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Interactions of Metabolic Hormones, Adipose Tissue and Exercise

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Contents

Abstract

Physiological and psychological systems work together to determine energy intake and output, and thus maintain adipose tissue. In addition, adipose tissue secretes leptin and cytokines, which induces satiety and has been linked to catecholamines, cortisol, insulin, human growth hormone, thyroid hormones, gonadotropin and lipolysis. Thus, adipose tissue is acted upon by a number of physiological stimuli, including hormones, and simultaneously, is an active component in the regulation of its own lipid content. All of the hormones mentioned above are associated with each other and respond to exercise and exercise training. Thus, exercise is one of the major links between the hormonal modulators of energy intake and output. It appears that the sympathetic nervous system and the catecholamines are key components facilitating the lipolytic activity during exercise. These two neuroendocrine factors directly affect adipose metabolism and metabolic hormones that influence adipose metabolism. Acute low- and moderate-intensity exercise causes hormonal changes that facilitate lipolytic activity. Exercise training reduces these hormonal responses, but the sensitivity to these hormones increases so that lipolysis may be facilitated. Large amounts of adipose tissue blunt the metabolic hormonal responses to exercise, but the sensitivity of these hormones is increased; thus maintaining normal lipolytic activity. Although the physiological role of the endocrine system during exercise

and training is significant, other training effects may have as great, or greater influence on lipolytic activity in adipose tissue.

Adipose tissue is maintained by a complex interaction of a number of physiological and psychological systems that regulate energy intake and energy output (figure 1). Typically, energy intake is controlled by hunger, appetite and satiety.[1] Hunger and satiety appear to be genetic or physiological in nature, receiving input from blood glucose, splanchnic neurons, endogenous opiates, neurotransmitters, the gastrointestinal system and leptin.[2] Conversely, appetite appears to be psychological or cultural, and is a learned response to foods. Energy output is related to metabolic rate, which, at rest, is controlled by various hormones and genetic factors. Physical activity (e.g. exercise) increases energy output directly, but also affects a number of hormones that control metabolic rate and hunger. Thus, exercise appears to be the one perturbation that has the potential to influence both sides of the energy balance equation (i.e. energy intake and energy output).

Adipose tissue is not passive, as it influences metabolic activity in other tissues including muscle and liver.[3] Adipose tissue secretes the hormone leptin, which has a controlling effect on satiety and hunger. In animals, leptin has also been shown to influence spontaneous activity levels and increase energy expenditure.[4,5] In humans, studies on the effects of leptin on spontaneous activity levels are not as convincing.[6,7] Leptin has been linked to several other hormones[3,8,9] that have direct effects on carbohydrate and lipid metabolism. In addition, adipose tissue releases a number of cytokines (e.g. adiponectin, interleukin [IL]-6, tumour necrosis factor-α [TNFα], resistin) that can influence insulin,[10,11] stimulate corticotropin-releasing hormone (CRH)[12] and ultimately cortisol,[13] which in turn increases lipolysis.[11,14] Leptin may also be affected by exercise.[15,16] Thus, adipose tissue is an active component in the regulation of the body's overall fat content.

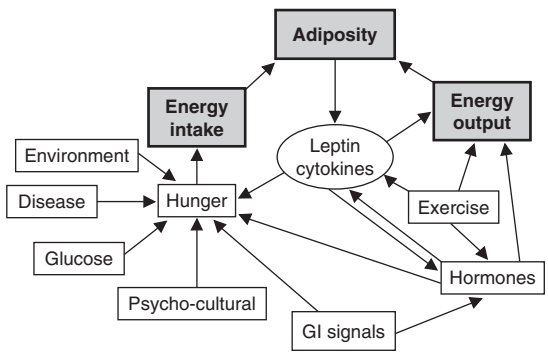

Fig. 1. General schematic of the factors that influence energy intake, energy output and their relationship to adiposity. **GI** = gastrointestinal.

From an endocrine perspective, a number of hormones regulate lipid metabolism including, catecholamines, corticosteroids, human growth hormone (hGH), thyroid hormones and gonadotropins (androgens and estrogens). All of these hormones can, therefore, have an influence on adipose tissue and all of these hormones have been in some way related to, or associated with, leptin.[3,9] In addition, these hormones appear responsive to exercise and exercise training.[17] Thus, exercise is one of the major links between the hormonal modulators of energy intake and output. This article will attempt to explore the relationship between these hormones and adipose tissue with emphasis on how exercise influences this relationship.

A vast body of literature has shown relationships between androgens, catecholamines, cortisol, hGH, insulin and thyroid hormones. Most of this information has come from studies of isolated cell, animal, disease states, drugs and correlation studies in humans. In addition, the relationship between these hormones at rest, during stress and exercise is influenced by the sex of the individual.[17] These sex-related effects in turn, influence energy substrate metabolism. The role of sex is a treatise beyond the scope of this article. This topic is addressed in a recent article by Braun and Horton.[18] Finally, many other factors besides exercise influence these hormones, such as circadian rhythm, thermoregula-

tion or dietary composition, but a full discussion of these factors is beyond the scope of this review.

1. Hormonal Regulation of Lipid Metabolism

In order to understand the influence of exercise on the interaction of the endocrine system and body fat, a brief précis of the interaction of the metabolic hormones and lipid metabolism is needed. Much further in-depth discussions of this can be found in Tremblay et al.,[19] Goldberg and Elliott,[20] Brouns and van der Vusse,[21] and three companion articles by Jeukendrup and colleagues.[22-24] The primary hormones involved with lipid metabolism are the catecholamines, cortisol, hGH and thyroid hormones; however, other hormones, including glucagon, insulin, androgens and estrogens, can be involved in specific situations. Of this list of hormones, the catecholamines, epinephrine (adrenaline) and norepinephrine (noradrenaline), appear to be the most important. The hypothalamus of the brain appears to centrally integrate the various metabolic, nervous, hormonal signals and interacts with the anterior pituitary to determine functional status of many of these hormones.[25]

Stressful events (physiological or psychological) cause activation of the sympathetic nervous system (SNS) and the release of the catecholamines. The catecholamines influence both food intake and metabolic rate. The catecholamines suppress food intake via an effect on the appetite centre within the hypothalamus, reducing the sensation of hunger. Regarding metabolism, initially the SNS responds, releasing mostly norepinephrine. The SNS has been shown to innervate adipose tissue, causing lipolysis and the release of glycerol and free fatty acids into the circulation.[26,27] In addition, high levels of activity in the SNS inhibit food intake and food absorption.[28] If the stress is perceived as significant, the adrenal glands are activated and release mainly epinephrine, further increasing adipocyte lipolysis via activation of hormone-sensitive lipase. The effects of these adrenergic hormones are dependent upon the type of receptor (α- or β-receptor) at the target tissue. Subcutaneous adipose tissue appears to contain a majority of α_2-receptors that when activated, have the propensity to inhibit lipolysis; whereas intra-abdominal adipose contains more β-receptors that, when activated, increases lipolysis.[28] Thus, this activation of the catecholamines has the tendency to reduce abdominal fat while sustaining subcutaneous fat.[29] The effect of the catecholamines on lipolysis is most apparent during exposure to stress. In a normal sedentary state, the catecholamines appear to account for only 2–3% of 24-hour energy expenditure.[28]

Insulin exerts an influence on lipolysis. Insulin increases adipocyte lipoprotein lipase activity, thus promoting fat storage particularly in the subcutaneous tissues.[30] Insulin enhances the incorporation of glucose into the triglyceride molecule, mostly as the glycerol portion. Concomitantly, insulin inhibits lipolysis by inhibiting the effects of hormone-sensitive lipase, cyclic adenosine monophosphate and protein kinase A.

α-Adrenergic receptors are also located in the β-cells of the pancreas and, when stimulated, suppress insulin secretion. Conversely, β-adrenergic receptors are more prevalent in the α-cells of the pancreas and when activated release glucagon. The inhibition of insulin and the secretion of glucagon work in concert to increase adipose tissue lipolysis. In healthy individuals, this effect is only mediated during stressful events, such as thermal stress, hypoglycaemia or exercise.

The thyroid hormones, in particular triiodothyronine (T_3) can stimulate metabolic rate and increased adipose tissue lipolysis, potentially via an interaction with the catecholamines. The combined effects of thyroid hormones and catecholamines enhance mobilisation of triglycerides from adipose tissue and increase fatty acid lipogenesis in the liver.[31] Yamaki et al.[32] have suggested that increased T_3 exposure causes an augmentation in mitochondrial density, which elevates resting metabolic rate. Thus, with consumption of an isocaloric intake, elevated T_3 results in weight loss, while decreased T_3 levels results in weight gain.[33] Conversely, weight loss causes circulating T_3 to decline.[34] The thyroid hormones are controlled by the

hypothalamus (thyrotropin-releasing hormone [TRH]) and the pituitary (thyroid-stimulating hormone [TSH]). TSH has been shown to activate hormone-sensitive lipase and increase lipolysis, but this effect appears weak.[30] In general, these hormones respond slowly and their involvement is thought of as a more long-term control mechanism.

In a resting state, both the glucocorticoids (cortisol) and hGH have roles in regulating lipid metabolism.[35-37] A recent microdialysis study using men has shown that glucocorticoids and hGH can increase systemic and regional lipolysis.[38] Infusion of hydrocortisone succinate elevated palmitate (a marker of systemic lipolysis) approximately 70% and lowered interstitial glycerol flux (an index of regional lipolysis) by approximately 50%. The infusion of hGH increased systemic lipolysis and glycerol flux similarly to the cortisone infusion.[38] When both hormones were infused the effects were greater, but not additive, suggesting some synergistic activity. Studies on post-surgery[37] or obese[33] patients also provide support for a lipolytic effect of cortisol. In contrast, studies on exogenous hGH administration in normal individuals do not completely support the lipolytic effect of hGH.[34,39,40]

Sex-steroid hormones also have lipolytic activity. Estradiol and estrogens have been shown to increase lipolytic activity in women.[41-43] The actions appear to be mediated by: (i) estradiol reducing insulin-binding capacity;[41] (ii) a direct effect of estradiol on liver lipolytic enzymes, namely acetyl coenzyme-A carboxylase and fatty acid synthetase;[42] or (iii) possibly by reducing glucose uptake in muscle.[44] Androgens may also have a minor influence on lipid metabolism at rest.[36,45] This effect has been inferred from studies that administered testosterone to overweight individuals and found decreases in visceral fat without loss of lean body mass.[46,47] The mechanism of this response is presently unknown but some researchers have suggested that testosterone may directly influence enzymes of adipose metabolism,[45,48] while Seidell and colleagues[49] suggest that testosterone may impart its lipolytic effects indirectly on sex-hormone binding globulin, which in turn, affects insulin.

2. Hormonal Interrelationships

Figure 2 is a model representing the interrelationships of the major metabolic hormones that influence energy intake. The relationships are very complex with some pathways enhancing the activity of other hormones and others having an inhibitory influence. Still, other relationships have been proposed, but not proven to exist. In addition, many of the hormones have central nervous system receptors that have differing effects from the somatic system, further complicating the understanding of these relationships. To simplify the complexity of these relationships, this article will examine each of these hormonal relationships independently; presenting the information on the pathways with what knowledge is presently known.

The relationship between the catecholamines and various hormones has been extensively studied. β-Adrenergic receptor blockage with propranolol, which reduces the influence of catecholamines, appears to enhance the hGH response to growth hormone-releasing hormone (GHRH) or hypoglycaemia.[50] Relationships appear to exist between the catecholamines and thyroid hormones, pancreatic hormones and possibly glucocorticoids, as mentioned above. Also, there is also some suggestion that elevated insulin levels cause SNS stimula-

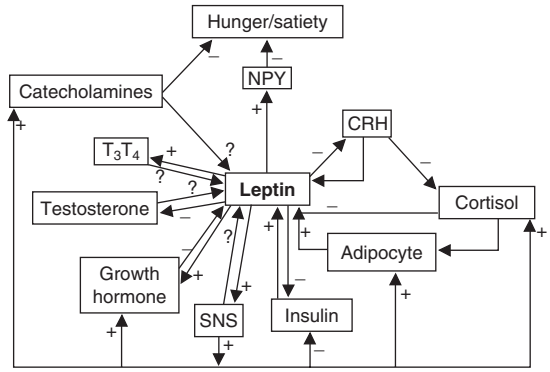

Fig. 2. The interrelationship between metabolic hormones, leptin and hunger. **CRH** = corticotropin-releasing hormone; **NPY** = neuropeptide-Y; **SNS** = sympathetic nervous system; T_3 = thyroxine; T_4 = tri-iodothyronine; **–** indicates pathway inhibits the activity of other hormones; **+** indicates pathway enhances the activity of other hormones; **?** indicates relationship has been proposed, but is not proven to exist.

tion.[51] Presently, this relationship is not well understood and the causes and purpose(s) are in need of investigation.

At rest, cortisol is negatively associated with hGH.[52-54] This effect may be mediated centrally, as Rosmond et al.[55] has shown that abdominal obesity is related to weak glucocorticoid receptor reactivity in the hippocampus, which ultimately modifies the hypothalamic-pituitary-adrenal axis (HPA) responses. Thus, GHRH is suppressed,[52,53] resulting in a reduction of hGH. This effect may be genetic.[55] The cause/effect relationship between these two hormones is still equivocal, as Hermida et al.[56] have shown that in short-stature boys, a normal circadian rhythm for cortisol exists despite the abnormal hGH pulse amplitude. Ghizzoni et al.[57] using time-course studies, has suggested that any interactions between cortisol and hGH is mediated by leptin. As mentioned earlier, cortisol and hGH may be correlated, but their effects on lipolysis are not totally additive when co-administered.[38] With respect to the influence of cortisol on other metabolic hormones, a relationship between cortisol and insulin may exist as cortisol may induce insulin resistance.[26] In addition, cortisol is also negatively associated with testosterone[58] and estrogens.[59]

Connections also exist between the sex hormones and other metabolic hormones. Studies have proposed that a high level of free testosterone increases insulin sensitivity.[60,61] In support, obese individuals generally have decreased circulating testosterone levels with concomitant decreased insulin sensitivity[26] and the administration of testosterone appears to alleviate the insulin resistance.[49] Although evidence supports a relationship between androgens and estrogens and other metabolic hormones, there appears to be no relationship between androgens and hGH. Ovesen et al.[62] administered exogenous hGH for 14 days to healthy men and found no increases in testosterone. Hackney and Ness[63] found that 8 weeks of intensive exercise training elevated hGH, while testosterone was suppressed.

With regard to estrogens, Hansen and Weeke[64] have shown that fasting hGH levels were related to estradiol, but not all studies agree.[65] Estrogens have been negatively associated with insulin[41,42,64] Whether this relationship is due to a direct effect of estrogen on pancreatic β cells or a decrease of insulin receptor activity to a given insulin level is still debatable. Ding et al.[59] have suggested that elevated cortisol may disrupt the hypothalamic-pituitary-gonadal axis resulting in decreased estrogen levels. Whether this relationship is because of a stress response or insufficient energy intake is also debatable.[66] Estradiol appears to be related to leptin.[67] Leptin could be the signal that informs the reproductive system about the energy status; thus, permitting or blocking reproduction and menses in women.[68] Once again, it is not known if this effect of leptin is directed to the ovaries or mediated through the hypothalamic-pituitary-gonadal axis.

The thyroid hormones also interact with hGH. Giustina and Wehrenberg[69] summarised information from eu-, hyper- and hypothyroid patients. Hyperthyroid men with elevations of T_3 and thyroxine (T_4) seem to have elevated somatostatin, which suppresses GHRH and consequently hGH. Conversely, depressed thyroid function (hypothyroidism) also appears to suppress nocturnal hGH secretion by decreasing hGH production in the pituitary. Harvey[70] noted that hypothalamic TRH may actually be a releasing hormone for hGH, which has resulted in TRH being used as a clinical test for hGH insufficiency.[71] In addition, hGH also appears to have an influence on thyroid hormones, as the administration of hGH stimulates the conversion of T_4 to the active state T_3 and a concomitant increase in energy expenditure.[72] Thus, a possible link between the thyroid hormones and hGH; however, not all studies agree with this relationship. Coiro et al.[73] studied this relationship in obese and non-obese men using the TRH challenge test. They found that men with normal, basal TSH levels did not increase hGH levels in response to the TRH challenge; whereas, individuals with elevated basal TSH levels responded to the TRH with a release of hGH. Thus, the relationship between thyroid hormones and hGH is not clear.

Leptin appears to have a role in both energy intake and energy expenditure (see figure 1). When

energy intake is restricted, leptin decreases, causing energy conservation and decreased thermogenesis. Conversely, leptin increases as body fat increases in an attempt to reduce food intake and increase thermogenesis.[74] Leptin's action on hunger/food intake appears to be regulated through its effect on hypothalamic neuropeptide-Y (NPY).[74] With regard to energy expenditure, leptin appears to activate the SNS and ultimately thermogenesis; possibly through galin-like peptide, as Hansen et al.[75] have shown that in mice the central administration of galin-like peptide decreased body mass and increased core temperature. Conversely, activation of the SNS decreases leptin production in white adipose tissue, while sympathetic blockade increases circulating leptin. Thus, there appears to be a reciprocal relationship between leptin derived from the white adipocytes and the SNS.[76] This relationship has been shown in sub-human species and needs to be verified in humans.[76]

Leptin may also be related to other metabolic hormones. Simsch et al.[77] have shown that in humans, low leptin causes a reduction in all the hypothalamic-releasing hormones (thyroid, gonadal and hGH), except adrenocorticotropic hormone (ACTH). Florkowski et al.[78] administered hGH to overweight adults, which lowered body fat and reduced leptin. Also in support, Tuominen et al.[79] found an inverse relationship between hGH and leptin. Ghizzoni and colleagues,[57] using time course analyses in prepubertal children, found a sex-specific 2–5 hour lag between hGH and leptin. They suggested that the lag appears appropriate since hGH affects leptin gene expression. Intriguingly, Ghizzoni and colleagues did not eliminate the possibility that the relationship may be more mathematical than physiological. Studies in adults have shown positive statistical associations between leptin and thyroid hormones.[15,80-82] A study on fasting animals found that decreased leptin caused increased production of NPY, which resulted in decreased thyroid hormone production.[83] In contrast, Alagna et al.[84] reported that leptin immediately declined with fat loss in 38 morbidly obese post-bariatric surgery patients, but TSH and free T_4 were unchanged. Thus, the effects of thyroid function and leptin may be associative rather than causal, although this point remains to be determined.

Convincing evidence from animal studies has shown a physiological feedback loop between leptin and HPA; thus, ultimately cortisol. Ahima et al.[74] administered leptin to ob/ob mice and found an inhibition of CRH. Also, the administration of synthetic glucocorticoids to mice elevated leptin production,[85] due to a presently unknown mechanism that reduces messenger RNA (mRNA) for CRH receptors.[86] In contrast to the animal and isolated cell studies, human studies on the relationship between resting (non-stressful situations) leptin and cortisol concentrations are equivocal at best.[87,88] However, some research on human adults suggests that leptin inhibits cortisol production;[89-91] while others indicate increases in cortisol acutely stimulate leptin secretion in adipocytes.[92] These relationships in humans appear time-dependent, as an elevation of cortisol typically occurs hours before a leptin response.[57]

There appears to be a moderate relationship between leptin and sex steroid hormones. Paolisso et al.,[67] using 80 healthy men and women, have shown moderate association between leptin and testosterone or estradiol, independent of body fat or insulin. They speculated that leptin could modulate gonadal activity by informing the reproductive HPA about nutritional status. More recent evidence suggests that testosterone suppresses leptin mRNA; thus, implying a direct link between changes in testosterone and leptin production.[93] The relationship between leptin and estrogens may actually be moderated by cortisol;[58] however, more research is needed in humans to substantiate this hypothesis.

A reciprocal relationship may exist between leptin and insulin.[94] Tanizawa et al.[95] have noted that leptin acts directly on the pancreatic β cells stimulating insulin secretion at rest. *In vitro* human studies, as well as animal studies, have also noted that insulin-mediated increased cellular glucose uptake stimulates leptin expression and secretion.[96,97] These studies on insulin, combined with the other studies on leptin and metabolic hormones, suggest that lep-

tin may be the central focal point (figures 1 and 2) and that energy balance may be the product of the interactions between leptin and these metabolic hormones.[98-100] However, a growing body of evidence also suggests that the SNS or catecholamines may be equally as important.[29,57] As a note of caution with regard to accepting the interpretation of these results, the majority of studies presented above derived their conclusions from correlations, which show associations but not direct cause or effect. Thus, further confirmatory research is needed.

Since all of these hormones appear to interact with each other, the question remains as to how these hormones interact to influence overall lipid metabolism at rest. Substrate use is generally controlled by substrate availability and is related to blood glucose status. If glucose is in abundance (e.g. post-prandial), insulin elevates, activating adipose lipoprotein lipase, which encourages the storage of fats and a reduction in β-oxidation or the use of lipids for energy. Increased lipid storage increases leptin, reducing hunger and theoretically, food intake. Leptin may also inhibit cortisol allowing for greater glucose uptake and metabolism. Furthermore, the increased leptin could influence T_3 to maintain resting metabolic rate.

When glucose levels are low, as occurs after an overnight fast, adipocyte lipolysis is increased. The hypothalamus activates the SNS and adrenal glands so that the catecholamines tend to elevate, resulting in suppressed insulin and enhanced glucagon to increase gluconeogenesis. The presence of the catecholamines increases hormone sensitive lipase and also increases adipocyte sensitivity to T_3. This combination enhances lipolysis and fatty acid oxidation. The catecholamines and SNS subsequently stimulate the hypothalamus to release CRH, resulting in a rise in ACTH and ultimately cortisol, which improves glucose conservation and lipid use for energy. Although in a resting, fed state the lipolytic effect of cortisol may be small, if the fasting becomes chronic, then the inhibition of leptin on ACTH is attenuated and cortisol-induced lipolysis is enhanced and peripheral cellular glucose uptake is reduced. Although the decline in leptin may inhibit GHRH, and therefore hGH, the influence of the catecholamines on the GHRH appears stronger, and hGH output increases.[101,102] The combined effect of hGH and catecholamines further increases lipolysis. Concomitantly, fasting causes circulating T_3 to decline, which lowers resting metabolic rate. Thyroid hormones are controlled by TRH from the hypothalamus, which is influenced by the SNS and circulating catecholamines. In addition, the lower leptin could interact with TRH or TSH production and thus T_3 to reduce resting metabolic rate. Therefore, the SNS and leptin appear to be central to the control of substrate utilisation.

3. Obesity-Induced Modifications of Hormonal Interactions

Large amounts of adipose tissue can modify hormonal profiles and the relationships between these hormones. Obesity has been shown to cause 'resistance' or loss of sensitivity (loss of response per unit of hormone) for several hormones. Obese individuals appear to have higher levels of SNS activity;[51,103] however, the metabolic response to SNS stimulation appears reduced in obese individuals.[104] This suggests that in obesity any compensatory effect of the SNS on metabolism to increase energy expenditure may not occur, making weight loss more difficult.[79] In contrast to the SNS activity, circulating epinephrine levels in the obese can be either normal or reduced and the epinephrine response to stress (e.g. hypoglycaemia, exercise) is typically blunted.[105] Del Rio[105] has suggested that the blunted amine response to stress could be related to the exaggerated cortisol response that occurs in obese individuals, since glucocorticoids inhibit catecholamine production. Finally, the lipolytic action of catecholamines on visceral adipose is blunted.[28,29] This blunted effect is probably related to the elevated leptin production associated with obesity,[78] as increased leptin has been shown to be related to a down-regulation of the β-adrenergic receptor in white adipose tissue, resulting in a decreased responsiveness to sympathetic stimulation.[76]

Resting insulin[61,106] and leptin[78] levels are generally higher in obese individuals. Monroe et al.[107] have shown that there is an association between these two hormones and sympathetic nerve activity and that leptin can act perhaps as a 'signal' to the sympathetic response. This suggests that the increase in leptin associated with obesity is necessary for the insulin response to occur. However, this time course has not been investigated. Although these two hormone levels are higher than normal, there appears to be a loss of systemic sensitivity to their presence in many obese individuals.

Obesity seems to enhance cortisol production and clearance in most studies; however, not all studies report this finding.[26] Specifically, any stress, psychological and physiological, appears to elevate cortisol in individuals with central obesity more than in normal weight individuals.[26] This could possibly be related to the increased SNS tone previously mentioned.[108] Resting thyroid hormones appear to be within normal limits for obese individuals, provided no comorbidities exist.[73] Total and free testosterone, free estrogen and sex hormone binding globulin levels are usually lower in obese individuals, but could also be normal.[33,60,109,110] Low testosterone appears to decrease the lipolytic response to catecholamines; however, it may also decrease lipid uptake in the adipocyte.[93] In addition, Jockenhoval et al.[111] have suggested that low androgens permit leptin to increase, while testosterone treatment in hypogonadal men lowered leptin. Thus, the low testosterone would increase leptin, which could influence energy intake. Any reduction in circulating sex steroids appears to be related to lower luteinising hormone pulsitility, but since some obese women have normal menstrual function, further study is needed to elucidate the hormonal interactions.[112]

The interactions of these hormones seen in normal weight people are still apparent in obese individuals; however, the interactions are somewhat modified and we do not know which are the precedents or antecedents. Clearly, there must be some signal external of adipose tissue that initiates weight gain. Genetic factors are most likely initially involved,[26,113] although environmental factors such as chronic stress may play a role.[114] Possibly genetic factors may alter the SNS,[28,115] HPA[26] and leptin receptors. The SNS has a role in both energy intake and energy expenditure. The literature suggests that SNS tone is often increased by obesity.[51,76,103] The increased SNS tone has been linked to the hypertension associated with obesity. However, the metabolic response to SNS stimulation in these individuals appears to be blunted.[104] The disregulation of SNS activity could be conceptualised as the antecedent to the hormonal responses. SNS also influences insulin; thus, diminished responsiveness to SNS stimulation, as seen in obesity, would allow insulin to increase encouraging fat storage and increased adiposity.[115,116] Conversely, elevated insulin levels may cause SNS stimulation.[51] Although this effect in overweight subjects has been related to renal and circulatory systems, an increased adrenergic effect on muscle may serve as a compensatory mechanism to increase energy expenditure, while a similar effect on adipose tissue may increase circulating fatty acids.[103] These combined effects could help the body maintain weight homeostasis.[105] However, the metabolic adrenergic effects are mediated mostly by the adrenal glands and their function may be suppressed by obesity.[105] Thus, this hypothesis needs further verification in humans.

As previously noted, obese individuals typically have elevated insulin levels and can develop frank diabetes mellitus.[61,106] The reason for the increased insulin secretion associated with obesity and the relationship between obesity and diabetes is not clear. Unger[117] has speculated that initially, increased deposition of fat in pancreatic β cells increases β-cell proliferation and a secondary increase of insulin secretion (the pre-diabetic state). As the obesity progresses, the lipid content increases and β-cell degeneration occurs reducing insulin production. Although not the major focus of the discussion, this hypothesis, which is based on animal research, is intriguing, as it suggests that the infiltration of fat into non-adipose tissue can have an impact on the homeostasis of other cells. Leptin may up-regulate IL-6 and TNFα, both of which have a negative

impact on the insulin-signalling pathway within the cell (particularly muscle). Thus, obesity not only influences the pancreatic cell insulin output, but the cellular insulin response, leading to hyperglycaemia.

As adipose tissue develops it releases leptin and cytokines (e.g. IL-1, IL-6, TNFα, adiponectin, resistin) into the blood. IL-1 plays a role in lipid metabolism by directly increasing adipocyte lipase activity, and indirectly by lowering insulin[118] and increasing cortisol.[13] Cytokines are powerful stimulants of the HPA and through this cascade cause the release of cortisol; however, the cytokines may also exert their effects directly on the adrenal glands to release cortisol.[26] The increased cortisol level, as well as the cytokines, in some way contribute to insulin resistance.[115] Elevated cortisol and leptin may reduce GHRH and therefore hGH secretion, eliminating the normal lipolytic and calorigenic effect of hGH. In addition, elevated cortisol and leptin could indirectly reduce estrogens; thus, increasing lipoprotein lipase activity and decreasing lipolytic activity.[60] Adipose tissue contains metabolic pathways for sex steroids. Accumulating large amounts of adipose may enhance the conversion of androgens to estrogen (testosterone aromatisation process), which would contribute to adipose deposition.[48,119] Although these hormonal relationships appear logical and potentially could contribute to obesity, they are mostly theoretical at this time and are in need of future research.

4. Energy Restriction and Metabolic Hormones

Negative energy balance results in a significant change in the hormone milieu. In general, most circulating metabolic and anabolic hormone levels decline with energy restriction. The literature consistently shows that weight loss reduces insulin levels.[120-122] Several mechanisms previously mentioned could account for this reduction: (i) reduction of fat infiltration into the islet of the pancreas; (ii) a reduction in SNS activity that would elevate leptin and, therefore, lower insulin; or (iii) the loss of fat resulting in less cytokine release and improved cellular glucoregulation requiring less insulin. Presently, these mechanisms are speculation and in need of verification. Most importantly, the reduction of insulin is a positive response, as insulin sensitivity (glucose uptake/unit of insulin) increases[121,122] and the risk of diabetes may be reduced.[123,124] The improvement in sensitivity, however, will not cause the conversion of frank diabetes to a normal glycaemic state.[125]

Studies on hypocaloric diets and thyroid hormone are also consistent, showing a decline in T_3 or T_4,[126,127] with a concomitant decline in basal metabolic rate. Similarly, significant weight loss reduces norepinephrine[128,129] and leptin levels.[130-132] Conversely, energy restriction increases hGH.[101,102,133,134] Cortisol may be reduced by dietary-induced weight loss.[135-137] Ironically, the ACTH response to CRH appears to be intact and free cortisol remains normal; thus, any reduction in cortisol may be related to a decrease in cortisol binding globulin.[137] Kraemer et al.[135] have also noted that if exercise is added to the weight-loss regimen, circulating cortisol may increase, or possibly remain unchanged.

Most studies support a reduction in circulating testosterone during energy restriction.[126,136,138,139] However, not all studies agree, as Kraemer et al.[135] found that 12 weeks of weight loss via dieting, resulting in ~9kg loss, caused no significant change in testosterone. Dieting may also reduce estrogens, but the reduction does not appear to disrupt normal ovulation[140] unless the energy restriction becomes severe.[141] Any decrease in sex steroid hormones appears to be related to an altered luteinising hormone pulsitility.[66,140] Thus, all the metabolic hormones are modified with energy restriction. However, it appears that once weight is stabilised and the diet becomes isocaloric, the hormonal milieu returns to normal.

Weight loss appears to be more difficult to achieve in women than men. This sex difference in weight loss could be related to women having less SNS and catecholamine response at a given intensity of exercise than men. Women may or may not have greater rates of lipolysis compared with men.[142]

Braun and Horton[18] have speculated three possible mechanisms for the sex differences in lipolytic activity: (i) an interaction of SNS with estrogen, which increases the lipolytic actions; (ii) intramuscular stores of lipids may be more sensitive to SNS activity; and (iii) decreased carbohydrate metabolism, which causes more fat to be used simply by default. Additional research in this area is needed to determine the exact mechanism(s).

5. Exercise-Induced Changes in Lipid Metabolism

The influence of exercise on lipid metabolism is beyond the scope of this article but has been extensively studied and published in other articles.[19-24] These review articles identify an inverse relationship between lipid metabolism during exercise and exercise intensity. Figure 3 is a summary of effects of exercise on lipid metabolism. Acute bouts of exercise appear to cause an increase the circulating levels of most hormones, while exercise training seems to lower (or have no effect) on resting hormonal concentrations. The increased hormones with acute exercise have the ability to enhance lipid oxidation and lipolysis, assuming adequate oxygen supply. Interestingly, the lower resting hormonal concentrations associated with aerobic training also result in greater lipid utilisation.

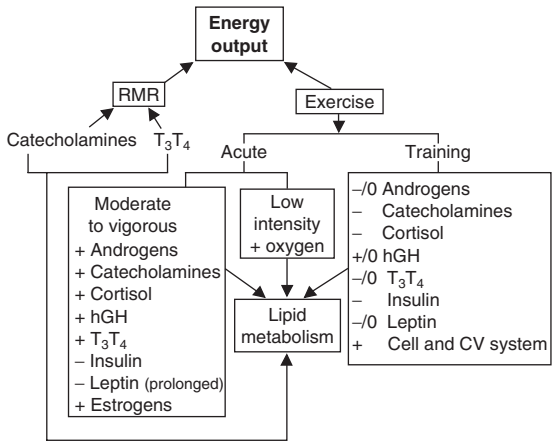

Fig. 3. Schematic representation of the metabolic hormonal that affects resting metabolic rate (RMR) and substrate use during exercise. **CV** = cardiovascular; **hGH** = human growth hormone; T_3 = thyroxine; T_4 = tri-iodothyronine; **0** indicates unchanged; **–** indicates decrease; **+** indicates increase.

Low-intensity exercise (<30% maximum oxygen consumption [$\dot{V}O_{2max}$]) uses predominantly lipids, which appears to be related to: (i) oxygen availability; (ii) the recruitment of slow twitch fibres that have extensive aerobic capabilities to metabolise lipid; and (iii) the capacity of the mitochondria to transport and metabolise fatty acids.[143] In addition, low-intensity exercise relies mostly on adipose stores of lipid rather than intramuscular stores.[22] Low-intensity exercise does not appear to cause significant changes in any of the major metabolic hormones, unless the activity becomes prolonged and causes a decline in plasma glucose concentrations.[17,22]

Moderate-intensity exercise (40–65% $\dot{V}O_{2max}$) still uses significant amounts of fats for energy, but the source appears to be both adipose tissue and intramuscular stores. At this intensity, catecholamines increase, activating hormone-sensitive lipase. hGH increases, facilitating the effects of catecholamines on lipid metabolism.[23] The SNS suppresses insulin and increases glucagon. In addition, the hypothalamus releases CRH causing the cascade of events that ultimately increases cortisol. These hormonal changes facilitate lipid metabolism until the rate of energy demand is greater than oxygen availability.

High-intensity exercise (≥70% $\dot{V}O_{2max}$) still uses small amounts of fats to produce energy, but glucose and glycogen are the predominant energy substrates. This reduced lipid metabolism could be related to increased lactate concentration, vasoconstriction in the adipose tissue, or inhibition of long-chain fatty acid uptake in the mitochondria.[23] Interestingly, Yoshioka et al.[144] have noted that fat oxidation after high-intensity exercise is greatly increased, possibly mediated by adrenergic mechanism. Finally, aerobic/endurance training allows for lipid metabolism to occur at a higher percentage of maximal capacity and is probably related to: (i) improved cellular capacity to metabolise lipids; (ii) improved oxygen availability; and (iii) an attenuated SNS/catecholamine response to submaximal exercise.[145,146] These physiological responses to exer-

cise suggest that if dietary intake remains constant, then exercise should result in a loss of adipose stores.

6. Exercise-Induced Changes in Adiposity

Although a number of studies support exercise-induced loss of fat stores without energy restriction,[147-149] not all forms of exercise result in the same amount of loss. The majority of studies using low-intensity exercise programmes, such as walking, which should metabolise mostly fat, appear to result in little or no weight loss.[150-153] However, Miyatake et al.[154] using 31 obese Japanese men on *ad lib* diets, found that increased daily walking was directly associated with the decreased visceral adipose tissue. Moderate- to high-intensity endurance training, including running, cycling or aerobics, appears to cause loss of adiposity.[147,150,155-157] Resistance, or strength, training may contribute to loss of fat stores, but it does not appear to have the same magnitude, or as significant an effect, as aerobic exercise.[158,159] Other forms of exercise have not been extensively studied.

If one assumes that a typical exercise session lasts 30–60 minutes at a moderate intensity, then the total energy expenditure will range from 200 to 700 kcal (840–2900kJ). Since the intensity is usually moderate, then 40–60% of the energy will be derived from fat. Therefore, a typical exercise session will utilise between 9 and 47g of fat, a relatively small amount of weight loss. However, if energy intake remains stable, this amount of exercise could have an impact on total adiposity over a prolonged period of time. Although, the loss of adiposity may be modest at best, the exercise will cause T_3 levels to be maintained during the recovery from the exercise period,[160,161] thus preserving resting metabolic rate; whereas diet-induced (i.e. energy restriction) weight loss causes a lowering of T_3 and resting metabolic rate. Exercise also causes protein sparing, potentially via hGH, which will facilitate the maintenance of muscle mass.[162,163] Preserving muscle mass helps sustain resting metabolic rate and therefore resting energy expenditure, which will help maintain equilibrium in the energy balance equation. Again, this effect is in opposition to the findings with diet-induced weight loss.

7. Exercise-Induced Modifications of Hormones

7.1 Acute Exercise: Normal Weight Individuals

A schematic of the effects of exercise on metabolic hormones and lipid metabolism is presented in figure 3. The effects of acute exercise on metabolic hormones have been extensively reviewed in earlier work by us.[17] In summary, the catecholamines appear to elevate in direct relation to increasing exercise intensity.[164,165] Stallknecht et al.[166] has suggested that the exercise-induced catecholamines release increases subcutaneous adipose tissue lipolysis. The mechanism appears to be an increased responsiveness of adipose tissue to β-adrenergic stimulation, as shown by a study using fat biopsies and isoprenaline, a β-adrenergic agonist.[167] Cortisol may have a threshold for response such that exercise <50% of $\dot{V}O_{2max}$ causes cortisol to decline, while exercise >50% maximal capacity causes cortisol to increase.[168] The increase in cortisol could be related to elevation of lactic acid in some way stimulating ACTH,[169] increased IL-6,[13] or it is possible that the increased SNS activity results in an elevation of NPY in the hypothalamus, resulting in an increase in CRH, with a concomitant release of ACTH and cortisol.[170]

hGH is an important regulator of fat metabolism during exercise.[35,171] hGH appears to have a response threshold, as Jenkins[172] has shown that exercise intensity has to be >30% of maximal capacity and for longer than 10 minutes to elicit a response. The mechanism appears to be a cholinergic pathway influencing the pituitary to secrete hGH or the hypothalamus to release GHRH. In addition, Farrell et al.[169] have suggested that the increase may be due to lactic acid; however, this mechanism is equivocal.[164] On the other hand, insulin declines with as little as 10 minutes of submaximal exercise,[173,174] as long as the intensity is >40% of $\dot{V}O_{2max}$. [173] The

decline in insulin appears to be a direct influence of the SNS on pancreatic β cells.[17] Leptin does not appear to be influenced by low- or moderate-intensity exercise,[175,176] unless the exercise is prolonged for several hours, such as a marathon, then leptin appears to decline.[177] Some reports have suggested that the leptin response to exercise is delayed, peaking up to 48 hours post-exercise.[178,179] The mechanism for such a delayed response is presently unknown.[180] Interestingly, the studies supporting the delayed decrease in leptin used hour-long exercise sessions with a total energy expenditure of approximately 900 kcal (3770kJ). One must keep in mind that most individuals would find it difficult to participate in an exercise session that would require that amount of energy. We are unaware of studies that have shown a similar effect of moderate-intensity exercise using shorter duration exercise.

The thyroid hormones do not appear to respond to acute bouts of submaximal or maximal exercise.[181-183] In contrast, hypothalamic TSH appears to respond in proportion to exercise intensity or duration.[181] However, preliminary studies from our laboratory have found decreases in TSH during recovery from acute exercise (personal observation). Since TSH has a delayed effect on the thyroid, an immediate post-exercise release of T_3 or T_4 from the thyroid would not be expected. Submaximal exercise appears to elevate both total and free testosterone as well as estradiol.[63,164,173,181] Some of the change in the sex steroid hormones is related to haemoconcentration,[164,184] but decreased hepatic clearance is also important.[17] With prolonged exercise, testosterone appears to initially elevate, then decline.[63,181] The mechanism for the decline appears to be hypothalamic in origin, possibly involving opioids, prolactin, CRH, or gonadotrophic hormone-releasing hormone.[58] In contrast to the androgens, we know little about the estrogen response to prolonged exercise; however, some studies have suggested that it increases.[65,165]

7.2 Acute Exercise: Obese Individuals

Although obese individuals appear to have a capacity for fat oxidation similar to normal weight individuals,[185,186] obese individuals present different hormonal responses to exercise than normal weight individuals. The most significant changes are blunted SNS and catecholamine responses.[29] Although a blunted adrenergic response is evident, Hardman et al.[152] has shown that prolonged exercise in obese men results in an increased responsiveness of adipose tissue to β-adrenergic stimulation of lipolysis.[167] Thus, less stimulation could bring about lipolytic responses, similar to normal weight individuals.[187] Obesity also appears to blunt the hGH response to moderate-intensity (60–70% $\dot{V}O_{2max}$) exercise,[188,189] but not the response to low-intensity exercise.[64] The mechanism of the suppressed hGH activity may be related to the blunted SNS and catecholamine activity previously mentioned.[190,191] Lower circulating hGH could diminish the normal impact of hGH on lipolysis and body fat. The insulin, leptin, T_3 and testosterone responses to exercise do not appear altered in obese compared with normal weight individuals.[185,192]

7.3 Training

The influence of aerobic exercise training is somewhat different from the acute effects of aerobic exercise. Aerobic training results in lower resting levels of most metabolic hormones.[17] For example, Winder et al.[174] has shown that the catecholamine levels at rest and in response to exercise diminish with aerobic training. Similarly, insulin appears to decline with training, but insulin sensitivity increases.[174] Resting cortisol levels may or may not be reduced by training, but the magnitude of the response of cortisol to submaximal exercise appears to decline with training,[77,193] apparently as a result of altered ACTH functioning.[193,194]

Studies have reported that resting concentrations of leptin may decline with endurance or resistance training.[74,135,176,195-198] However, this may not be the case for all individuals, as Kraemer et al.[199] have shown that 9 weeks of training in obese women did not cause any significant change in either body fat or leptin; suggesting that extreme adiposity may alter the training response of leptin. In some studies, the response to exercise training has been associated

with weight loss;[175,198] however, other studies have concluded the effect to be independent of weight loss and more related to energy expenditure.[77,196-198] Although resting levels of leptin may generally decline with training, Kraemer et al.[200] using an intermittent, graded high-intensity exercise protocol in highly trained runners, did note transient increases in leptin after exercise, which abated quickly. This rapid response suggests that the changes were related to exercise-induced haemoconcentration, rather than leptin production. Studies have also suggested that trained subjects may have a delayed leptin response to exercise, apparently peaking 48 hours post-exercise.[178,179] The mechanism for this response is presently unknown. The changes in resting leptin are not related to changes in catecholamines, but appear to be associated with changes in insulin.[197,201] One study has raised the possibility that the response may be inversely coupled with hunger post-exercise not related to training *per se*.[202]

Resting hGH levels may not be influenced by training;[184,188] however, it appears that the hGH response to exercise may be suppressed.[191] Resting thyroid hormones do not appear to change with exercise training unless the training is extremely strenuous,[15] but training may in turn, increase the sensitivity of cells to T_3.[160,161] Resting total and free testosterone levels may be reduced with training, but not in all subjects.[138] Kraemer et al.[200] noted coinciding transient increases in testosterone and leptin after high-intensity exercise. Since all of their subjects exhibited an increase in testosterone but not leptin, the hormonal responses were not related. Other possible mechanisms for testosterone changes include alterations in the hypothalamus (GnRH), pituitary (luteinising hormone or prolactin), or possibly hypothalamic disruption by cortisol.[138] Thus, the training physiology of testosterone is not completely understood and is still in need of further investigation. Finally, training appears to decrease estrogens.[203,204] The decrease may be related to lower circulating follicle-stimulating hormone and luteinising hormone, or chronic elevation of β-endorphin and cortisol.[17] Severe training that disrupts energy balance can lead to menstrual function disruption;[66] however, recreational exercise training may not disrupt reproductive functioning.[205,206]

Although we know that acute and chronic exercise cause perturbations in the hormones, we know little of the exact interactions between these hormones. Clearly, a relationship exists between the SNS, catecholamines and insulin during exercise.[17] Similarly, relationships exist between catecholamines and cortisol,[164,181] and catecholamine and hGH.[164] However, these relationships appear to be more associative rather than causative. Since thyroid hormones, testosterone and estrogens may not consistently respond to acute or chronic exercise, we know little about the interrelationships between these and the other mentioned hormones during exercise. However, exercise does increase energy expenditure, with adipose tissue being a contributor to the sources of energy. Thus, if energy intake remains constant and energy expenditure is increased, lipid content of adipose tissue should ultimately decline. Therefore, in our view (figure 1), exercise would provide two signals influencing energy balance. First, it would directly influence the SNS and the HPA axis, which could directly influence energy intake. Secondly, exercise would affect the general hormonal milieu, which in turn, would influence energy balance. As to which of these signals has the greatest impact is currently unknown and is in need of resolution.

The reduction of these hormones with training seems to contrast the increased use of fats for energy during submaximal exercise reported in most exercise physiology texts and in detail by Coggan and Williams.[207] Martin et al.[208] and others[167,187] have suggested that low levels of epinephrine and insulin, combined with normal T_3 can work together to improve tissue lipolysis. An earlier study by Martin et al.[209] using a detraining protocol in humans, has shown that training actually increases the response to catecholamines, potentially via increased β-adrenergic receptor sensitivity. With regard to insulin, low levels would permit lipolysis. In addition, data from a 6-week training study by Balsam and Lep-

po[160] suggest that the activity of the T_3 is not reduced. Thus, these training-induced hormonal changes may have some supportive role in the extent of lipolysis.

The training-induced lipolytic activity is most significantly enhanced by adaptations that occur within the muscle and cardiovascular systems.[207] Aerobic training increases blood flow and oxygen delivery to muscle, providing the key element for lipid metabolism. Within the muscle, there is increased mitochondria (size and content) and increased fatty acid transport proteins (e.g. carnitine palmitoyltransferase); thus, greater ability to use fats for energy. Training also decreases lactate formation at a given workload. Less lactate reduces its inhibitory effects on β-oxidation. Although fat oxidation increases, there is some question as to whether or not the source is from adipose tissue stores or intramuscular fat stores.[145] If the source was intramuscular, then exercise training could have minimal impact on adipose tissue-derived lipolysis. This does not appear to be the case, at least for obese individuals, as Malenfant et al.[210] have shown that 15 weeks of energy restriction and 21 weeks of training resulted in no change in intramuscular fat content, although there was considerable loss of fat mass. Since this was the first study on this topic and used a small sample size, there is a need for further verification of their results.

8. Relationship Between Exercise-Induced Hormonal Changes and Body Fat

The question remaining to be answered is what is the relationship between adiposity and exercise-induced hormonal changes? Clearly, adipose tissue is actively involved in energy production during exercise, providing both free fatty acids and glycerol for energy production. The effects of exercise on the hormone milieu during submaximal exercise potentiates the lipolytic effect, provided there is adequate blood flow and oxygen (figure 3). The SNS and the catecholamines appear to provide the underlying stimulus for lipid metabolism. The SNS and the catecholamines also act on insulin to lower its antilipidaemic effect and act to increase hypothalamic CRH and GHRH, resulting in increases in cortisol and hGH. These latter two hormones work synergistically to enhance lipolysis to a greater extent than either one would independently.[38] Any feedback between cortisol and inhibition of hGH appears to be suppressed,[211] potentially by the catecholamines;[190] thus hGH increases. Also, cortisol appears to have only a small influence on lipid metabolism, but a major effect on gluconeogenesis.[26] Since thyroid hormones, estrogens and testosterone may not respond substantially to acute exercise, the acute neuroendocrine responses to exercise regulating lipolysis appear to be related to catecholamines, insulin, hGH and cortisol.

Synergistically, all these hormones appear to maximise lipid metabolism more than expected from any one hormone acting individually. For example, studies have also shown that when exogenous hGH is administered to exercising individuals, no change in body composition occurs. This appears to be true with strength and power athletes,[39,212] or with aerobically trained individuals.[34] Marin et al.[47] administered testosterone to 11 obese men for 8 months and found no changes in body mass index or waist circumference and only a very small change in total adiposity. It must be kept in mind that low levels of some hormones provide facilitative or permissive effects for other hormones and high concentrations of the hormone may negate this facilitative effect.[17]

9. Conclusions

The study of metabolic hormonal interactions with adiposity is presently just beginning and much further work is needed to clarify these basic research findings so that we fully comprehend their implications and can ultimately use them in clinical situations. Our present state of knowledge suggests that a number of physiological and psychological systems that regulate energy intake and energy output work synergistically to maintain adipose tissue. However, adipose tissue is not passive in this process, as it secretes leptin, which has been linked to catecholamines, cortisol, insulin, hGH, thyroid hormones

and the sex steroid hormones, all having some effect on lipid (and carbohydrate) metabolism. In addition, adipose tissue releases cytokines that can affect insulin, increase lipolysis and stimulate HPA to release cortisol. Thus, adipose tissue is acted upon by a number of physiological stimuli, including hormones, and at the same time, is an active component in the regulation of its own fat content via various hormonal feedback mechanisms.

All of the hormones mentioned above respond to exercise and have been in some way related to, or associated with each other. Thus, exercise is one of the major links between the hormonal modulators of energy intake and output. It appears that the key neuroendocrine components facilitating the lipolytic activity during exercise are the SNS and the catecholamines. These two stimuli have a direct effect on adipose metabolism and a direct effect on metabolic hormones, which influence adipose metabolism. Acute low- and moderate-intensity exercise results in hormonal changes that facilitate lipolytic activity. Exercise training appears to reduce these hormonal responses, but increases the sensitivity of these hormones so that lipolysis may be facilitated. Large amounts of adipose tissue appear to blunt the metabolic hormonal responses to exercise (circulating levels), but the sensitivity of these hormones to exercise seems to be increased, thus off-setting the lower levels and maintaining normal lipolytic activity. However, the influence of hormones on adipose tissue lipolysis during exercise may not be as significant as other physiological changes that occur with training, such as oxygen delivery and mitochondrial changes. Therefore, although the physiological role of the endocrine system during exercise and training is significant, other training effects appear to have as great, or greater, influence on lipolytic activity in adipose tissue.

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