

# Fast Acting Hormones and their Role in Fuel use during Exercise

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## Abstract

Galen who lived from 129 - 216 AD has been regarded as a father of exercise physiology. He suggested that "it does not seem that all movement is exercise, but only when it is vigorous. But since vigor is relative, the same movement might be exercise for one and not for another. The criterion of vigorousness is change of respiration; those movements, which do not alter the respiration, are not called exercise. But if anyone is compelled by any movement to breathe more or less or faster, that movement becomes exercise for him." 2000 years latter, it is recognized that this transient increase in minute ventilation reflects the need to supply oxygen to meet the higher energetic requirements of exercise. While at rest, and especially during meal absorption the physiological environment is one which favors the biosynthesis of molecules such as proteins, carbohydrates, and lipids. Exercise is characterized by an altered state which favors the catabolism of stored nutrients to supply the working musculature with adequate substrates for ATP formation. Both rest and recovery are primarily under the control of the parasympathetic nervous system, and storage hormones such as insulin. While exercise is mediated by the sympathoadrenal system, which, from a chemical standpoint can be characterized by the catecholamines: epinephrine and norepinephrine. Other hormones involved include growth hormone, cortisol, thyroid hormone, aldosterone, and glucagon. Therefore the purpose of this paper, was to review each of the hormones discussed and clearly relay their role in nutrient (carbohydrate, lipid, and protein) utilization during exercise.

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## Epinephrine and Norepinephrine's Roles in Nutrient Utilization during Exercise

Epinephrine (E) and Norepinephrine (NE) are classified as [catecholamines](#). Catecholamines fall under the class of amine hormones, or hormones derived from amino acids. E and NE are derivatives of the amino acid tyrosine. Further, E and NE fall under a subgroup of chemical messengers known as counter regulatory hormones. Insulin is said to regulate glucose by promoting its uptake into tissues. The overall effect is hypoglycemia, or lowered blood glucose levels. Counter regulatory hormones promote the release of glucose from muscle, as well as the hepatic system (liver) and are therefore counter the regulatory role of insulin. In short, E and NE act to increase catabolism and release of stored nutrients during exercise, while antagonizing (opposing) hormones which promote storage and synthesis of biological molecules (i.e. anabolism).

Catecholeamines are part of the sympathoadrenal (SA) system. Physiologically it is

known as the fight or flight system, while anatomically it is referred to as the thoracolumbar system. It is comprised of sympathetic nerves which arise out of the thoracic (chest region of spinal cord) and lumbar (lower back region of spinal cord) regions of the body; the adrenal medulla (the core of the adrenal gland); and executive control centers located in the central nervous system, such as the hypothalamus and brain stem. The sympathetic nerves are characterized by direct synapses (connections) with their effector tissues, and therefore can elicit a response within milliseconds. This is therefore the neurological control of the system. However, the SA system also has a hormonal component, in that the adrenal medulla secretes catecholamines directly into the blood stream. When E and NE are released by neurons directly to the target tissue they are referred to as neurotransmitters. When released into the blood stream by the adrenal gland, they are referred to as hormones. If secreted by neurons into the blood stream, they are referred to as neurohormones.

Catecholamines exert their effects by binding to beta 1-3 adrenergic receptors, and to alpha 1 and 2 receptors (See Wilson, 2004 [Exercise Endocrinology Principles and Catecholamines](#)). A receptor can be thought of as a receiving station, which accepts the message carried by said hormone. In general, beta receptors are stimulatory, while alpha receptors are inhibitory (emphasis on generally as this is not always the case) (Wilson, 2004). For example, beta receptor stimulation initiates lipolysis (the break down of fats), while alpha receptor stimulation, inhibits lipolysis (Richterova, 2004, Stich, 2002, Riviere, 1989). This provides an important mechanism of differential effects. A tissue with primarily alpha receptors may experience inhibition, while a tissue with primarily beta receptors may experience stimulatory effects (Mauriege et al., 1987). Further, it has been proposed that obese individuals have a higher concentration of alpha receptors than lean individuals. In this context Stich et al. (2000) investigated the effect of administering an alpha antagonist ( a chemical which blocks the ability of catecholamines to bind to alpha receptors ) to obese and lean people during exercise. Lean and obese participants were tested with and without the antagonists. It was found that the obese had a 6 fold greater increase in lipolysis (fat breakdown or catabolism ) than the lean individuals. This suggests that they were experiencing more inhibition of lipolysis from alpha receptors than lean individuals. However, as will be discussed further, exercise as well as diet can actually cause significant changes in receptor concentrations. Further, the nervous system has direct alpha and beta influence, meaning it can selectively target one aspect over another.

E and NE bind to receptors located on the membrane or outer portion of a cell. The binding triggers a secondary messenger to carry out the message into the cell. This is known as transduction, or the path which connects a hormone to its effector mechanism within a cell. One of the primary ways E and NE work is through the cyclic adenosine monophosphate (cAMP) secondary messenger system. Said hormones activate cAMP, which then activate a protein kinase. A protein kinase is an enzyme which adds a phosphate group to a protein, which has the effect of activating or changing the effects of that protein. For example, when epinephrine binds to beta 2 receptors on muscle, it activates cAMP, which activates cAMP dependent protein kinase, which activates glycogen phosphorylase ( Richter et al. 1981b, 1982). Glycogen phosphorylase is responsible for the break down of glycogen (the body's stored form of carbohydrates) into glucose so that it can be used to form ATP. Studies indicate that when the adrenal gland is removed that glycogenolysis is lower in contracting muscles than when the adrenal gland is in tact (Richter et al. 1981a; Sonne et al. 1985). However, both Arnall et al. (1986) and Winder et al.

(1987) found that rats who were administered epinephrine, experienced the same amount of glycogenolysis even with their adrenal glands removed, supporting its role in the process.

### **Catecholamines Effect on Fat Mobilization**

Fatty acids are oxidized or used to form ATP through a process known as beta oxidation. The first step to beta oxidation is the catabolism of a triglyceride. A triglyceride is comprised of a glycerol backbone and three fatty acids. The enzyme responsible for catalyzing this reaction is known as hormone sensitive lipase (HSL). This has implications for dieting. For example, Martins-Afferri et al. (2004) found that a low carbohydrate diet reduced whole body lipolytic activity compared to a balanced diet in rats. When studying the underlying biochemical mechanisms, it was found that adipocytes had a 40 % reduced lipolytic response to epinephrine and norepinephrine, compared to the balanced diet group. Much of this is attributed to hormone sensitive lipase. For example, in the balanced diet group catecholamines stimulated a 50 % increase in HSL translocation ( its expression and activity in the cell). However, the low carbohydrate group only showed a 20-25 % increase in HSL activity, strongly suggesting HSL's role in fat metabolism, and its correlation to lowered lipolytic activity in nutrient deficient diets. Once fatty acids are cleaved off of the glycerol molecule, they must enter the mitochondria for further catabolism. Transfer of fatty acids into the mitochondria is carried out by the rate limiting enzyme carnitine transferase. Once inside they can be utilized for energy (oxidized).

Fatty acids can come from circulating fatty acids and lipoproteins, intramuscular stored lipid droplets (storage depot of triglycerides), and adipose tissue. Fatty acids are released from adipose tissue, after they have been broken down by hormone sensitive lipase. Lipoproteins are large molecules comprised of proteins and lipids. They are too large to enter either adipose or muscle tissue. In order to escort the fat into the tissue, a rate limiting enzyme which lies on the capillary lining layer called endothelium cleaves or breaks fatty acids off of the lipoprotein (Eckel, 1989, Zechner, 1997). It then enters the tissue through a 'fatty acid transport protein;' or if the fatty acid is small enough it can diffuse into the cell. The enzyme that catalyzes this process is known as lipoprotein lipase (LPL). The greater the expression of LPL, the greater the tissues ability will be to take up and either store, or oxidize fat.

Catecholamines increase the rate of fat break down by acting on beta receptors in adipose and muscle tissue. Beta 1-3 are acted on in adipose, while beta 2 are found in the musculature (See Wilson, 2004 [Exercise Endocrinology Principles and Catecholamines](#)). However, alpha receptors inhibit lipolysis. Therefore the relative distribution of alpha and beta receptors on certain regions of the body, will in large part determine where a participant primarily stores fat, and how easily they metabolize it from a region. In general however, the net whole body effect of E and NE is increased lipolysis in adipose tissue and muscular tissue. Further, it powerfully reroutes lipids in the blood stream towards muscle tissue for oxidation, while inhibiting its uptake in fat tissue (Deshaies, 1993, Eckel, 1996, Friedman, 1986. Pedersen, 1999).

Lipoprotein lipase is enhanced in skeletal muscle by a cAMP transduction mechanism (Deshaies, 1993, Eckel, 1996, Friedman, 1986. Pedersen, 1999) however it is inhibited in adipose tissue, causing the rerouting effect discussed previously (Ball et al, 1987). Ball et al. (1987) found that the inhibition in adipose was due catecholamine's ability to both enhance degradation of LPL as well as decrease its

synthesis. Further, Eckel et al. (1996) found a significant increase in muscular LPL and LPL mRNA concentration in the vastus lateralis (outer quad sweep) after administration of catecholeamines.

### **Catecholamines Effect on Glucose Utilization**

Catecholamine's counter regulatory actions on glucose are initiated by an increase in NE during systemic hypoglycemia (low blood glucose levels); however, to stimulate a full epinephrine response an additional sharp decline in the liver's glycogen stores must occur (Donovan et al., 1991). For example Donovan et al. (1991) investigated the effects of insulin induced hypoglycemia and liver depletion on NE and E secretion. It was found that both E and NE rose significantly from resting levels in the hypoglycemia and lowered liver glycogen condition. In a second condition, a glucose infusion maintained normal liver glycogen stores. It was found that NE rose as before, but that the rise in E was 40 % less than the liver depleted condition. This is significant because at low levels Epinephrine can powerfully stimulate lipolysis (Romijn, 1993). However, Galster et al. (1981) demonstrated that epinephrine's effect on the liver, in terms of counter regulation (i.e. stimulating the liver to increase glucose output) requires double its concentration in the blood plasma than to stimulate lipolysis. This suggests that catecholamine's counter regulatory actions are secondary to its lipolytic effects. Though this is the case, its hyperglycemic actions increase during high intensity exercise, when its secretion is maximized, and glucose is rapidly being depleted by the working musculature. Its effects are elicited through the following mechanisms: hepatic and muscular glycogenolysis (Richter et al. 1981b, 1982); hepatic gluconeogenesis (Chu et al, 1996, 1997a, 1997b); auxiliary (supplementary) actions on other counter regulatory hormones; and suppression of the regulatory hormone insulin (Lee, 1997).

Glycogenolysis is the process by which glycogen is broken down into molecules of glucose, and is mediated by the enzyme glycogen phosphorylase. This process acts in the liver to increase hepatic glucose release, and therefore, promotes hyperglycemia. In the liver, catecholamines glycogenolytic effects are unique, in that they act on both beta (Steiner et al, 1985) and alpha (Kmiec et. al, 1990) adrenergic receptors. Beta A-R's activate a cAMP-dependent protein kinase (explained earlier), which subsequently phosphorylates (adds a phosphate group) the enzyme phosphorylase, effectively activating it, and thus, increasing glycogenolysis. While alpha receptors utilize calcium to stimulate glycogenolysis (Althaus-Salzman et al. 1980). Calcium can act as a secondary messenger on numerous occasions—for instance, calcium release in a muscle for the initiation of muscular contractions, can also cause other stimulatory effects such as activation of GLUT-4 receptors during exercise (Wilson, 2003, Wilson and Venom; 2004), which carries glucose into the muscle. In muscles, epinephrine stimulates glycogenolysis by binding to beta receptors.

Gluconeogenesis is the formation of glucose from non-glucose molecules such as lactate, pyruvate, and amino acids. This process occurs plentifully in the liver, and helps to preserve stable blood glucose levels. Catecholamines have both direct and indirect effects on gluconeogenesis. They directly stimulate gluconeogenesis through activating gluconeogenic enzymes (Kessar, 1990). They indirectly stimulate this process through up regulation of other counter regulatory hormones such as glucagon. They also help provide the raw precursors for gluconeogenesis through stimulation of the production of lactic acid, pyruvate, and glycerol. Glycolysis is the

first stage for the utilization of ATP formation, when glucose is the substrate. The end products of glycolysis are either pyruvate, or lactic acid (see Wilson and Venom 2004 [Energetic Transference Occurring in the Biosphere Part II](#) for more information). By stimulating glycolysis, E and NE increase the release of gluconeogenic precursors, if they diffuse out of the musculature and into the blood stream for conversion back to glucose in the liver.

Lastly, catecholamines suppress insulin secretion by binding to inhibitory alpha receptors ( Lee, 1997, Sieg et al., 2004, Sharp, 1996, Debuyser, 1991, Nilsson et al, 1988 ). This inhibition allows an unopposed release of fuels for use during exercise in the form of gluconeogenesis, lipolysis, and glycogenolysis.

### **Glucagon's Effect on Nutrient Utilization During Exercise**

The pancreas contains a group of cells known as the islets of langerhans. These cells can secrete glucagon, insulin, pancreatic polypeptide, and somatostatin. More specifically, glucagon is secreted from alpha cells, insulin by beta cells, pancreatic polypeptide by pp cells, and somatostatin from delta cells.

The liver is a major store house of fuels, and therefore plays a highly substantial role in exercise. To accommodate its function, a portal system was designed which carries hormones secreted by the pancreas almost directly into the liver. A portal system can be defined as a circulatory system which contains two beds of capillaries. In the body, blood is circulated to and through most organs in the following fashion:

1. Blood is pumped from the heart via the left ventricle through the aorta( and further elastic arteries), then to muscular arteries, followed by arterioles.
2. Blood is then delivered to a bed of capillaries, where nutrient exchange occurs.
3. Blood then enters venules, small veins, and finally large veins, which end in the Vena Cava which carries blood back to the right ventricle.

However, the liver receives two sources of blood. For nourishment, it receives blood from the heart via the hepatic arteries. Secondly it receives it from veins which carry blood that has just passed through capillaries of organs involved in digestion, such as the stomach, small intestine, large intestine, and pancreas. This blood which previously coursed through the digestive organs, rather than going straight to the heart, enters the 'hepatic portal vein' which then meets capillaries in the liver where nutrient exchange occurs again. Therefore all the nutrients from the GI tract, must first be filtered through the liver.

As a consequence, the liver is exposed to much higher hormone concentrations than other organs. As such, it is subject to the law of mass action, which states that a reaction is directly proportional to the concentration of reactants. Therefore the liver is affected to a greater extent than other organs by the secretion of pancreatic hormones.

Glucagon is a counter regulatory hormone in that its overall effect is hyperglycemia. It is stimulated by hypoglycemic conditions, particularly when blood glucose levels drop below 50 milligrams per deciliter, and blocked at 150 milligrams per deciliter.

(Galbo et al. 1977). Galbo et al. (1977) found that the effect of exercise on glucagons secretion was highly diminished when participants were fused with glucose. Further, catecholamines stimulate its release (Knudtson, 1984) Insulin, directly inhibits glucagon, and when lowered glucagon becomes relatively greater in its response to its secretagogue. Secretagogues are defined as substances which stimulate the secretion of a hormone. Amino acids serve as secretagogues for glucagon (Kraus-Friedmann, 1984).

This hormone, promotes glycogenolysis through the activation of protein kinase A through a cAMP mechanism( Jiang and Zhang, 2003 ) . When inactive, or dephosphorylated, the enzyme which breaks down glycogen is known as glycogen phosphorylase B. When phosphorylated it is known as glycogen phosphorylase A, which explains the name given to protein kinase A.

**Note:** In more detail protein kinase A, activates glycogen phosphorylase kinase, which then phosphorylates glycogen phosphorylase (Jiang and Zhang, 2003)

Phosphorylase A also phosphorylates the enzyme responsible for glycogen synthesis known as glycogen synthase. Unlike glycogen phosphorylase, glycogen synthase is inactivated when phosphorylated (Roach, 1990), which again facilitates more glucose availability for exercise (Jiang and Zhang, 2003 ). Further, Glucagon stimulates the enzyme glucose 6 phosphatase (Barthel and Schmoll, 2003). Glucose 6 phosphatase will be discussed in the insulin section of this article.

Glucagon works with E and NE to stimulate the Cori cycle (Kusaka and Ui, 1977) The Cori cycle begins as glycogen phosphorylase breaks down glycogen into glucose. Glucose is then released into the blood plasma, where it enters skeletal muscle through specialized receptors known as GLUT-4 receptors. As previously stated, the glucose enters the enzymatic pathway glycolysis and can form the gluconeogenic substrates pyruvate and lactate. If they enter the circulation and reach the liver, they may be transformed back into glucose. Glucagon facilitates this process through specific gluconeogenic enzymes. One such enzyme is known as phosphoenolpyruvate carboxykinase (PEPCK) which is important in the formation of glucose. It takes a substrate from the krebs cycle ( Oxaloacetic acid or OAA) and converts it to phosphoenolpyruvate ( this is the substrate in glycolysis that is actually itself converted to pyruvate)(Jiang and Zhang, 2003). Current evidence suggests that glucagon actually increases PEPCK mRNA in the cell (Beale, 1984, Iynedjian, 1985) (mRNA carries the nuclear instructions for building PEPCK in the cell, the higher the concentration of these 'instructions' the more PEPCK that can be built) through a protein kinase A mechanism (Jiang and Zhang, 2003).

Think of gluconeogenesis as a reversal of glycolysis. For example, in glycolysis one substrate known as fructose-6 phosphate is turned into fructose-1,6-bisphosphate by the addition of a phosphate group. In gluconeogenesis, this process is reversed, such that the phosphate group is again removed (known as hydrolysis) to again form fructose-6 phosphate. The enzyme responsible for this dephosphorylation is known as Fructose-1,6-bisphosphatase. 'Phosphatase enzymes are removers of phosphate

groups. Glucagon is again postulated to stimulate the enzyme through use of protein kinase A (Jiang and Zhang, 2003).

Additionally glucagon facilitates the glucose alanine cycle through increasing the liver's uptake of amino acids (Kraus-Friedmann, 1984). In order for amino acids to participate in the gluconeogenic process, the nitrogen containing group must first be removed from the molecule, so that the carbon skeleton can be used. This can occur through oxidative deamination, or transamination. In Oxidative Deamination, the nitrogen group is removed directly. For example the amino acid glutamate and the coenzyme NAD<sup>+</sup> enter the enzymatic complex glutamate dehydrogenase, forming alpha keto glutarate + NADH + H<sup>+</sup>. Alpha keto glutarate is a substrate which can be utilized for energy in the krebs cycle. The Krebs cycle is the second pathway involved in the oxidation of glucose ( For more information on NAD<sup>+</sup> see Wilson and Venom Energetic Transference in the Biosphere ). However, in transamination, the nitrogen group is transferred to an intermediate of the krebs cycle. Alanine is a primary amino acid used in gluconeogenesis. In the liver, transamination of an amino group from alanine to alpha keto glutarate produces pyruvate and glutamate. Pyruvate then can be converted to glucose and complete the glucose alanine cycle.

Glucagon also has a lipolytic role, in that it suppresses the lipogenic enzyme known as Acetyl Co-Enzyme A Carboxylase (ACC) (Girard et al., 1994). ACC catalyzes the reaction which produces malonyl co enzyme A. Malonyl coA is an important substrate in the biosynthetic pathway which forms triglycerides. It acts to inhibit carnitine transferase from escorting fatty acids into the mitochondria.

### **Insulin's Role in Nutrient Utilization during Exercise**

Generally, insulin antagonizes the counter regulatory hormones. In fact, many of the effects of counter regulatory hormones are indirect and yet extremely powerful in their ability to suppress insulin secretion. For example, when catecholamines suppress this hormone, fat lipolysis is increased exponentially.

Insulin opposes counter regulatory hormones by the degradation of cAMP. It stimulates this process by activating the enzyme known as phosphodiesterase which degrades cAMP. Enoksson et al. (1998) found that hyperinsulinemia decreased glycerol content in adipose by 40 % and in muscle tissue by 33 % ( glycerol is a by product of fat lipolysis or breakdown). However, when participants were administered a phosphodiesterase blocker, the decrease in glycerol content was counteracted. Insulin also stimulates the dephosphorylation of enzymes (or lowers the activity of phosphorylating protein kinases), thereby deactivating them. As an illustration, glucagon and epinephrine stimulate the phosphorylation of phosphorylase to its active A form, while insulin causes its dephosphorylation to inactive B form. This dephosphorylation process essentially negates cAMP's phosphorylating actions. Gabbay and Lardy (1984) investigated the effect of insulin on the breakdown of glycogen by blocking the action of phosphodiesterase. It was found that even with maintained cAMP levels that insulin still antagonized its actions on activating glycogen phosphorylase. Gabbay and Lardy (1987) suggest that this occurs as insulin lowers cAMP dependent protein kinase's (which will phosphorylate glycogen synthase) affinity for cAMP.

Amino acids stimulate insulin, as well as glucose levels above 80 mg per deciliter in terms of plasma concentration. Circulating glucose binds to Glut-2 receptors on the beta cells of the islets. An enzyme known as hexokinase (discussed shortly) or glucokinase then adds a phosphate group to the glucose molecule. This stimulates potassium channels in the cell to close (Hellman et al., 1994, Gylfe et al., 1998, Sato et al., 1999). The closure is linked to various mechanisms, which appear to be linked to glucose metabolism (Meglasson and Matschinsky, 1986, Meglasson, 1990). For example, glucose increases the amount of ATP in the cell (ATP/ADP ratio). ATP is postulated to directly close K<sup>+</sup> channels (these are known as ATP sensitive K<sup>+</sup> channels – Sieg et al., 2004). The cell is slightly negative relative to the outside or extra cellular environment. Potassium leaking out of the cell through channels ( i.e. positive charge leaving) helps this process. However, when potassium channels close, the positive charge is trapped in the cell, making the intracellular environment more positive. Therefore the polarity or separation of charge in the cell relative to the outside of the cell is dissipated. That is, the inside of the cell loses its negativity relative to the outside. This is known as depolarization. Within the cell are storage bins for calcium known as the sarcoplasmic reticulum. They are stimulated to release calcium when the cell becomes positive. Calcium binds to insulin vesicles and allows them to bind to the cell membrane for exocytosis. The parasympathetic nervous system can also directly stimulate insulin release, through its neurotransmitter acetylcholine (Al-Majed, 2004). As mentioned earlier, catecholamines inhibit insulin release (Lee, 1997, Sieg et al., 2004, Sharp, 1996, Debuyser, 1991, Nilsson et al, 1988). In this context, Sieg et al. (2004), provided evidence that epinephrine can activate a separate pool of K<sup>+</sup> channels, which hyperpolarizes (makes it more polar) beta cells, making it harder for them to be stimulated to depolarize.

Insulin inhibits lipolysis at low concentrations by increasing phosphodiesterase (Enoksson et al. 1998, Hagstrom-Toft, 1995). This has the effect of degrading cAMP. Therefore cAMP cannot activate the protein kinase responsible for the activation of hormone sensitive lipase. At extremely high concentrations insulin inhibits fatty acid oxidation as well as the formation of triglycerides by stimulating the synthesis of (Saha et al., 1995, Ruderman, 1999).

Insulin inhibits glucose output by the liver in several ways. First, as discussed it inhibits glycogen phosphorylase. Secondly, it antagonizes the synthesis of the enzymes PEPCK and fructose-1,6-bisphosphatase ( Barthel and Schmoll, 2003). Thirdly insulin inhibits a key enzyme known as glucose-6-phosphatase ( Barthel and Schmoll, 2003). In order to enter a cell, glucose must first be phosphorylated. However, the phosphate group contains a charge which traps the glucose in the cell. The glucose-6-phosphatase enzyme effectively removes this phosphate, which allows the glucose to enter the blood plasma. Muscle tissue lacks this enzyme ( Wilson 2003, [Pre Contest Week - An In Depth Analysis](#)), however liver is specialized with it, to elicit a hyperglycemic effect.

Interestingly enough, glycolysis is stimulated by insulin (Hamer and Dickson, 1990, Probst et al. 1985, Probst et al. 1989, Meacci et al., 1993). The main point is to utilize glucose as fuel, as opposed to lipids when glucose is more plentiful, such as during post absorptive (after eating) stages. For example, Kelley et al. (1990) found that hyperinsulemia (high insulin levels) increased the respiratory exchange ratio (RER) in the leg from .74 to .99. The RER measures the rate of glucose or fat metabolism. The closer the RER is to 0.7 the more fat is relied on, however the

closer it is to 1.0, the greater the reliance on glucose is. Therefore an increase in RER, demonstrates that insulin may increase carbohydrate utilization. It stimulates glycolysis through increasing the activity of its rate limiting enzymes phosphofructokinase (PFK) (Silva, 2004) pyruvate dehydrogenase (PDH) (Johnson, 2003) as well as hexokinase (Hamer and Dickson, 1990). Further, insulin stimulates glucose uptake by triggering the translocation of GLUT-4 receptors (Elmendorf and Pessin, 1999, Martin et al., 1999) and up regulating hexokinase and glucokinase (what hexokinase is called in the liver) (O'Keefe et al., 2004). Recall that hexokinase is involved in the first step of glucose uptake into the cell through its phosphorylation. This again entraps the glucose into the cell.

Hexokinase (glucokinase in the liver) is a fascinating enzyme. The isoform (particular subtype) of hexokinase differs in skeletal muscle, and is meant to take up glucose at lower levels of glucose concentration (Tsao, 1996), such as during exercise, while glucokinase is specialized at taking up glucose after a meal, or during higher blood sugar levels (Kietzmann et al., 1998). The difference lies in a concept known as  $K_M$ .

$K_M$  can be defined as the concentration needed of a substrate to saturate half of the enzymes available in a solution. If a  $K_M$  is high, then a high concentration of a substrate is needed to saturate the enzyme. The reaction rate is directly proportional to the number of enzymes occupied. While the level of saturation refers to the percentage of enzymes occupied. A low  $K_M$  means that a small concentration of substrate is needed for saturation or to cause a high reaction rate. Skeletal muscle tissue's hexokinase has a low  $K_M$  and can therefore facilitate glucose uptake at low concentrations, while the liver has a high  $K_M$  conducive to postprandial states.

Aside from inhibiting fat lipolysis and oxidation, insulin directly stimulates lipogenesis or the formation of lipids. As stated, malonyl co enzyme A is the first step in the biosynthetic pathway for lipogenesis. Insulin stimulates its formation by increasing the synthesis of ACC (Saha et al., 1995, Ruderman, 1999). It also stimulates fat synthesis by increasing the production of NADP and NADPH. In review, NAD<sup>+</sup> and NADH are coenzymes involved in glucose oxidation. These serve to oxidize molecules. Oxidation is a process which takes electrons from other molecules. The electrons are then taken to the electron transport chain, and used to form ATP (Again for an in depth discussion on this topic, see Wilson and Venom, 2004 - Energetic Transference in the Biosphere 1-3). Therefore NAD<sup>+</sup> and NADH are used for catabolic processes which release energy. NADP and NADPH are identical to NAD<sup>+</sup> and NADH with the exception of an added phosphate group (Pi). They have the opposite function, in that they serve to reduce molecules (Mathews, et al, 1999). Reduction is a process which adds electrons to atoms or molecules. This is why the formation of molecules such as various lipids is known as reductive biosynthesis. Insulin also increases production of the molecule alpha glycerol phosphate, which again serves as the backbone of a triglyceride.

This pancreatic hormone accomplishes the above increases through a mechanism known as the pentose monophosphate shunt (Gupte et al., 2005, Ammon, 1983). The Pentose Monophosphate pathway, is a parallel pathway to glycolysis (Mathews, et al, 1999). Insulin increases enzymes involved in this pathway, which acts to accept glucose as an alternative to glycolysis. This is why it is called a shunting mechanism. The primary purpose of this pathway is the production of alpha glycerol

phosphate, NADP, and NADPH (Mathews, et al, 1999). Further, insulin reroutes fatty acids towards adipose tissue, and away from muscle tissue by the opposite mechanism of the catecholamines in that it stimulates adipose LPL, while inhibiting muscular LPL. Picard et al. investigated the effect of a high carbohydrate meal on LPL expression in adipose and muscle tissue in the soleus. It was found that LPL in adipose increased 65 percent, while decreasing 25 % in the soleus. To confirm that insulin was involved, a mechanism was used to block insulin secretion. This negated the effect of the high carbohydrate meal, suggesting that insulin has an adipose specific lipogenic partitioning effect after its concentration has risen. A further anabolic action of insulin is to activate the enzyme glycogen synthase in muscle, adipose, and liver tissue( See Wilson, 2003, [Pre Contest Week - An In Depth Analysis](#)). Glycogen synthase is responsible for the synthesis of glycogen from glucose residues. It is activated through dephosphorylation, which is unlike other enzymes mentioned.

A further lipogenic effect of insulin is to increase cellular uptake of glucose into adipose tissue by increasing expression of glucose receptors. Glucose taken up by adipose is used to form alpha glycerol phosphate.

Protein metabolism is positively effected by insulin, in that it increases amino acid uptake into muscle, inhibits protein degradation, and triggers the translation of proteins (the synthesis of proteins) ( Maroni, 1986, Wilkening, 1994, Henriksen, 1991).

## Conclusion

In conclusion, counterregulatory hormones appear to facilitate the release of substrates for the elevated energetic needs of exercise. Insulin antagonizes these effects, and places the body in an anabolic state. A clear understanding of these processes will enhance the reader's ability to manipulate them through various exercise modalities.

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