# Endocrinology and Metabolic Processes Regulation

## Athletic Success via Biochemical Supplementation


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***Note**: This is a work in progress for my own purposes. It is currently evolving. Resources are listed in brackets with source links at the end of the document. If otherwise not noted/bracketed, the writing is from the author's own contextual knowledge. Conclusions are bolded where deemed relevant to a topic.*

# A Quick Intro to Endocrinology and Metabolism

Prior to getting into any concepts or useful conclusions there are several background terms and elements that the reader should be familiar with. We'll start with fundamentals and touch on several core elements before introducing the cyclical elements of endocrinology and the metabolic cycle. These terms, concepts, and cycles are essential to understanding how one's diet and hormonal balances are controlled by diet, which in turn defines how our physical form is capable of performance, growth, decline, and overall change.

## Fundamental Terms

The following terms will come up occasionally throughout this document and, as such, one would benefit from knowing the context around them prior to continuing.

### Endogenous

Originating from within an organism, not attributable to any external or environmental factor. eg: biologically produced estrogen created by the ovaries.

### Exogenous

Originating from outside an organism, caused by an agent or organism outside the body. eg: hormone replacement medication taken by injection.

### MacroNutrients

The combined requirements of base nutrition required to sustain healthy human existence. There are three primary macronutrients: protein, fat, and carbohydrate. [1] Macronutrients are defined as a class of chemical compounds which humans consume in the largest quantities (must be above a threshold amount) and which provide humans with the bulk of energy. [31]

## CNS, The Central Nervous System

The central nervous system is composed of the brain and spinal cord. Your brain and spinal cord serve as the main "processing center" for the entire nervous system, and control all the workings of your body.

## PSN, The Peripheral Nervous System

The peripheral nervous system consists of the nerves that branch out from the brain and spinal cord. These nerves form the communication network between the CNS and the body parts. The peripheral nervous system is further subdivided into the somatic nervous system and the autonomic nervous system. The somatic nervous system consists of nerves that go to the skin and muscles and is involved in conscious activities. The autonomic nervous system consists of nerves that connect the CNS to the visceral organs such as the heart, stomach, and intestines. It mediates unconscious activities.

## Endocrinology

A branch of biology and medicine dealing with the endocrine system, its diseases, and its specific secretions known as hormones. It is also concerned with the integration of developmental events proliferation, growth, and differentiation, and the psychological or behavioral activities of metabolism, growth and development, tissue function, sleep, digestion, respiration, excretion, mood, stress, lactation, movement, reproduction, and sensory perception caused by hormones.

## Metabolism

The set of life-sustaining chemical transformations within the cells of living organisms. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments.

## Pharmacokinetics

Sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body - the time course of its absorption, bioavailability, tissue distribution, metabolism, and excretion. [52]

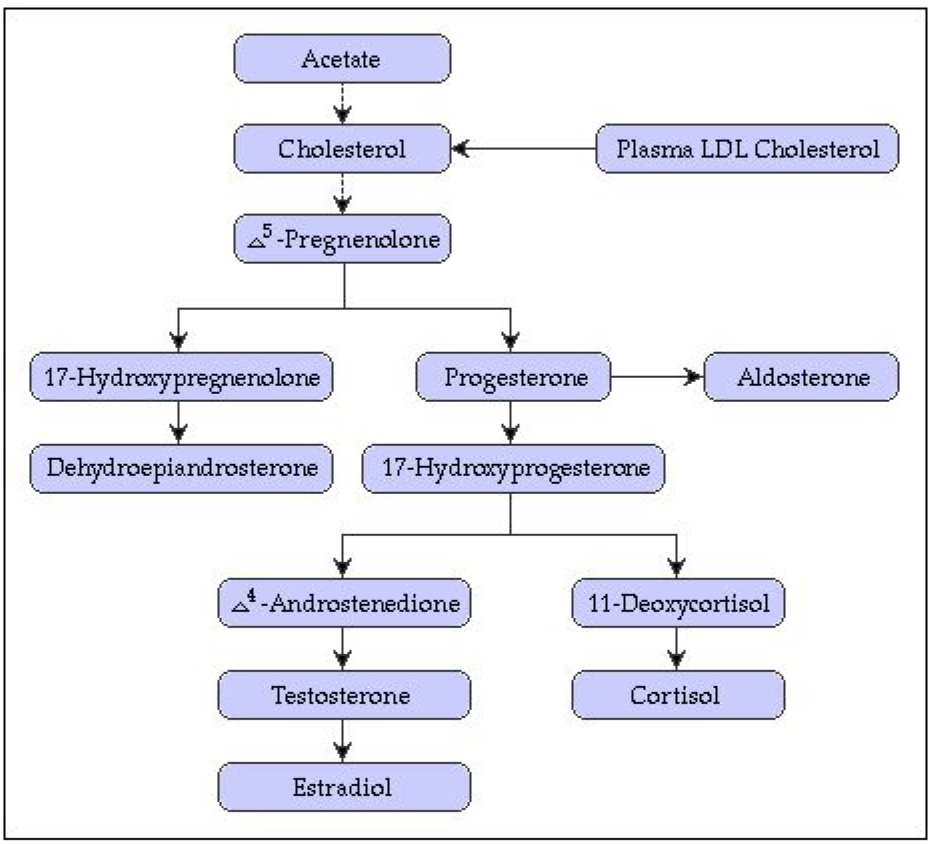
# Endocrinology: Communication and Message Relays

The endocrine system is a collection of glands that secrete hormones directly into the circulatory system to be carried towards distant target organs. The major endocrine glands include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid, parathyroid, hypothalamus, gastrointestinal tract, and adrenal glands.

## The Role of Hormones in Endocrinology

Hormones are the body's signaling molecules that are used to communicate between organs and tissues. They regulate physiological and behavioral activities, such as digestion, metabolism, respiration, tissue function, sensory perception, sleep, excretion, lactation, stress, growth and development, movement, reproduction, and mood. The particulars of each hormone are covered in the section titled "Neurotransmitters, Hormones, and Histamines".

### An Overview of Hormonal Biosynthesis



# Receptors

In biochemistry and pharmacology, a receptor is a protein molecule usually found embedded within the plasma membrane surface of a cell that receives chemical signals from outside the cell. When such chemical signals bind to a receptor, they cause some form of cellular/tissue response, e.g. a change in the electrical activity of the cell. In this sense, a receptor is a protein molecule that recognizes and responds to endogenous chemical signals. [51]

## Androgen Receptor

The androgen receptor is a type of nucleus receptor that is activated by binding either of the androgenic hormones, testosterone, or dihydrotestosterone in the cytoplasm and then translocating into the nucleus. The androgen receptor is most closely related to the progesterone receptor, and progestins in higher dosages can block the androgen receptor. [29]

## Estrogen Receptor

Estrogen receptors are a group of proteins found inside cells. They are receptors that are activated by the hormone estrogen (17β-estradiol). [28]

# Steroids of the Endocrine System

Hormones that affect change in the body by binding to cellular receptors. Cells are capable of changing their fundamental expression based on the type and quantity of hormones are attached to their receptors.

## Sex Steroids

These hormones influence sexual evolution of the human form and support reproduction; these include androgens, estrogens, and progestogens. These are the hormones that signal primary and secondary sexual characteristics of our exterior selves as well as internal expressions of cellular growth and change over time.

## Corticosteroids

Responsible for regulation of many aspects of the metabolism and immune function that help maintain blood volume and control renal excretion of electrolytes.

## Anabolic steroids

Natural and synthetic, that interact with androgen receptors to increase muscle and bone synthesis. In popular expression, use of the term "steroids" often refers to anabolic steroids. These include Testosterone, Insulin, Androstenedione, and many exogenous compounds used for both medical, research, and athletic purposes; examples including Oxandrolone, Drostanolone, Oxymetholone, Methenolone, Boldenone, and many others.

# Core Elements of the Metabolic System

## Adenosine triphosphate (ATP)

Often called the "molecular unit of currency" of intracellular energy transfer. ATP transports chemical energy within cells for metabolism. It is one of the end products of photophosphorylation, cellular respiration, and fermentation and used by enzymes and structural proteins in many cellular processes, including biosynthetic reactions, motility, and cell division. [45]

## Glutamine

Glutamine is the most abundant amino acid (building block of protein) in the body. The body can make enough glutamine for its regular needs. But during times of extreme stress (the kind you experience after heavy exercise or an injury), your body may need more glutamine than it can make. Most glutamine is stored in muscles, followed by the lungs where much of the glutamine is made. [49]

# Cycles of the Metabolic Process

Note: This is not a complete list.

## Alanine Cycle

A glucose generating process involving the cycling of nutrients between skeletal muscle and the liver. When muscles degrade amino acids for energy needs, the resulting nitrogen is transaminated to pyruvate to form alanine. This alanine is shuttled to the liver where the nitrogen enters the urea cycle and the pyruvate is used to make glucose. [48]

## Gluconeogenesis

A metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates such as pyruvate, lactate, glycerol, and glucogenic amino acids. [47]

# Elements of the Metabolic Process

Note: This is not a complete list.

## Metabolic Transporters

### Albumin

The primary transport protein, created by the liver. Serum albumin is the main protein of human blood plasma. It binds water, cations (such as Ca2+, Na+ and K+), fatty acids, hormones, bilirubin, thyroxine (T4) and pharmaceuticals - its main function is to regulate the colloidal osmotic pressure of blood. [46] Low serum levels of albumin can inhibit the functionality of all involved transports, thus negatively affecting healthy and mobility.

### Insulin

Insulin is a peptide hormone produced by beta cells in the pancreas. It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver. [7]

## Neurotransmitters

### GABA (γ-Aminobutyric acid)

GABA is the chief inhibitory neurotransmitter in the mammalian central nervous system. It plays the principal role in reducing neuronal excitability throughout the nervous system. In humans, GABA is also directly responsible for the regulation of muscle tone.

### Histamines

Histamine is an organic nitrogenous compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter. Histamine is involved in the inflammatory response and have central role as a mediator of pruritus. As part of an immune response to foreign pathogens, histamine is produced by basophils and by mast cells found in nearby connective tissues. Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues. [50]

# An Overview of The Metabolic Loop

Luckily or unluckily, the human body is not a simply machine. It is capable of using multiple types of food (proteins, fats, carbohydrates) as sources of fuel and it will process and store that fuel in different ways depending on patterned behavior and immediate metabolic requirements. The body burns endogenous sources of stored fuel in a defined manner, with preferences for fuel types depending on the organ being fueled.

In exercise physiology we need to be aware of how we tune our nutritional needs to maximize our physical abilities based on our fitness goals. As such, choosing the proper fuels and in what ratios they are consumed is of primary importance. Whatever our end goal for fitness, we must maximize our efficiency of generating ATP - the “molecular unit of currency” for energy.

## The major fuels for muscle

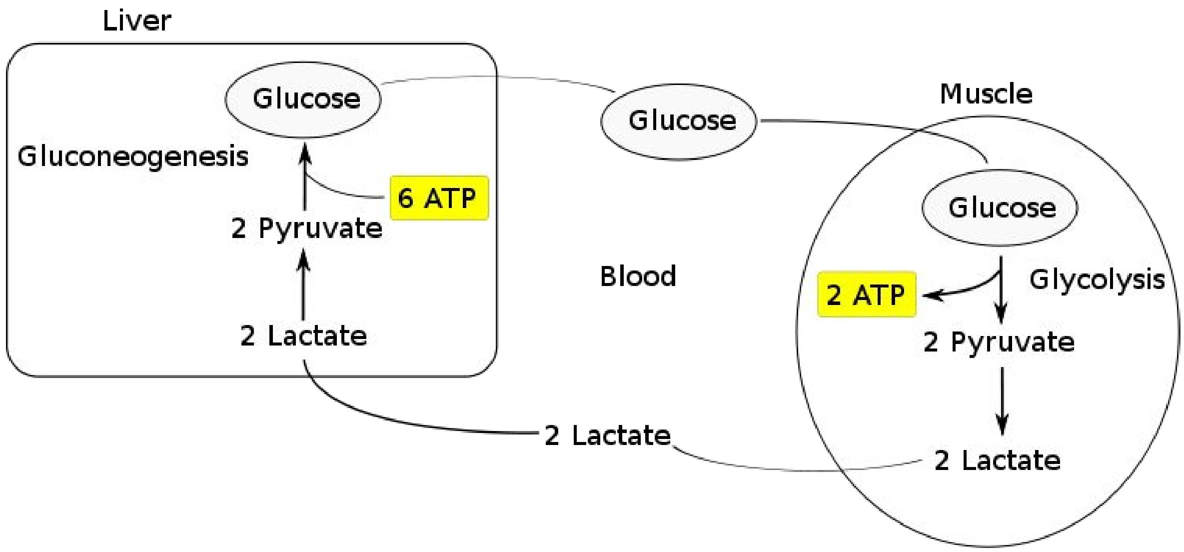
These include: glucose, fatty acids, and ketone bodies. Muscle differs from the brain in having a large store of glycogen. In fact, about three-fourths of all the glycogen in the body is stored in muscle.

This glycogen is readily converted into glucose 6-phosphate for use within muscle cells. Muscle, like the brain, lacks glucose 6-phosphatase, and so it does not export glucose. Rather, muscle retains glucose, its preferred fuel for bursts of activity. [42]

In actively contracting skeletal muscle, the rate of glycolysis far exceeds that of the citric acid cycle, and much of the pyruvate formed is reduced to lactate, some of which flows to the liver, where it is converted into glucose. [42] This is one of the reasons why proper liver health is so important for exercise physiology. Additionally, a healthy liver produces proper amounts of Albumin - the primary protein used to transport hormones and other vital resources in the bloodstream.

## The metabolic activities of the liver

The liver is essential for providing fuel to the brain, muscle, and other peripheral organs. Indeed, the liver, which can be from 2% to 4% of body weight, is an organism's metabolic hub. Most compounds are absorbed by the first pass through the liver, which is thus able to regulate the level of many metabolites in the blood. [42]

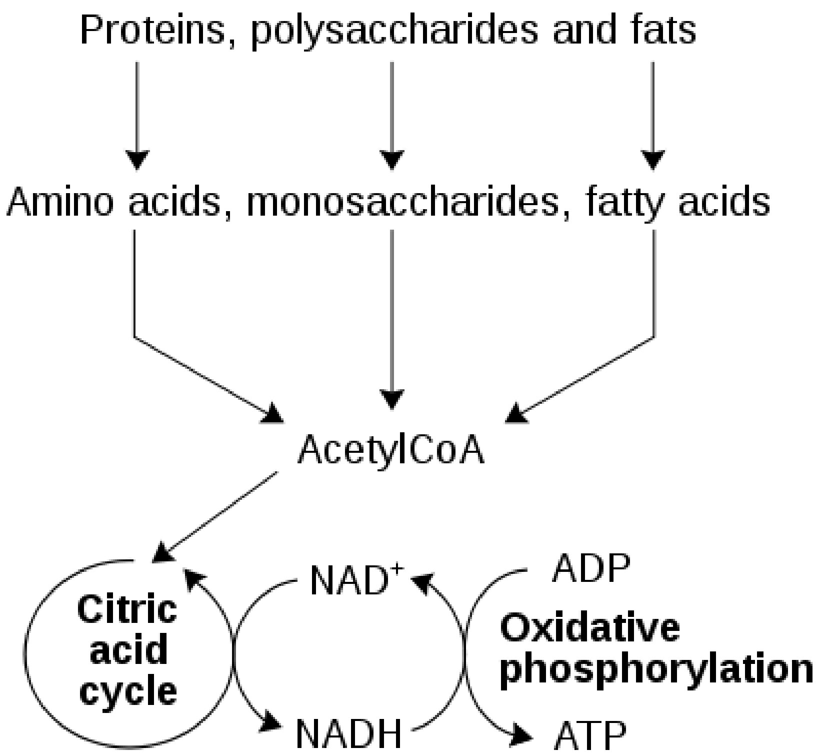



[image source: 44]

## The kidney, hydration, and oxygen

The major purpose of the kidney is to produce urine, which serves as a vehicle for excreting metabolic waste products and for maintaining the osmolarity of the body fluids. The blood plasma is filtered nearly 60 times each day in the renal tubules. Water-soluble materials in the plasma, such as glucose, and water itself are reabsorbed to prevent wasteful loss. The kidneys require large amounts of energy to accomplish the reabsorption. During starvation, the kidney becomes an important site of gluconeogenesis and may contribute as much as half of the blood glucose. [42]

## ATP Generation via the Metabolic Process

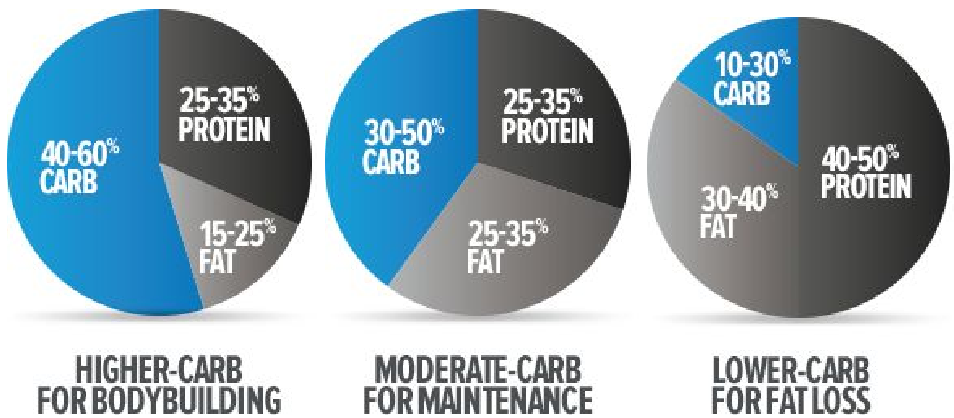



[image source: 41]

# Macro-nutrition Basics for Fitness Goals

Nutrition is the most important aspect of physical and mental health. You are what you eat, as the saying goes.

The following graphics show standard ratios that can be applied to your diet for controlling body composition, aesthetics, and fitness goals. [images: 32]




## On the importance of properly managing fat intake

Notice that fat never goes below 15 percent of total calories. Since hormones are constructed from cholesterol and other fat molecules, getting any less than that can actually suppress normal hormone levels. This also has a negative effect on the bodily functions driven by those hormones, including growth and development, metabolism, reproduction, and mood. Low fat intake can also impair absorption of the fat-soluble vitamins A, D, E, and K. [32]

## Nutrition for the bulking process

In order to achieve large gains in muscle mass along with significant body fat decreases, many hormonal events need to occur in the body. The amount of success that that can be achieved in these endeavors is determined by how much testosterone, growth hormone, and insulin are produced by the body and whether or not they are produced at the right times. These events are affected to a large extent by the quality, timing, amount, and ratio of the macronutrients consumed on a daily basis. [33]

## Gender’s role in macro-nutrition based energy production

Research suggests a variety of reasons that women have a greater reliance on fats for fuel during exercise, including [32]:

- Estrogen enhances epinephrine production, the primary hormone that stimulates lipolysis (fatty acid breakdown).
- Estrogen promotes the release of human growth hormone (HGH), which inhibits the uptake of carbohydrates and increases the mobilization of fatty acids from adipose tissue.
- Women have increased blood flow to adipose tissue, which could assist in fatty acid mobilization.
- Women have higher levels of intramuscular triglycerides (IMTG), a fat-based source of fuel that spares muscle glycogen during moderate to high intensity exercise. This

sparing of muscle glycogen may actually give women an endurance edge when performing at high intensities against men.
- According to one study, men appear to rely more on stored carbohydrate for fuel than women when doing the same exercise.

# Neurotransmitters, Hormones, and Histamines

Neurotransmitters are endogenous chemicals that transmit signals across a synapse or junction from one neuron (nerve cell) to another "target" neuron, muscle cell or gland cell. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by receptors on other synapses. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available from the diet and only require a small number of biosynthetic steps to convert them. Neurotransmitters play a major role in shaping everyday life and functions. [12]

## Anabolic Hormones and Neurotransmitters

### Insulin - Endogenous and Exogenous

- required to store energy (glucose as glycogen) and synthesize proteins from amino acids.
- insulin allows us to use blood sugar in the fuel mix for our cells.
- produced in the pancreas after meals and when blood sugar is elevated.
- when insulin levels are **low** you feel tired because your cells do not receive enough glucose, you get **cold**.
- when insulin levels are **high** insulin receptors shut down and you store excess glucose as body fat, you get **warm**.
- elevated insulin levels cause artery and vascular walls to swell, which decrease their diameter and makes it more difficult to circulate nutrients and oxygen.
- elevated insulin levels of insulin are the norm for individuals who are overweight due to the fact that insulin production is greatly influenced by body weight.
- eating excess carbohydrates and processed foods sends our insulin production through the roof and burns out our receptor sites making it extremely difficult for us to stop our cravings for sweets, which leads us on a downward spiral towards adult-onset diabetes and obesity.

### Testosterone

- equally important for men and women
- increases muscle mass, metabolic rate, red blood cells and promotes strong bones
- initiates protein synthesis
- promotes the release of growth hormone (GH)
- reference [22]

## Estrogen

- protein synthesis: Increase hepatic production of binding proteins
- structural: Increase fat store, accelerate metabolism
- secondary Sexual Characteristics: promote formation/feminization
- lipids: Increase HDL, triglyceride
- lipids: Decrease LDL, fat deposition
- fluid balance: Salt (sodium) and water retention
- bones: Reduce bone resorption, increase bone formation
- SHBG: Increase cortisol, increase levels of SHBG
- other: Maintenance of vessel and skin
- reference [9]

## Progesterone

- increases core temperature (thermogenic function)
- reduces spasm and relaxes smooth muscle. Bronchi are widened and mucus regulated.
- acts as an anti-inflammatory agent and regulates the immune response.
- normalizes blood clotting and vascular tone, zinc and copper levels, cell oxygen levels, and use of fat stores for energy.
- appears to prevent endometrial cancer by regulating the effects of estrogen.
- plays an important role in the signaling of insulin release.

## Growth Hormone (GH)

- released from the pituitary gland during deep sleep
- provides us with a sense of well being, increases muscle mass, strengthens bones, reduces body fat, and strengthens our immune systems

## Serotonin

- a neurotransmitter that affects our cravings, obsessive behavior, appetite, tranquility, peace of mind, and comfort
- serotonin mitigates negative impulses and behaviors
- too much causes nausea and diarrhea, while too little causes a person to be anxious, restless, depressed, impulsive, and aggressive
- serotonin has to be balanced with melatonin (below), imbalances cause increases in stress, poor impulse control, depression, overeating and drinking
- serotonin is produced in the brain from the amino acid tryptophan
- when levels of tryptophan rise and fall so do levels of serotonin
- reference [22]

### Melatonin

- influences our biological clock
- effects a wide range of functions including fertility, immune function and insulin production
- is the strongest anti-cancer hormone
- made from serotonin
- production and release is influenced by day/night cycles and seasonal variations
- turned on from daylight and off by darkness
- reference [22]

### Dopamine

- stimulating neurotransmitter
- naturally is released before we wake up and causes that get up and go feeling we should have when waking up
- if you go to bed too late in the dark cycle it will not be released and you'll feel sluggish and drowsy
- operates the fight or flight response with the release of adrenaline
- causes involuntary movements like blinking, emotional drive and spontaneity
- dopamine reduces with age and can be burnt out faster by abusing drugs like marijuana, speed, crack and cocaine
- dopamine deficiency is known as Parkinson's disease
- reference [22]

### Dehydroepiandrosterone (DHEA) [22]:

- the most abundant hormone in our bodies
- produced in the adrenal glands
- considered the mother hormone because it is used to produce other hormones such as estrogen, progesterone, testosterone and cortisol
- balanced levels of DHEA send messages to each of our 100 trillion cells to repair, rebuild, restore and revitalize
- improves our memory, mood, immune system and longevity

## Catabolic Hormones, cellular degradation

### Cortisol

- produced in the adrenal glands
- designed to be a short term coping mechanism to deal with extreme stress
- today most of us function on chronically elevated levels of stress, not only from the obvious causes (work, traffic, politics) but also from poor diets full of processed foods with increase stress on the cellular level to deal with such pollutants

- when cortisol levels are too high the immune system is suppressed, insulin, blood pressure, and blood sugar levels increase which may lead to brain damage
- reference [22]

### Glucagon

- processes glucose
- balance between insulin and glucagons dictates whether there is storage or depletion of energy stores
- produced in the pancreas and causes increases in blood glucose levels between meals by stimulating the breakdown of glycogen by the liver
- Glucagon increases with age and promotes elevated glucose levels
- reference [22]

### Epinephrine and Norepinephrine

- both work with cortisol during times of danger to stimulate the nervous system, increase heart rate and make us more alert
- epinephrine is also called adrenalin
- norepinephrine is also called noradrenalin
- too much can cause anxiety attacks and mess up the insulin-glucagon balance
- reference [22]

### Thyroid Hormones (TSH, T3, T4)

- controls our resting metabolic rate
- we are very sensitive to any imbalance
- too much increases metabolism, aging, and makes you agitated or jumpy
- too little makes you depressed and unresponsive
- reference [22]

## Histamine H1 = modulation of physiological systems

See reference [50]

### Reactions of the central nervous system (CNS)

- sleep-wake cycle
- body temperature
- nociception
- endocrine homeostasis
- appetite management
- mood
- learning + memory

### Reactions of the peripheral nervous system (PNS)

- Causes bronchoconstriction
- bronchial smooth muscle contraction
- vasodilation
- separation of endothelial cells (responsible for hives)
- and pain and itching due to insect stings
- the primary receptors involved in allergic rhinitis symptoms and motion sickness

### Medications that alter H1 activity

Anti-histamines that address the H1 receptors affect the reverse of the above mentioned changes to CNS and PNS. Hence, for athletic performance, anti-histamine medications that target the H1 receptor will induce drowsiness, alter mood, affect memory, cause bronchodilation, and cause vasoconstriction (potentially increasing blood pressure negatively).

## Beta Alanine, an endogenous metabolic stimulant

### Research basics of Beta Alanine

Beta-alanine is technically a non-essential beta-amino acid, but it has quickly become anything but non-essential in the worlds of performance nutrition and bodybuilding. Also known by its trademarked name CarnoSyn, it has become a shining star due to claims that it raises muscle carnosine levels and increases the amount of work you can perform at high intensities.

Beta-alanine, or 3-aminopropionic acid is a naturally-occurring beta-amino acid and a component of the histidine dipeptides carnosine and anserine, as well as vitamin B5, or pantothenic acid. Structurally, beta-alanine is a hybrid between the potent neurotransmitters L-glycine and GABA, which may explain why consumers often claim to experience a caffeine-like response from it. Beta-alanine is even gaining support within the scientific community for being secondarily classified as a neurotransmitter.

Your body can produce beta-alanine in at least three ways. It can be released during the breakdown of histidine dipeptides, such as carnosine or anserine, or it can be formed as a secondary byproduct of a reaction that converts L-alanine to pyruvate. Additionally, beta-alanine can be formed during digestion, when intestinal microbes remove a carbon atom from L-aspartate, releasing both beta-alanine and $CO_2$.

When consumed as a dietary supplement, beta-alanine passes from the bloodstream into skeletal muscle via a beta-alanine and taurine transporter that's dependent upon both sodium and chloride availability. Once it enters a skeletal muscle cell, it binds with the essential amino acid L-histidine to form the dipeptide carnosine. That's where the fun really begins. Supplementation with beta-alanine has been shown to increase muscle carnosine concentrations by up to 58 percent in just four weeks, and 80 percent in 10 weeks. [11]

## The role of healthy fat in exercise physiology

Healthy fat sources are comprised of Monounsaturated Fats, Polyunsaturated Fats, Medium-Chain Triglycerides (MCT oils), and Omega-3 Fatty Acids. Unhealthy fat sources are Saturated Fats and Trans-Unsaturated Fatty Acids, also known as Trans-Fat.

Fatty acids, stored as triglycerides in an organism, are an important source of energy because they are both reduced and anhydrous. The energy yield from a gram of fatty acids is approximately 9 kcal (37 kJ), compared to 4 kcal (17 kJ) for carbohydrates. Since the hydrocarbon portion of fatty acids is hydrophobic, these molecules can be stored in a relatively anhydrous (water-free) environment.

Carbohydrates, on the other hand, are more highly hydrated. For example, 1 g of glycogen can bind approximately 2 g of water, which translates to 1.33 kcal/g (4 kcal/3 g). This means that fatty acids can hold more than six times the amount of energy per unit of storage mass.

Put another way, if the human body relied on carbohydrates to store energy, then a person would need to carry 31 kg (67.5 lb) of hydrated glycogen to have the energy equivalent to 4.6 kg (10 lb) of fat. [43]

### Monounsaturated fat

This is a type of fat found in a variety of foods and oils. Studies show that eating foods rich in monounsaturated fats improves blood cholesterol levels, which can decrease your risk of heart disease. Monounsaturated fats may benefit insulin levels and blood sugar control. Examples include: avocados, egg yolks, olives, nuts, peanut butter, canola oil, olive oil, high-oleic sunflower oil. [34]

### Polyunsaturated fat

This is a type of fat found mostly in plant-based foods and oils. Evidence shows that eating foods rich in polyunsaturated fats (PUFAs) improves blood cholesterol levels, which can decrease your risk of heart disease. PUFAs may also help decrease the risk of type 2 diabetes. [34]

### Medium-Chain Triglycerides

Medium-chain triglycerides are generally considered a good biologically inert source of energy that the human body finds reasonably easy to metabolize and are absorbed rapidly by the body.

- Some studies have shown that MCTs can help in the process of excess calorie burning, thus weight loss. MCTs are also seen as promoting fat oxidation and reduced food intake. [38]
- They have potentially beneficial attributes in protein metabolism, but may be contraindicated in some situations due to their tendency to induce ketogenesis and metabolic acidosis. [38][39][40]
- Examples include: coconut oil, palm kernel oil

### Omega-3 fatty acids

This type of fat helps protect the cardiovascular system, aids in liver health, and aids in the metabolic process. [34][35][36]

- As an anti-arrhythmic agent, Omega-3 helps prevent abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.
- Omega-3 helps regulate hepatic lipid metabolism, adipose tissue function, and inflammation.
- There are plant sources of omega-3 fatty acids. However, the body doesn't convert it and use it as well as omega-3 from fish.
- Sources include: salmon, and other fish, grass-fed beef, chia seeds, ground flax seeds, soybeans, tofu, edamame, beans, wild rice, and walnuts.

### Saturated fat

This is a type of fat that comes mainly from animal sources of food, such as red meat, poultry and full-fat dairy products. Saturated fat raises total blood cholesterol levels and low-density lipoprotein (LDL) cholesterol levels, which can increase your risk of cardiovascular disease. Saturated fat may also increase your risk of type 2 diabetes. [34]

### Trans-Unsaturated Fat

This is a type of fat that occurs naturally in some foods in small amounts. But most trans fats are made from oils through a food processing method called partial hydrogenation. By partially hydrogenating oils, they become easier to cook with and less likely to spoil than do naturally occurring oils. Research studies show that these partially hydrogenated trans fats can increase unhealthy LDL cholesterol and lower healthy high-density lipoprotein (HDL) cholesterol. This can increase your risk of cardiovascular disease. [35]

### Protein for exercise physiology

Protein is the key building nutrient for a variety of bodily tissues, many of which support muscle growth (enzymes, skin, hair, nails, bones, and connective tissue are all constructed from protein). Protein makes up 15-20% of one's body weight and is thus, next to water, the body's second most abundant substance. [37]

Nitrogen balance is a method of determining protein metabolism via input-output efficiency and the outcome of being anabolic or catabolic in terms of protein synthesis, balance or degradation.

- Positive Nitrogen Balance: Protein intake is at a level that encourages weight gain.
- Neutral Nitrogen Balance: Protein intake is at a level that maintains body weight.
- Negative Nitrogen Balance: Protein intake is at a level where weight loss occurs or muscle proteins are at risk of being catabolized to make up the deficit.

### Whey, the daytime protein

The use of whey protein as a source of amino acids and its effect on reducing the risks of diseases such as heart disease, cancer and diabetes has been the focus of ongoing research as of 2007. Whey is an abundant source of branched-chain amino acids (BCAAs), which are used to stimulate protein synthesis. [24]

When leucine is ingested in high amounts, such as with whey protein supplementation, there is greater stimulation of protein synthesis, which may speed recovery and adaptation to stress (exercise). Whey has approximately three grams of leucine per serving and the threshold for optimal protein synthesis is three grams. [24]

As with other forms of protein, consumption of whey protein shortly after vigorous exercise can boost muscle hypertrophy. Scientific evidence has shown that proteins high in essential amino acids (EAA), branched chain amino acids (BCAA), and particularly leucine (Leu) are associated with increased muscle protein synthesis, weight loss, body fat loss, and decreased plasma insulin and triglyceride profile. [24]

### Casein, the nighttime protein

An attractive property of the casein molecule is its ability to form a gel or clot in the stomach, which makes it very efficient in nutrient supply. The clot is able to provide a sustained slow release of amino acids into the blood stream, sometimes lasting for several hours. [23]

## Non-Steroidal influencers on the metabolic process and liver health

### Cimetidine (Tagamet)

This Over The Counter (OTC) medication, which functions as a proton pump in the digestive system, Inhibits the activity of CYP450 enzyme and decreases the levels of AST + ALT liver enzymes which will aid in treatment of hepatotoxicity (liver stress or damage). If GGT (gamma-glutamyl transferase) is in an elevated status in conjunction with elevated AST/ALT this indicates liver damage, whereas standard range GGT in presence of elevated AST/ALT indicates liver stress. This is important because some exogenous supplements used in high level fitness training can put stress on the liver, especially during the cutting phases where low body-fat percentages + low dietary fat intake is being observed in the athlete. Cimetidine also is a potentiator, meaning that it increases and prolongs the effects of opiate medication.

We observed the levels of ALT, AST, blood sugar in model group increased significantly, then kept increasing through the study.The decrease of CYP450, CYP2E1 in therapeutic groups was obvious.There was an obvious difference of ALT, AST between therapeutic group and model group, while the other indexes be not obviously distinguished from each other.The hepatic injury in therapeutic groups was significantly lessened. So cimetidine can prevent nonalcoholic hepatic injury, inhibit the expressions of CYP450 and CYP2E1, and decrease the expression of ALT and AST, but have no effect on blood sugar, insulin, TG, TC and lipoprotein. [1]

### R-ALA, ALA

Lipoic acid (LA), also known as α-lipoic acid and alpha lipoic acid (ALA) and thioctic acid is an organosulfur compound derived from octanoic acid. ALA is made in animals normally, and is essential for aerobic metabolism. It is also manufactured and is available as a dietary supplement in some countries where it is marketed as an antioxidant, and is available as a pharmaceutical drug in other countries. [16] R-ALA is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

### Tauroursodeoxycholic acid (TUDCA)

TUDCA is an ambiphilic bile acid. It is the taurine conjugate form of ursodeoxycholic acid (UDCA). Humans are found to have trace amounts of TUDCA. TUDCA is produced in several countries for the treatment of gallstones and liver cirrhosis. [17] TUDCA is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

### N-acetyl-L-cysteine (NAC)

Acetylcysteine has also been hypothesized to exert beneficial effects through its modulation of glutamate and dopamine neurotransmission as well as its antioxidant properties. Acetylcysteine is sold as a dietary supplement commonly claiming antioxidant and liver protecting effects. Extensively liver metabolized; CYP450 minimal. Urine excretion 22-30% with a half-life of 5.6 hours in adults.

Acetylcysteine is the N-acetyl derivative of the amino acid L-cysteine, and is a precursor in the formation of the antioxidant glutathione in the body. The thiol (sulfhydryl) group confers antioxidant effects and is able to reduce free radicals. [18] NAC is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

### Silybum (Milk Thistle)

For many centuries extracts of milk thistle have been recognized as "liver tonics." Milk thistle has been reported to have protective effects on the liver and to greatly improve its function. It is typically used to treat liver cirrhosis, chronic hepatitis (liver inflammation), toxin-induced liver damage including the prevention of severe liver damage from Amanita phalloides ('death cap' mushroom poisoning), and gallbladder disorders. [19] Milk Thistle is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

## Intro to the metabolic enzyme Cytochrome P450 (CYP450)

Cytochrome P450 enzymes are present in most tissues of the body, and play important roles in hormone synthesis and breakdown (including estrogen and testosterone synthesis and metabolism), cholesterol synthesis, and vitamin D metabolism. Cytochrome P450 enzymes also function to metabolize potentially toxic compounds, including drugs and products of endogenous metabolism such as bilirubin, principally in the liver. [21]

A subset of cytochrome P450 enzymes play important roles in the synthesis of steroid hormones (steroidogenesis) by the adrenals, gonads, and peripheral tissue. CYP19A (P450arom, aromatase) in endoplasmic reticulum of gonads, brain, adipose tissue, and elsewhere catalyzes aromatization of androgens to estrogens. [21]

Steroids are oxidized mainly by cytochrome P450 oxidase enzymes, such as CYP3A4. These reactions introduce oxygen into the steroid ring and allow the cholesterol structure to be broken up by other enzymes, to form bile acids as final products. These bile acids can then be eliminated through secretion from the liver in the bile. The expression of this oxidase gene can be upregulated by the steroid sensor PXR when there is a high blood concentration of steroids. [30]

Steroid hormones, lacking the side chain of cholesterol and bile acids, are typically hydroxylated at various ring positions and/or oxidized at the 17 position, then conjugated with sulfate or glucuronic acid and excreted in the urine. [30]

### Grapefruit and it's effects on the CYP450 metabolic enzyme process

To study the effects of grapefruit and grapefruit products on body weight and metabolic syndrome, 91 obese patients were randomized to either placebo capsules and 7 ounces (207 mL) of apple juice, grapefruit capsules with 7 ounces (207 mL) of apple juice, 8 ounces (237 mL) of grapefruit juice with placebo capsule, or half of a fresh grapefruit with a placebo capsule three times a day before each meal. Metabolic syndrome parameters were measured at the beginning and end of 12 weeks. [22]

After 12 weeks, the fresh grapefruit group had lost 1.6 kg, the grapefruit juice group had lost 1.5 kg, the grapefruit capsule group had lost 1.1 kg, and the placebo group had lost 0.3 kg. The fresh grapefruit group lost significantly more weight than the placebo group ($P < .05$). A secondary analysis of those with the metabolic syndrome in the four treatment groups demonstrated a significantly greater weight loss in the grapefruit, grapefruit capsule, and grapefruit juice groups compared with placebo ($P < .02$). [22]

There was also a significant reduction in 2-hour post-glucose insulin level in the grapefruit group compared with placebo. Half of a fresh grapefruit eaten before meals was associated with significant weight loss. In metabolic syndrome patients the effect was also seen with grapefruit products. Insulin resistance was improved with fresh grapefruit. Although the mechanism of this weight loss is unknown it would appear reasonable to include grapefruit in a weight reduction diet. [22]

### Drug interactions

Grapefruit and grapefruit juice have been found to interact with numerous drugs (at least 85 known by 2013), in many cases resulting in adverse effects. Organic compounds that are furanocoumarin derivatives interfere with the hepatic and intestinal enzyme CYP450 isoform CYP3A4 and are believed to be primarily responsible for the effects of grapefruit on the enzyme. Bioactive compounds in grapefruit juice may also interfere with P-glycoprotein and organic anion transporting polypeptides (OATPs), either increasing or decreasing the bioavailability of a number of drugs. [2]

## The Ketogenesis Process

Ketogenesis is the process by which ketone bodies are produced as a result of fatty acid breakdown. Ketone bodies are produced mainly in the mitochondria of liver cells, and synthesis can occur in response to an unavailability of blood glucose. [39]

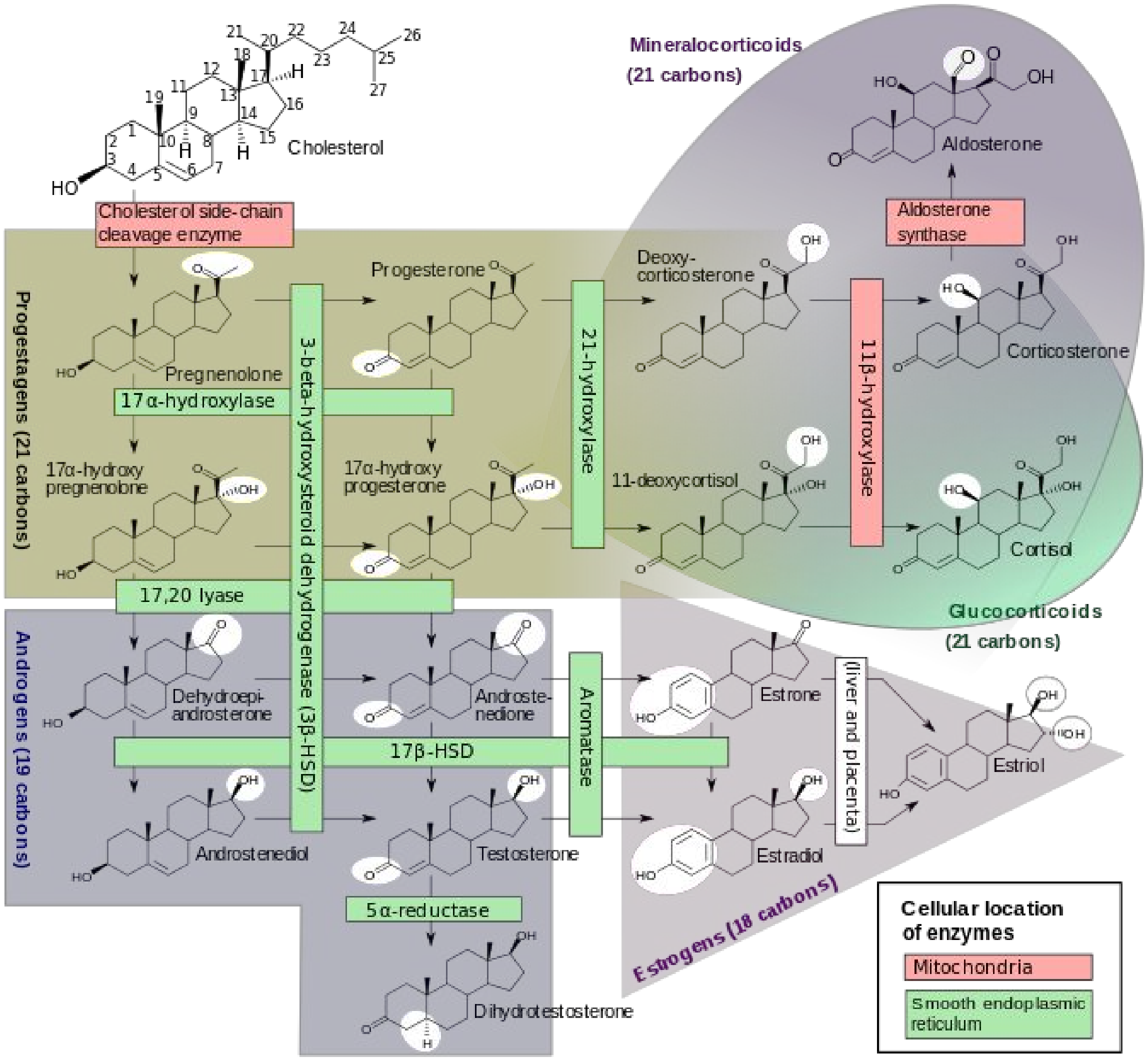
### Situational Causality

- Due to low glucose levels in the blood, after exhaustion of cellular carbohydrate stores, such as glycogen. [39]
- Due to excessively high levels of blood glucose that are unable to be stored as glycogen in liver and muscle. The production of ketone bodies is then initiated to make available energy that is stored as fatty acids. [39]

### Why this matters for exercise physiology

Ketogenesis occurs during the above situations due to dietary choices. You can control how your body burns endogenous calorie sources based on what you eat. If this does not make sense, see the section of this document that discusses “The Metabolic Loop”.

## The Steroidogenesis Process (they're all related)[13]




## DHEA basics concepts

Also known as androstenolone or prasterone (INN), as well as 3β-hydroxyandrost-5-en-17-one or 5-androsten-3β-ol-17-one, is an important endogenous steroid hormone. DHEA is produced from cholesterol through two cytochrome P450 enzymes.

It is the most abundant circulating steroid hormone in humans, in whom it is produced in the adrenal glands, the gonads, and the brain, where it functions predominantly as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids. However, DHEA also has a variety of potential biological effects in its own right, binding to an array of nuclear and cell surface receptors, and acting as a neurosteroid. [26]

DHEA is a steroid hormone. High [ed: exogenous or supplemented] doses may cause aggressiveness, irritability, trouble sleeping, and the growth of body or facial hair on women [ed: this is due to DHEA being a pre-cursor to Testosterone, of which elevated levels lead to virilization/masculinization of the body). It also may stop menstruation and lower the levels of HDL ("good" cholesterol), which could raise the risk of heart disease. [26]

Although it predominantly functions as an endogenous precursor to more potent androgens such as testosterone and DHT, DHEA has been found to possess some degree of androgenic activity in its own right, acting as a low affinity (Ki = 1 μM), weak partial agonist of the androgen receptor. However, its intrinsic activity at the receptor is quite weak, and on account of that, due to competition for binding with full agonists like testosterone, it can actually behave more like an antagonist depending on circulating testosterone and dihydrotestosterone (DHT) levels, and hence, like an antiandrogen. [26]

DHEA and other adrenal androgens such as androstenedione, although relatively weak androgens, are responsible for the androgenic effects of adrenarche, such as early pubic and axillary hair growth, adult-type body odor, increased oiliness of hair and skin, and mild acne. Women with complete androgen insensitivity syndrome (CAIS), who have a non-functional androgen receptor and are immune to the androgenic effects of DHEA and other androgens, have absent or only sparse/scanty pubic and axillary hair and body hair in general, demonstrating the role of DHEA, testosterone, and other androgens in body hair development at both adrenarche and pubarche. As a neurosteroid, DHEA has important effects on neurological and psychological functioning. [26]

Regular exercise is known to increase DHEA production in the body. Calorie restriction has also been shown to increase DHEA in primates. Some theorize that the increase in endogenous DHEA brought about by calorie restriction is partially responsible for the longer life expectancy known to be associated with calorie restriction.[26]

Catalpol and a combination of acetyl-carnitine and propionyl-carnitine on 1:1 ratio also improves endogenous DHEA production and release due to direct cholinergic stimulation of CRH release and an increase of IGF-1 expression respectively. [26]

### DHEA’s impact on endocrinology and metabolism

- DHEA is the precursor steroid to androgen and estrogen hormones, and is created by the adrenal gland. Exogenous DHEA can be supplemented for managing levels of this steroid available to the endocrine system.
- Excessive levels of DHEA can cause issues with androgenization/virilization, a negative consequence for women.

- Low levels of DHEA can impair neurological processes and hormonal balances.
- Exercise increases DHEA production in the body, which in turn enhances the body's ability to create and manage other hormones as well as manage neurological processes.
- Endogenous DHEA production can be improved by supplementing "Catalpol and a combination of acetyl-carnitine and propionyl-carnitine on a 1:1 ratio."

## Testosterone basics

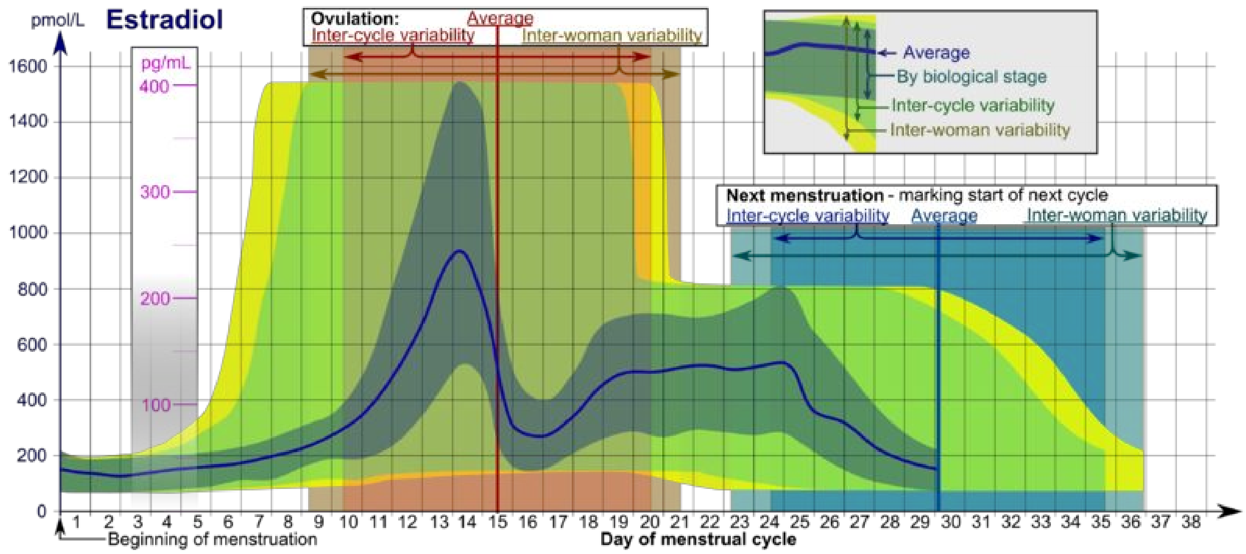
The "male hormone". There are typically two levels tested: Total and Free. Total is the amount circulating in the body, Free is the amount that is *not* bound to SHBG and is available to muscle tissue, skeletal structures, the brain, and other androgen receptor sites. Excess testosterone is converted into estradiol (estrogen/E2) by the aromatase enzyme process. Medications such as Amiridex can be used to prevent the aromatization process, which is typically used in some forms of breast cancer treatment or by male body builders to prevent gynecomastia side effects of anabolic testosterone-based steroid usage (Testosterone Propionate, Equipoise, Dianabol, etc).

Testosterone is also converted into the more potent Dihydrotestosterone (DHT) sex steroid via the 5-alpha reductase enzyme process (this can be prevented via medications such as Avodat/Dutasteride). DHT is responsible for follicle stimulation (body hair growth), and various other masculinization effects on the body.

## Estrogen basics

The "female hormone". Typically known as 17β-estradiol, or E2. While estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. They promote the development of female secondary sexual characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle. In males, estrogen regulates certain functions of the reproductive system important to the maturation of sperm and may be necessary for a healthy libido.[9]

Estradiol level fluctuations during the menstrual cycle [14]




Estrogen and weight loss [27]

Estradiol also reduces LPL, just like testosterone does, so uptake of fatty acids in adipocytes is reduced. Apart from that, estrogen's effects can be divided in three categories:

- Estrogen's effect on insulin-related events
- Estrogen's effects on Growth Hormone
- Estrogen's effects on reducing appetite

1. Estradiol can cause a reduction in weight, with only a minimal effect in insulin itself, but that does not mean it does not alter the body's reaction to insulin. Estradiol lowers insulin receptor number, and in very high doses even actual insulin sensitivity. It does so in various ways, not in the least by reducing GLUT4 recruitment and translocation in adipocytes, which results in less glucose uptake in fat cells. This will result in a negative energy balance and a greater activation of lipolysis, right where we want it, in the fat tissue. The effect of estradiol on insulin is quite acute, and clearly evident in the fact that short-term modulation drastically reduces glucose appearance (release) and disappearance (uptake), suggesting a dysfunctional glucose transport system.
2. The second way in which estradiol may increase fat loss, is its effect on growth hormone. Unlike testosterone, which stimulates the GH/IGF-1 axis, the effect of estrogen may actually be in reducing systemic (liver-derived) IGF-1, which lowers inhibition of Growth Hormone. In doing so it obviously reduces the anabolic capacity of the body (which is why we don't use estrogen to build muscle) but increases the fat burning capacity since whole-body IGF-1 is reduced, leading to a reduction in adipogenic markers (since IGF-1 and insulin activate the same cascades) and a

concurrent increase in Growth Hormone, leading to further decreases in LPL and upregulation of beta-adrenoreceptors. Estradiol may even reduce IGF-1, while increasing IGFBP-3.

3. A third way in which estradiol helps as a fat loss agent is by reducing appetite. It reduces sensations of hunger via modulation of melanin-concentrating hormone (MCH). Estradiol was able to completely abolish this increase in MCH, making it a very potent appetite suppressor during low-calorie diets.

### Estrogen In a Testosterone dominant endocrine system (male)

Estradiol can also prevent muscle loss, once again only in the presence of testosterone, by blocking the low affinity glucocorticoid receptors (22), protecting against the effects of cortisol. Testosterone, or another blocker of the high affinity receptors must be present however, otherwise the blocking of the low affinity receptor would not yield very good results.

## Progesterone basics [25]

Progesterone is an endogenous steroid and progestogen sex hormone. It belongs to a group of steroid hormones called the progestogens, and is the major progestogen in the body. Progesterone is also a crucial metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids, and plays an important role in brain function as a neurosteroid.

Progesterone enhances the function of serotonin receptors in the brain, so an excess or deficit of progesterone has the potential to result in significant neurochemical issues. This provides an explanation for why some people resort to substances that enhance serotonin activity such as nicotine, alcohol, and cannabis when their progesterone levels fall below optimal levels.

## Insulin basics

Insulin is a peptide hormone produced by beta cells in the pancreas. It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver. [7]

Except in the presence of the metabolic disorder diabetes mellitus and metabolic syndrome, insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. When blood glucose levels fall below a certain level, the body begins to use stored glucose as an energy source through glycogenolysis, which breaks down the glycogen stored in the liver and muscles into glucose, which can then be utilized as an energy source. [7]

As a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). In addition, it has several other anabolic effects throughout the body. [7]

### Insulin as an anabolic enhancer

Insulin is actually a protein, and it is produced and released by the pancreas whenever you eat carbs, protein, or both. (That is, if the pancreas is working properly). Yet unlike the proteins that are the physical building blocks of muscle, this is a functional protein, much like growth hormone. [8]

### Insulin level impacts of diet [8]

COMMON HIGH GI (I.E. FAST) AND LOW GI (I.E. SLOW) FOODS

| | | |
|---|---|---|
| **LOW** | | |
| - Oatmeal | - Most 100% fruit juice | - Whole-grain/wheat bread |
| - Sourdough bread | - Rye bread | - Beans (black, kidney, pinto, etc.) |
| - Whole-wheat pasta | - Sweet potatoes | - Most fruit (apples, bananas, oranges, peaches, etc.) |
| - Wheat germ | - Most brown rice | |
| - Most waxy maizes | - Quinoa | |
| **HIGH** | | |
| - Table sugar | - Couscous | - White bread/plain bagel |
| - Vitargo | - Regular pasta (semolina) | - Rice Krispies, Corn Flakes |
| - White potatoes | - Angel food cake | - Sports drinks (Gatorade, etc.) |
| - Regular soda | - Most white rice | - Sugary cereals (Froot Loops, |
| - Dextrose | - Pixy Stix, gummy bears | - Flakes, Lucky Charms, etc...) |

### Playing with fire (exogenous self-administered insulin therapy) [10]

Humulin R (regular human insulin injection [rDNA origin]) is a short-acting insulin that has a relatively short duration of activity as compared with other insulins. Humulin is identical in chemical structure to human insulin.

Self-administered insulin therapy can be used to enhance the metabolic process. Most pharmacies in the USA will sell Humulin R without a prescription + insulin syringes. Typical doses range from 2iu to 10iu 30-minutes before the end of an intense workout. One *must* consume at a minimum of 10g/carb per 1iu of insulin injected within 30 min post-injection + a regular meal within the hour to prevent hypoglycemia. It should be noted that Insulin is the most potent anabolic non-steroidal hormone in the human body and that elevated levels that do not have sufficient carbohydrates and protein to bind to and transport to muscle tissue will cause the body to go into hypoglycemic shock. This is not recommended for a novice bodybuilder or anyone who does not have very strict control of their daily nutritional planning and execution. A lack of self control or simple mistake with exogenous insulin therapy can result in coma and death.

## SHBG, Sex Hormone Binding Globulin

Testosterone and estradiol circulate in the bloodstream, bound mostly to SHBG and to a lesser extent serum albumin and corticosteroid-binding globulin (CBG) (AKA transcortin). Only a very small fraction of about 1-2% is unbound, or "free," and thus biologically active and able to enter a cell and activate its receptor. SHBG inhibits the function of these hormones.

SHBG (sex hormone binding globulin) is a protein created primarily by the liver that binds to sex steroids, and renders them inactive for as long as SHBG is bound to them. SHBG is a hormone reservation system... it has affinity binding preference as such: dihydrotestosterone (DHT) > testosterone > androstenediol > estradiol (E2) > estrone. [5]

SHBG has both enhancing and inhibiting hormonal influences. It decreases with high levels of insulin, growth hormone, insulin-like growth factor 1 (IGF-1), androgens, prolactin and transcortin. High estrogen, and thyroxine cause it to increase. [5]

SHBG levels are decreased by androgens, administration of anabolic steroids, polycystic ovary syndrome, hypothyroidism, obesity, Cushing's syndrome, and acromegaly. Low SHBG levels increase the probability of Type 2 Diabetes. SHBG levels increase with estrogenic states (oral contraceptives), pregnancy, hyperthyroidism, cirrhosis, anorexia nervosa, and certain drugs. Long-term calorie restriction of more than 50 percent increases SHBG, while lowering free and total testosterone and estradiol. DHEA-S, which lacks affinity for SHBG, is not affected by calorie restriction. [5]

SHBG as affected by estrogen Hormone Replacement Therapy / Birth Control [3]: "Plasma SHBG levels were higher in the group treated with estrogen alone than in groups of women treated with sequential or combined HRT."

Exogenous Insulin and its effect on SHBG levels in newly diagnosed diabetes-type-2 patients [4]: "Insulin Therapy increases serum SHBG likely through improving insulin resistance and liver function." This is the opposite effect of Exogenous Insulin Therapy in non-diabetic patients. It can be inferred that insulin therapy brings diabetic patients back into homeostasis for proper insulin levels vs exogenous insulin therapy by non-diabetic patients which would decrease serum level SHBG levels due to excessive levels of insulin.

### Primary effect of SHBG on hormone levels

Higher SHBG = more of the Total Testosterone will be bound to it, thus reducing Free Testosterone... thus reducing virilization (masculinization effects) in women. Lower SHBG levels allow males to have additional masculinization due to the increase of Free Testosterone that can bind to androgen receptors. These factors are critical to understanding the hormonal balance and influence of SHBG on the overall functional ability of endogenous and exogenous sex-steroid levels. If SHBG is too high, your body will suffer for lack of sex-steroid levels that are needed for receptor bindings. The proper level of SHBG that determines your Free Testosterone and Free Estradiol depends on your fitness goals. Since you can modify SHBG levels via diet, you will want to tune your diet accordingly to your fitness goals.

### How diet affects SHBG levels [6]

"One of the major controlling factors on SHBG synthesis is insulin. This intake of protein has been shown to increase insulin levels (32), and insulin has been shown to reduce SHBG levels (33, 34)." *Thus a diet higher in protein = higher insulin levels = lower SHBG levels = more Free Testosterone = higher anabolic abilities and androgen receptor contact.*

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