

Slow Acting Hormones and their Role in Fuel use during Exercise

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Abstract

Slow acting hormones act via cytoplasmic or nuclear receptors thereby activating the synthesis of various proteins and enzymes. The purpose of this paper was to investigate the slow acting hormones triiodothyronine, thyroxine, growth hormone, and cortisol, in their relation to exercise and nutrition partitioning.

Thyroid Hormones Roles in Nutrient Utilization during Exercise

The thyroid gland—which resembles the shape of a butterfly, and is located in the neck—secretes two hormones: triiodothyronine (T3) and thyroxine (T4) (see King, 2003 [Endocrine Insanity Part I](#) for more information on these two hormones). Thyroid hormones are slow acting; thus, their effects on exercise are primarily chronic, rather than acute. At high concentrations, these hormones increase the number of beta adrenergic receptors; thereby, enhancing the lipolytic and glycogenolytic effects of catecholamines. Hadri et al. (1996) observed a 2.3-fold increase in beta 3 adrenergic mRNA levels, which was correlated with a parallel initiation of beta 3 adrenergic number and of beta 3 adrenergic coupling to the adenylate cyclase system, after increasing T3 levels. Wahrenberg et al. (1994) investigated the influence of thyroid hormones on the adrenergic regulation of lipolysis in hyper and hypothyroid women. Results demonstrated that noradrenaline significantly enhanced lipolysis in hyperthyroid patients, whereas noradrenaline inhibited lipolysis in hypothyroid patients compared to that in controls. This may be attributed to the lack of beta receptors, while alpha receptors remained constant. Moreover, beta-adrenergic sensitivity and responsiveness were increased by 10 and 2 fold, respectively, in hyperthyroid patients. Conversely, in hypothyroid patients, beta-adrenergic responsiveness was reduced by 50%, whereas beta-adrenergic sensitivity remained unchanged compared with that in controls.

Further, thyroid hormones increase cellular energy utilization by increasing activity and synthesis of the sodium, potassium ATPase pump in the plasma membrane. For example, Lindvall et al. (1985) induced hyperthyroidism in rats by administering T3 for 10 days. Results showed a 16% increase in Na⁺-K⁺-ATPase activity. Conversely, inducing hypothyroidism lead to a 40% reduction in the sodium, potassium ATPase pump. This pump is a form of cellular machinery that utilizes ATP to carry out its function; therefore, energy utilization/metabolism in the body increases in proportion to the number of sodium potassium pumps (for more information on this pump, refer to Venom, 2004 [Sodium - A comprehensive Analysis](#)).

Growth Hormones' Role in Nutrient Utilization during Exercise

Growth hormone, also known as somatotropin, is a peptide hormone produced by the anterior pituitary gland. Exercise is a potent stimulant of GH release (Gorden et al., 1994); particularly during high exercise intensities (Sutten et al. 1976). Additional stimulants are: hypoglycemia (low blood sugar)—incidentally, insulin induced hypoglycemia is the most often used, and by many, considered the most reliable stimulus of GH (Sutten et al. 1976)—reduced plasma free fatty acid (FFA) concentrations (Peino et al., 1996), among other occurrences during states of energy deprivation (Sutten et al. 1976; Grottoli et al., 1997; Casanueva et al., 1987).

Sutten et al. (1976) performed an excellent study to compare the serum growth hormone (GH) response with quantified exercise to that obtained with other stimuli. Eight healthy male medical students (21-24) partook in various random studies, which occurred on separate occasions over a six week period. Participants exercised on a cycle ergometer for 20 minutes at various exercise intensities ranging from 25-33%, 40-66%, and 75-90% VO₂ max. Insulin induced hypoglycemia was also analyzed. Results showed that the most potent stimulators of GH were insulin induced hypoglycemia, and exercise at 75-90% VO₂ max. Conversely, the lowest exercise intensity elicited no significant GH response. It was found that max GH response to insulin induced hypoglycemia, occurred 45-60 minutes after administration, and 15-30 minutes after maximum hypoglycemia. After high intensity exercise, maximal GH secretion occurred 5-15 minutes following the activity. The authors noted from this, the fallacious nature of studies that only analyze GH secretion immediately after a stimulus. Since GH is a slow acting hormone, studies should analyze its secretion for several hours after a stimulus, to assure validity. Although, when duration of work is lengthened, it may peak during exercise (Gorden et al., 1994)

Duration is also an important factor. For instance, 20 minutes at 450 kpm per minute did not increase GH; whereas, 40 minutes at the same intensity did (Sutton and Lazarus, 1974).

The mechanism by which exercise increases growth hormone secretion is under sharp debate. There is an abundance of evidence that lactic acid is a potent mediator of GH (Lassarre et al., 1974; Vigas et al., 1974). Vanhelder, Radomski, and Goode (1984) examined five male participants during 2 workouts of identical rest intervals, duration, and work out put; but at varying intensities, and number of repetitions. In workout one, participants performed seven sets of seven repetitions on a vertical leg lift at 85% of their seven rep max. Five days later, they performed a much lighter load, (1/3 of previously used load) and got 21 reps for seven sets. After exercise one, there was a significant increase in GH at 5-15 minutes after cessation of exercise. Conversely, exercise two showed no significant elevation in GH. Of great significance is that there was a large correlation ($r=.99$) between lactate levels—which increased closely before GH—and GH levels. This experiment makes sense, as glycolysis would be more heavily relied upon during 7 repetition sets, effectively increasing lactic acid, and presumably, GH. Kraemer et al. (1990) tested work load during resistance training and its influence on GH secretion. Nine male participants performed each of six randomly assigned lifts, either with a 5 or 10 repetition max, and either with a rest period of one minute, or three minutes. Performing 10 repetitions with only one minute rest between sets resulted in maximal GH concentrations—much higher than low repetition sets. This would again support the lactate hypotheses, since the phosphagen system would be used more readily during a 5 rep max, while glycolysis would be much more dominant during 10 reps.

Moreover, shorter rest would decrease the time to clear lactate. These authors noted that their experiment does support the hypothesis of lactic acid induced increases in GH through an enhanced reliance on glycolysis. Moreover, it was noted that 10 repetitions with less rest, resulted in higher lactic acid levels, than 5 repetitions, and or taking more rest between sets.

Yet another experiment by Hakkinen and Pakarinen (1993) supported the LA-GH hypothesis. To examine endogenous hormonal responses to heavy-resistance exercise, ten male strength athletes performed two fatiguing but different types of sessions on separate days. In session A, the participants performed 20 sets of 1 repetition maximums (100%). During session B, the loads were sub maximal (70%), and the subjects performed each of the 10 sets at 10 repetition maximums. The recovery time between sets was always 3 minutes. Increases in the concentrations of serum total and free testosterone, Cortisol, and growth hormone, were observed during session B; whereas, the corresponding changes during session A were statistically insignificant. Of course, a 10 rep set would utilize glycolysis much more than a 1 rep max. Incidentally, blood lactate concentration during exercise correlated significantly ($P < 0.01$) with the increase in serum GH concentration.

It has been postulated that lactic acid indirectly stimulates GH when it disassociates into lactate (its salt) and H^+ (its acid) effectively decreasing pH. Thus, pH may be a potent mediator of GH secretion. This hypothesis has been supported in observation of clinical states of metabolic acidosis such as renal failure (Samaan et al., 1970), and diabetes (Gerich et al., 1970), in which GH is elevated. Gorden et al. (1994) investigated the acute effects of increased blood hydrogen ions on serum GH concentrations after a short high-intensity anaerobic exercise bout of controlled intensity and duration. The control group, and alkaline (higher pH group) performed exercise consisting of 90 seconds of maximal effort cycle ergometer against an opposing force. Results demonstrated that in the control group, GH peaked at 10, 15, 20, and 30 minutes after exercise; in the alkaline group, it peaked at 20, and 30 minutes. Most notably, it was found that GH peak was significantly lower in the alkaline group than the controlled group; moreover, its peak GH secretion was delayed. These results indicate that decreased pH during physical exercise, may be partly responsible to increased GH secretion—particularly during high intensity exercise, when lactic acid is increased exponentially due to the enhanced reliance on glycolysis.

The mechanism by which decreased acidity works to increase growth hormone secretion has not been determined. However, there are several viable explanations. It has been proposed that a decreased pH will elicit a hypothalamic stress response that acts to increase GH by releasing growth hormone releasing hormone (GHRH); thereby, stimulating GH release from the anterior pituitary gland (Gorden et al., 1994). Results also indicate that GHRH binding in the AP is optimally stimulated at a pH of 5.0 (Sethumadhavan et al., 1991).

Results have also demonstrated that thermoregulation may be an important factor. For instance, exercise performed at 4d C results in a suppression of GH secretion; whereas, passive heating constitutes a potent stimulus for GH release (Jorgensen et al., 2003). GH also stimulates sweating, and therefore, heat loss through evaporation. Conversely, a decrease in GH results in diminished sweating, and consequently, more heat storage. GH in response to hyperthermia and dehydration helps conserve body fluids and sodium by activating the rennin-angiotensin-

aldosterone axis (Jorgensen et al., 2003; for more information on this, read Venom, 2004, [Sodium - A comprehensive Analysis](#))

GH is suppressed by increased plasma concentrations of glucose (*acutely*) and FFA's (Grottoli et al., 1997; Casanueva et al, 1987).

Pulsatile GH secretion increases basal (resting level) lipolysis, principally at night (Boyle et al., 1992). Moreover, it promotes lipolysis and lipid oxidation with a delay of 20 minutes, to three hours (Fain et al., 1970). There is a high correlation between high plasma FFA and peaked GH concentrations after exercise; thus, it is purported that GH contributes to the increased lipid utilization seen during recovery from intense exercise (Pritzlaff et al., 2000).

Growth hormones potent lipolytic and nutrient partitioning effects are well documented. First, as discussed previously the relative distribution of alpha and beta receptors in certain regions of the body will in large part determine where a person primarily stores fat, and how easily they metabolize it from a region. This again is because beta receptors promote lipolysis, while alpha receptors inhibit it. With that in mind, GH stimulates additional beta receptors in adipose, thus increasing the sensitivity of adipose tissue to catecholamine mediated lipolysis (Ottosson et al., 2000; Yang et al., 1996)! GH also plays a key role in nutrient partitioning, in that it increases the activity of muscle LPL, while inhibiting adipose LPL; thus, diverting fats towards the musculature where it can be oxidized and utilized for energy (Oscarsson et al., 1999). It also increases the activity of HSL (Doris et al., 1994). This is attributed to its inhibition of the antilipolytic actions of adenosine which inhibits adenylate cyclase—the enzyme needed for the formation of cyclic AMP, which as discussed previously, mediates numerous lipolytic effects.

GH also has a counter regulatory role. GH increases hepatic gluconeogenesis by decreasing the liver's sensitivity to insulin's action and increasing the metabolic shift towards lipid oxidation, through the aforementioned mechanisms (Moller et al., 1991). It also decreases muscle glucose uptake. It is postulated that this process is mediated by an interference with the activation of insulin receptors (Yakar et al., 2001).

Cortisols' Role in Nutrient Utilization during Exercise

The adrenal gland is located above the kidneys and is composed of two endocrine glands—the adrenal medulla (located in the center of the adrenal gland) and the adrenal cortex (located in the outer portion of the gland). The adrenal cortex has three zones—the current investigation is principally concerned with zone two. This zone, also known as the zona fasciculata, secretes glucocorticoid hormones, primarily *cortisol* (see King, 2003 [Endocrine Insanity Part I](#), for more information on this hormone). Cortisol is another counter regulatory hormone. Its actions include: muscle protein degradation; gluconeogenesis; glycogen synthesis; decreased glucose storage; and lipolysis. It also influences nutrient partitioning.

Cortisol release is highly connected to stress. Seyle identified cortisol as the chief hormone secreted in response to chronic intense stress. A component of physiological and pathological responses he called the general adaptation syndrome (for more information on this, see Wilson, 2003, [Hippocrates - Was He Hardcore?](#)). Accordingly, cortisol secretion is increased during forms of severe stress such as

exercise. Forty years have passed since the relationship between cortisol and exercise was first studied (Staehelin et al, 1955). Davies (1973) examined the effect of duration and intensity on plasma cortisol levels. It was found that as duration and intensity increased, cortisol increased. However, they found what appeared to be a threshold for cortisol secretion at 60 % V02 max intensity. Therefore at lower intensities cortisol is primarily controlled by metabolic need. In this context Sotsky et al. (1989) investigated the effect of hypoglycemia on moderate intensity exercise, below 60 V02 max over 50 minutes of cycling in participants with normal blood glucose levels of 87 mg / dl, and in participants with low blood glucose levels of 59 mg / dl. No significant difference in cortisol levels were found in the normal glucose condition, while a 400 % increase (!) was found in the low glucose condition. Therefore it appears that under normal dieting conditions that cortisol secretion may not significantly rise during an hour of low intensity exercise, suggesting that it is an effective tool for fat metabolism, without high catabolic effects.

Cortisol increases muscle protein catabolism; thereby, enhancing amino acid availability in circulation. Gore et al. (1993) investigated the effect of a 4-hour femoral arterial infusion of cortisol on fiver healthy participants. They found that the catabolic hormone infusion elicited a significant (65%) increase in the leg muscle protein breakdown rate. Its actions appear to be selective to type II fibers. Clark and Vignos (1979) administered cortisol to rabbits and found significant wasting of type 2 gluteus medius and psoas muscles without significant atrophy of type 1 soleus and gluteus minimus muscles.

Cortisol appears to directly (Friedman), as well as indirectly (Nielsen et al., 2003) gluconeogenesis. Its direct effects are through activation of the gluconeogenic enzymes fructose 1,6 bi-phosphate and PEPCK (Friedman, 1994, Fleig, 1984,). Its indirect actions appear to cause insulin resistance in the liver (Nielsen et al., 2003). The glucose molecules formed here can be either released into circulation, contributing to hyperglycemia, or used for glycogen synthesis.

It is well established that cortisol excess causes insulin resistance in men, but mechanisms by which it does so are still under investigation (Nosadini et al., 1983). Glucocorticoids are known to rapidly inhibit glucose transport (Rizza et al. 1982). Cortisol does so by decreasing the actions of glute-4-receptors, which carries glucose into the muscle as well as adipose tissue. Thus, it decreases uptake of glucose by adipose and muscle sites, effectively increasing glucose availability in the blood stream; thereby, promoting hyperglycemia. For example, Carter-Su and Okamoto (1985) demonstrated in vitro that administration of cortisol inhibited glucose uptake into vesicles by an average of 40%. Moreover, there was a 33% decrease in labeled plasma membrane glucose transporters. Several studies demonstrate that people with Cushing's disease (these individuals produce an abnormal amount of glucocorticoids) have decreased insulin sensitivity (Karnieli et al., 1985). Page et al. (1991) investigated the contributions of insulin secretion, insulin sensitivity and glucose-mediated glucose disposal to glucose tolerance in subjects exposed to chronic glucocorticoid excess. Do to so, he examined patients with Cushing's disease before and 3 months after corrective surgery, as well as in comparison with control groups. Results showed basal glucose and insulin levels were significantly raised preoperatively and fell towards normal post-operatively. Glucose tolerance assessed as glucose decay rate was reduced significantly preoperatively. In order to understand the subsequent results, here is a quote from King (2003, [Endocrine Insanity Part III](#)) "Insulin release is believed to occur in two separate phases; an

immediate phase, involving a sharp peak that lasts for several minutes, followed by a slow rising response lasting for two hours." Results demonstrated that the first phase of insulin release was similar in the Cushing's disease and control subjects. In contrast, second phase insulin release was significantly greater preoperatively. Insulin sensitivity was reduced by 60% preoperatively in the Cushing's disease subjects compared to the post-operative Cushing's disease and control subjects. Other studies show that it may cause post receptor defects (Nosadini et al., 1983).

There is a bit of a paradox concerning cortisol's effects on lipolysis. Acutely, Djurhuus et al. (2002) demonstrated that cortisol injection was a potent stimulator of lipolysis. Another experiment showed that that high physiological levels of cortisol led to 60% increase in free fatty acid concentrations and palmitate flux, an indicator of effective adipose tissue lipolysis, in humans (Divertie Divertie et al., 1991) its ability to decrease glucose uptake would also acutely shift metabolism towards lipid oxidation.

Cortisol is known to increase whole body lipolysis, yet chronic hypercortisolemia results in increased fat mass. For example, Cushing's disease leads to increased fat mass (Lamberts and Birkenhager, 1976). Jaswinder et al. (1998) investigated these opposed observations. Hypercortisolemia led to significantly increased arterialized plasma nonesterified fatty acid (NEFA) and blood glycerol concentrations, with an increase in systemic glycerol appearance. However, in abdominal adipose tissue, hypercortisolemia decreased veno-arterialized differences for NEFA and reduced NEFA efflux. Therefore, this suggests a rerouting and uptake of fatty acids via abdominal adipose depots, which are highly sensitive to cortisol. This reduction was attributable to decreased intracellular lipolysis, reflecting decreased hormone-sensitive lipase action in this adipose depot. Hypercortisolemia also caused a reduction in arterialized plasma triglyceride concentrations. The authors concluded that site-specific regulation of the enzymes of intracellular lipolysis (hormone-sensitive lipase) and intravascular lipolysis (lipoprotein lipase) may explain the ability of acute cortisol treatment to increase systemic glycerol and NEFA appearance rates while chronically promoting net central fat deposition. To elaborate on these findings, In vitro, cortisol increases LPL (Ottosson et al., 1994) and HSL (Slavin et al., 1994) activity in adipose tissue. As displayed earlier, this would promote fat storage, rather than lipid oxidation. Evidence suggests that hyperglycemia caused by hypercortisolemia leads to hyperinsulinemia, which then inhibits HSL activity and increases LPL activity in adipose (Johnston et al., 1982). Therefore acutely, cortisol appears to increase HSL activity in adipose; however, chronically, through its actions on insulin, it decreases its activity, as well as a two fold increase in adipose LPL, both directly, and indirectly through insulin, resulting in enhanced fat deposition. These results collectively have been used to explain the chronic influence of cortisol on increased fat storage. This hypothesis is further supported by patients with Cushing's disease who often have abdominal obesity, which is due to the fact that cortisol receptors are most prevalent in the abdominal region of the body (Djurhuus et al. 2002). Cortisol also decreases basal and catecholamine-stimulated lipolysis in human adipocytes from abdominal tissue (Malin et al., 2000).

Conclusion

Slow acting hormones act via cytoplasmic or nuclear receptors, leading to more chronic effects on nutrient utilization during exercise. In general thyroid hormones and GH potentiate the counterregulatory effect of catecholamine's through beta

adrenergic expression. Cortisol and GH are increased in proportion to intensity and duration; additionally, there appears to be a threshold for there exercise mediated activation. While thyroid and GH are potent stimulators of fat oxidation, cortisol chronically enhances fat deposition, while concomitantly decreasing insulin sensitivity, as seen commonly in individuals afflicted with Cushing's disease.

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