lehmann et al. (1999b)

hypothalamus was thought to be represented by cortisol, catecholamines and growth hormone; other feedback mechanisms were postulated to be neuronal afferents, amino acid imbalance, temperature and other non-specified error signals (Lehmann et al. 1993a, 1999b; Parry-Billings et al. 1992).

This picture is now changing. As mentioned above, there is experimental evidence that receptors for many cytokines are expressed in the hypothalamus so that these cytokines can act directly on the hypothalamic neuronal network (Gaillard et al. 2000; Haas and Schauenstein 1997; Rizk et al. 2001; Utsuyama et al. 2002). Furthermore, receptors have been identified in the hypothalamus for insulin (Brüning et al. 2000), leptin (Baskin et al. 1999; Mercer et al. 1997), and IGF-I (Wallenius et al. 2001; Withers 2001) which contribute to the responses to nutrition, fasting, starvation and exercise. There is evidence of action and interaction of IL-6, leptin, IGF and insulin at the hypothalamic level in animal models (Gaillard et al. 2000; Mohamed-Ali et al. 1998; Withers 2001) and we await more data on the hormonal role of cytokines in humans during physical training.

These regulatory processes are distinct from effects of systemic spillover of inflammatory cytokines such as TNF-α which mark the failure of local compensation mechanisms. Such inflammatory cytokines clearly have effects if they enter the circulation (e.g. as they do in infection) and may be responsible for some of the symptoms of fatigue in overtraining (Northoff and Berg 1991; Pedersen et al. 2001b; Smith 2000); however, this remains speculative until more data are available.

Hormonal and cytokine effects on skeletal muscle

The muscle cell has to manage the exercise-induced metabolic challenges and stress-induced damage and has to initiate metabolic adjustments, transport processes, cellular repair processes and protein synthesis, and it is very likely that cytokines such as IL-6 are part of the hormonal message emerging from the muscle cell as discussed above.

Fatigue and performance incompetence in overtraining were attributed to an ''overtraining myopathy'' in analogy to the clinically well known effects of hypercortisolemia on skeletal muscle (Lehmann et al. 1997, 1999b). TNF-α induced by muscle damage may have additional effects (Del Aguila et al. 2000). Typical findings are observed in skeletal muscle with depressed turnover of contractile proteins (e.g. in fast-type glycolytic fibres with a concomitant increase in slow type myosin) (Atalay et al. 1996). Since the myosin heavy chain (MHC) isoforms correspond to metabolic and contractile properties of muscle fibres, such as myofibrillar ATPase activity, unloaded shortening velocity, stretch-activation in muscle fibres and tension cost, MHC isoforms provide information about the functional state of the muscles (Billeter et al. 1980; Pette and Staron 1997; Schiffiano and Reggiani 1996). The transition of muscle fibre type underlined by changes in MHC isoforms takes place during physical training (Haddad et al. 1998; Pette and Staron 1997; Liu et al. 2003a, 2003b) and it has been proposed that changes in cellular energy content are a potent stimulus for the MHC transition (Ennion et al. 1995; Pette and Staron 1997; Schiffiano and Reggiani 1996). Studies in animals revealed that the hypertrophic response of skeletal muscle is closely linked to somatotropic hormones such as IGF-I, muscular IGF-I expression (Adams and Haddad 1996) and thyroid hormones (Eisenberg et al. 1991; Booth and Baldwin 1996).

Training-induced glycogen depletion, a decrease in free amino acids and a decrease in muscular energy stores and metabolism may lower protein turnover and synthesis rate. Because MHC IId is less stress resistant and has a higher tension cost than MHC I (Pette and Staron 1997; Schiffiano and Reggiani 1996), there may be an additional shift to MHC I expression and to a slow muscle type during overtraining. Semi-starvation acts in the same direction in the rat model (Svanberg et al. 2000). The catabolic-like hormonal pattern discussed above also acts in the same direction.

The second insulin signalling pathway through the mitogen-activated protein kinase (MAPK) induces, directly or indirectly, mitogenesis and cell growth and is involved in the exercise and training response (Widegren et al. 2000; Yu et al. 2001). The MAPK pathway is also activated independently of insulin by cytokines, cell stress and contraction (Kirwan and Jing 2002) and is a potential mechanism by which exercise and training induce gene transcription in skeletal muscle (Widegren et al. 2000; Yu et al. 2001). The MAPK pathway may be inhibited in the catabolic training state; however, to date there are no data from training in humans.

Exercise-induced cellular stress and damage is considered to be one of the stimuli which induce heat shock proteins (HSP) (Hammond et al. 1982; Liu and Steinacker 2001; Locke et al. 1990). It has been shown that physical exercise or chronic electric stimulation induces HSP70 in skeletal muscles (Febbraio and Koukoulas 2000; Liu et al. 1999; Locke et al. 1991; Puntschart et al. 1996). An effect of training intensity on HSP70 accumulation in the skeletal muscle of trained rowers has been reported (Liu et al. 2000) and muscle glycogen levels are related to HSP expression (Febbraio et al. 2002). The main function of the HSP is considered to be molecular chaperones which facilitate protein folding, assembling, translocation, and degradation, conferring cellular resistance to various stresses and stabilizing DNA (Liu and Steinacker 2001; Locke 1997; Powers et al. 1998).

Furthermore, HSPs are involved in the control of apoptosis (Beere and Green 2001; Moseley 2000; Todryk et al. 2000), which may be important for skeletal muscle fibre transformation in training. HSP may also act as cytokines (Mosser et al. 2000; Pratt 1998) and are involved in the processing and presentation of antigen in

antigen-presenting cells (Moseley 2000; Todryk et al. 2000). It remains speculative whether circulating HSPs (Pockley et al. 1998) indicate stress within tissues and whether they can be used as markers of overtraining. An increase in circulating HSP70 after exercise has been found (Walsh et al. 2001). However, the source of circulating HSP is not clear (Febbraio et al. 2002). Estrogen increases cellular resistance to oxidative stress but attenuates the HSP increase following exercise in rats (Paroo et al. 1999). Exercise stimulates HSP production in human leukocytes (Fehrenbach et al. 2000) and HSP70 may act as a chaperokinine in human monocytes (Asea et al. 2000). These experimental results suggest a potential role for HSP in the hormonal regulatory network during exercise which has yet to be evaluated.

Summary

Much information on the endocrinology of exercise and training has been gathered during recent years which allows refinement of the theories regarding the adaptation to exercise, training and overtraining. The central role of the hypothalamus is clearly identified in integrating a network of metabolic regulating hormones and cytokines as well as other afferents and error signals. Among others, leptin, IL-6 and IGF-I exert important effects on the hormonal regulation in response to exercise and training. Skeletal muscle can actively adapt to exercise and training by producing cytokines and stress proteins and by transforming structural proteins such as MHC isoforms. The skeletal muscle functions as a response system to central regulatory processes, but it also produces a series of physiological and pathophysiological signals that provide feedback to the central regulatory mechanisms at the hypothalamic level. Understanding the functions of hormones and cytokines, and the peripheral, regulatory role of the skeletal muscle, will help us to obtain deeper insight into the complex mechanisms of adaptation to exercise and training.

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