

## Crank Up those Catecholamines for Fat Loss!!

Contributed by Robbie Durand  
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"If you slow down...you die!" That's what Los Angeles hit man Chev Chelios was told in the 2006 movie "Crank" after he screwed up and was given a chemical concoction called the Beijing Cocktail. The chemical cocktail suppressed Chev's adrenal gland so he couldn't produce adrenaline. As a consequence, he had to keep his adrenaline constantly pumping by other means to keep his heart pumping. If he slowed down and rested he would die. Chev does everything he can to keep his adrenaline going (which would put any bodybuilder's pre-workout stack to shame). He increases his adrenaline by popping caffeine tabs, drinking Red Bulls nonstop, having sex in public, performing daredevil stunts, stealing epinephrine shots from a local hospital, sniffing Sudafed and putting his hand under a waffle iron. Yikes...talk about an adrenaline rush! No need to abuse Sudafed or stand on your motorcycle to increase adrenaline, a high-intensity bout of resistance exercise increases catecholamines (epinephrine and norepinephrine).

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Epinephrine is produced naturally in the body, not only can it increase your heart rate, but it's also a powerful fat burner. Epinephrine is secreted from the adrenal gland and binds to  $\beta$ -receptors located on fat cells, which enhance fat mobilization. The regulation of fat metabolism is complex and is regulated by multiple mechanisms, including fat-mobilizing agents (GH, cortisol, catecholamines, HSL) and fat-storage hormones (insulin) and their receptor-signaling pathways.

### "Crank" the Movie Meets Exercise Physiology

Hormone-sensitive lipase (HSL) is the rate-limiting enzyme that controls fat lipolysis (fat burning) at rest. Epinephrine, which is increased during high-intensity exercise, is a powerful stimulator of HSL activity. Research scientists were interested in how adrenaline affected HSL activity in their own version of "Crank" the movie meets exercise physiology.

Research scientists took patients who had their adrenal glands removed (adrenalectomized patients: their adrenal glands were removed because of adrenal tumors, so they didn't produce epinephrine and norepinephrine). The researchers were specifically interested in whether HSL would be activated in response to exercise in these subjects because they don't produce catecholamines (epinephrine/norepinephrine).

In one trial they exercised, while in the other trial they exercised while being infused with epinephrine. Sounds just like "Crank." Luckily, they didn't ask the subjects to have sex in public or sniff Sudafed!! Researchers found that without epinephrine concentrations rising during exercise, there was no increase in HSL activity in these patients. However, when infused with adrenaline, they produced increases in HSL similar to normal, healthy subjects.<sup>28</sup>

In another related study, subjects were asked to cycle on a bike. The second part of the experiment had the subjects come back and cycle again after they'd had an adrenaline infusion. The subjects had higher increases in HSL activity with the epinephrine infusion compared to the control trial.<sup>27</sup>

In this month's American Journal of Physiology Regulatory Integrative and Comparative Physiology, researchers reported that an increase in epinephrine at the start of both moderate- and high-intensity exercise results in an increased cyclic AMP content, which produces an increase in HSL activity in muscle within the first minute of moderate and intense exercise.<sup>33</sup> Increasing catecholamines during exercise is a powerful stimulator of fat metabolism.

### The Rate-limiting Enzyme for Fat Metabolism

How would you like to eat as much fat as you want and never gain weight? Researchers have developed a mouse model where they genetically altered the activity of a key fat-mobilizing hormone called hormone-sensitive lipase (HSL). These mice can eat higher calories and fat and are resistant to weight gain, have a higher body temperature and increased resting energy expenditure compared to normal mice. Even more impressive, HSL-genetically altered mice have white adipose tissue that's 70 percent lower compared to normal mice.<sup>8</sup> HSL is the rate-limiting step for the liberation of fats from adipose tissue and muscle into circulation and ultimately for use as a fuel source during exercise. HSL isn't only regulated by muscle contractions,<sup>3</sup> but also by epinephrine as well.<sup>4,5</sup>

When HSL is increased in muscle, fatty acids are liberated from intramuscular lipids where they're utilized by muscle fibers as an energy source. With regard to muscle contraction, HSL activity appears to be increased by the frequency and duration of exercise as a result of changes in muscle glycogen. Low glycogen stores induced by a low-carbohydrate diet increase HSL activity in muscle.<sup>27</sup> A recent 2006 study in the Journal of Lipid Research reported that stimulation with both muscle contractions and epinephrine can result in significant decreases in reduction in the number as well as the size of lipid droplets.<sup>31</sup> Good old caffeine has also been shown to cause a moderate increase (approximately 17 percent) in muscle HSL (TG) activity.<sup>34</sup> With muscle contractions able to stimulate HSL activity in muscle, it would probably make sense to use high repetition and high volume during precompetition for maximal stimulation of HSL activity during exercise.

### The Male Pregnant Gut Syndrome: A Deficiency in HSL

Catecholamines are the main stimulatory hormones accelerating fat burning. It's well established that catecholamine action in adipose tissue is reduced in obese people. This could be due to three mechanisms that alter adipose tissue function with obesity: 1) increased expression of  $\beta_2$  receptors, which promote fat storage; 2) decreased expression of  $\beta_2$ -adrenoreceptors, which stimulate fat utilization; and 3) decreased expression of HSL activity.

Ever notice that some men have normal lower body phenotypes, but also have the pregnant gut syndrome? It's interesting that when women become pregnant there's an increase in HSL activity in adipose tissue to supply the

baby with a rich source of energy from adipose tissue. In contrast to pregnant females, a reduction in adipose tissue HSL is part of the pregnant gut syndrome in men.

It's been observed that in obese individuals there's a decreased ability of catecholamines to induce fat mobilization in subcutaneous adipose tissue, partly explained by the decreased activity of HSL activity in obese subjects.<sup>9</sup> It's also interesting to note that in obese abdominal fat cells, larger fat cells secrete more HSL than smaller adipose cells.<sup>11</sup> Scientists have hypothesized that the reason for this is the body's fat-burning capacity is stimulated as an adaptive mechanism to limit further increases in fat cell size. It's your body's way of saying, "So fat-ass, since you won't stop eating I'm going to increase your fat-burning enzymes so you won't get any fatter!" Some males are born with a defect in the HSL gene in adipose tissue, which makes them obese. Researchers took adipose tissue samples from men with the defective HSL genetics and found that when they exposed adipose cells to several different drugs (norepinephrine, forskolin, cAMP agents, etc.) to stimulate fat mobilization, there was a 50 percent reduction in the activity of adipose cells to the agents.<sup>10</sup> This suggests that a reduction in adipose tissue HSL activity may be a mechanism whereby people become obese. A decrease in HSL activity may also contribute to age-related increases in fat mass as well. In elderly subjects, there's a decrease in catecholamine-stimulated lipolysis that's due to a decrease in HSL activity, in addition to an increase in insulin resistance.<sup>35</sup>

#### Excess Fat Causes "Epinephrine Resistance"

A trained bodybuilder's adipose tissue is much different than a sedentary person's adipose tissue. A trained individual in bodybuilding has increased fat-burning capacity compared to a sedentary person. Both basal and catecholamine-stimulated fat-burning capacities are higher in fat cells from trained individuals. An increase in fat mass results in an increase in insulin resistance and a reduced sensitivity to catecholamines. For example, young children who are overweight compared to lean children have a decreased triglyceride rate (approximately 30 percent) and are resistant to the actions of epinephrine.<sup>22</sup>

Obese patients tend to have elevated levels of circulating epinephrine, but are "epinephrine resistant," much like obese people are "insulin resistant." The reason for this could be that many obese patients are insulin resistant with high circulating insulin levels. Insulin causes a downregulation of the  $\beta$  receptors (stimulate fat loss) on adipose tissue, which could lead to the epinephrine-resistant effects.<sup>23</sup> Performing resistance exercise can increase insulin sensitivity and catecholamine sensitivity of adipose tissue, causing enhanced fat utilization.

In one experiment, 12 obese men performed three months of dynamic strength training. There was a significant reduction in fat mass with the strength training. Researchers took adipose tissue biopsies before and at the end of the study. In obese subjects, dynamic strength training improved whole-body and adipose tissue insulin sensitivity. The increased insulin sensitivity in adipose tissue also caused increased catecholamine sensitivity to epinephrine. It also increased lipolysis actions of catecholamines in fat cells.

#### Insulin Inhibits HSL Activity

As mentioned previously, insulin inhibits HSL activity. It should be no surprise that patients with type 2 diabetes mellitus (which results in elevated insulin levels) have decreased adipose tissue HSL mRNA and activity.<sup>12</sup> In the December issue of MD, Dr. Dan Gwartney discussed the role of interleukin-6 (IL-6) and its ability to enhance fat oxidation. IL-6 is secreted by adipose and exerts lipolytic effects in adipocytes.<sup>13</sup> Injections of recombinant human IL-6 infusion increase adipose tissue lipolysis in healthy humans, resulting in increased plasma fatty acid mobilization after prolonged (greater than two hours) infusion.<sup>14</sup> Furthermore, acute rh IL-6 administration to patients with type II diabetes was found to increase HSL gene expression in adipose tissue.<sup>12</sup> It may be that IL-6 exerts its effects on fat mobilization by increasing HSL activity, but further research is needed. So now that we've discussed the mechanisms of how HSL is reduced, let's examine how to increase HSL and kick-start fat loss.

#### Epinephrine Increases Fat Metabolism

The physiological role of the sympathetic nervous system (SNS) is a major target of study for modulation of bodyweight and composition. The principle players in the SNS are hormones called catecholamines and the adrenergic receptors (adrenoceptors) upon which they act. Aside from insulin, catecholamines are the primary regulators of fat breakdown in cells by way of stimulation of adrenoceptors on the fat cell membrane. The activation of the sympathetic nervous system is involved in diet-induced thermogenesis, exercise and thermogenic supplements.

It's also been reported that a reduced sympathetic nervous system may be a factor in future weight gain. In humans, catecholamines are potent activators of fat lipolysis, the breakdown of triglycerides from adipose tissue into glycerol and free fatty acids. Triglycerides are the stored form of fat used in energy metabolism. Fat cells are located in subcutaneous adipose tissue (under the skin), in the abdominal cavity surrounding organs (visceral fat) and between the cells of muscle and other tissues (intracellular lipids). Catecholamines (epinephrine and norepinephrine) are powerful stimulators of triglycerides from adipose tissue and exert their effect by binding to  $\beta$ -adrenergic receptors ( $\beta_1$ ,  $\beta_2$  and  $\beta_3$  receptors), stimulating fat oxidation. Additionally, catecholamines prevent fat cell formation by blocking the actions of  $\beta_2$  adrenoceptors on white adipose cells.<sup>21</sup> As stimulation of the  $\beta$ -adrenoceptors can be thought of as the "on" switch for lipolysis, the  $\beta_2$  adrenoceptors can be considered the "off" switch.

### Turning on the Metabolic Switches for Fat Burning

In human subcutaneous adipose tissue, adrenaline has a higher affinity for  $\beta_2$  receptors than for  $\beta$ -adrenergic receptors, suggesting the existence of a role for the  $\beta_2$ -adrenergic pathway in the control of fat lipolysis in humans.<sup>29</sup>  $\beta$ -adrenergic receptors modulate lipolysis during physical exercise and strong, sympathetic nervous system activation while  $\beta_2$  receptors appear to be involved in the modulation of lipolysis at rest.<sup>32</sup> Human fat cells contain three types of  $\beta$ -adrenergic receptors ( $\beta_1$ ,  $\beta_2$  and  $\beta_3$  receptors), but  $\beta_1$  and  $\beta_2$  are the most active in adipose tissue. Some studies suggest that obesity is attributed to an increase in  $\beta_2$  receptors in adipose tissue.  $\beta_2$  receptors could be an important component of the regulation of lipolysis in human fat cells; they're mainly recruited at rest, under weak SNS activation or when specific activation of epinephrine release occurs. As mentioned previously, epinephrine blocks  $\beta_2$  receptors on fat, which should prevent fat storage; however, for some reason obese people may have defects in this pathway. For example, using microdialysis (sticking probes directly into adipose tissue), exercise-induced fat mobilization was investigated in subcutaneous adipose tissue in obese subjects and compared with lean ones, and the effect of  $\beta_2$  receptors blocker. The epinephrine and norepinephrine responses to exercise weren't different in either group.

Interestingly, the changes in fat utilization from adipose tissue were greater in the lean group compared to the obese group during exercise (sixfold lower in obese men). In response to the  $\beta_2$  receptors blocker, lean subjects didn't have any change in lipolysis. However, lipolysis was strongly enhanced in the obese subjects and reached the concentrations found in lean subjects. These findings demonstrate that using an  $\beta_2$  receptors blocker during exercise may enhance sympathetic nervous system activation and enhance lipolysis during exercise in obese men.<sup>30</sup> So based on these findings, taking an  $\beta_2$  receptors antagonist (yohimbine) can enhance fat utilization at rest, while taking a  $\beta$ -receptor agonist before exercise can increase fat utilization during exercise.

The ideal fat-burning combination is one that increased  $\beta$ -adrenergic activity and decreases  $\beta_2$  adrenoceptors activation. The major drugs that contribute to fat loss involve several major pathways via: 1) agents that increase cAMP levels through adenylate cyclase ( $\beta$ -agonists, caffeine, glucagon, forskolin), 2) suppression of adenosine effects in fat cell incubations (caffeine); and 3) the blocking action of  $\beta_2$  adrenoceptors (yohimbine).

### Muscle Contractions Increases HSL Activity

Fat oxidation increases during exercise. The magnitude of the increase and the relative contribution it makes to energy transfer depends on the complex interaction of a number of factors that aren't entirely understood at this time. The intensity of exercise, the duration of exercise, the state of training and nutritional status are important factors influencing fat oxidation.

With intense exercise, epinephrine, norepinephrine and insulin levels are suppressed. Raising exercise intensity from 25 percent of your maximal aerobic capacity to 65 percent of your maximum aerobic capacity appears to be related to increasing levels of epinephrine concentration with a similar rise in HSL activity.<sup>1</sup> It's been reported that muscle contractions by themselves can increase HSL activity in muscle. It's also been reported that electrically induced contractions can increase HSL activity without increased circulating levels of catecholamines. In one experiment, HSL activity in muscle increased significantly within the first minute of contractions, and this increase was maintained for 5 minutes of stimulation.<sup>24</sup>

During exercise, consuming carbohydrates may not be the way to go if you're trying to get ripped. Researchers have found that carbohydrate ingestion during exercise increases plasma insulin and decreases plasma epinephrine concentrations induced by carbohydrate ingestion, which also led to suppression in HSL activity.<sup>26</sup> The results of the study suggest that increases in plasma insulin and suppression of catecholamines will suppress HSL activity.

### High-intensity Exercises Drives Catecholamines and EPOC

Epinephrine and norepinephrine are potent stimulators of energy metabolism during exercise through  $\beta$ -receptor activation in fat and muscle. During dynamic exercise, catecholamines increase linearly with exercise duration and intensity.<sup>16,17</sup> Catecholamines have also been reported to be one of the many regulators of metabolism after exercise (called exercise post-oxygen consumption or EPOC). EPOC consists of two components: a fast component that lasts less than an hour and a slow component that lasts several hours. The presumed metabolic components responsible for the fast component of EPOC are replenishment of O<sub>2</sub> stores in blood and muscle, resynthesis of ATP, creatine, lactate removal and increased ventilation circulation.<sup>19</sup> Mechanisms of the slow EPOC component are more complex. Some of the components responsible for the slow phase include elevated temperature, catecholamines and replenishment of muscle glycogen.

Increasing both GH and catecholamines by increasing exercise intensity may provide a dual effect on fat loss by different mechanisms. Weltman et al.<sup>8</sup> reported a dose-dependent response between lactate and GH levels to low- and high-intensity running protocols. In that study, five treadmill-running intensities were studied at various percentages of the subjects' lactate threshold (LT; 0.25 LT, 0.75 LT, LT, 1.25 LT and 1.75 LT). The results of the study concluded that the degree of fat utilization post-exercise was directly related to the increases in GH and epinephrine secretion during exercise.<sup>36</sup> Additionally, the degree of fat utilization during the recovery period was related to the exercise intensity level. High-intensity resistance exercise leads to a rapid increase in catecholamines, which may enhance EPOC. In one study, researchers reported that when subjects were given a drug that suppresses catecholamines during exercise, there was no increase in metabolism or EPOC after exercise.<sup>18</sup> Bureson et al.<sup>25</sup> compared EPOC in response to resistance exercise and treadmill exercise performed at the same caloric energy expenditure. Results of the study concluded that resistance exercise led to a significantly higher EPOC than the treadmill due to greater increases in heart rate, lactate and fat utilization during resistance exercise. EPOC was approximately 50 percent higher than the treadmill protocol. Another possible mechanism for enhanced fat loss with epinephrine is increased blood flow to adipose tissue. In last month's research update column, it was reported that an increase in blood flow during exercise may enhance fat mobilization. Simonsen et al. reported that blood flow and O<sub>2</sub> uptake increased in skeletal muscle and adipose tissue after infusions of adrenaline, but the largest contributor of thermogenesis was from adrenaline's action on skeletal muscle.<sup>20</sup>

### Crank Up those Catecholamines for Fat Loss

It's been known for many years that white adipose tissue is innervated (connected by nerves) by the sympathetic nervous system. Taking drugs that increase catecholamines stimulate the sympathetic nervous system, which is why, in addition to feeling a little jittery, there's increased fat mobilization occurring. Every bodybuilder knows that getting the glutes ripped is much harder than getting a six-pack. The reason is that abdominal adipose tissue is rich in  $\beta$  receptors and is more responsive to  $\beta$  agonists (catecholamines, clenbuterol) than adipose tissue from the glutes.<sup>7</sup> The stimulation of the sympathetic nervous system leads to decreases in fat cell number.

If you cut the nerves to adipose tissue or block the actions of catecholamines, there's an increase in fat cell size.<sup>6</sup> When you gain fat mass, adipose tissue fills with lipids and gets to a critical size, then precursor cells are stimulated to make new adipose tissue. In one study, within a week of reduced sympathetic stimulation there was an increased number of preadipocytes and also an increase in the number of mature adipocytes. Interesting, the reduction of sympathetic nervous activity didn't affect any metabolic parameter such as glucose metabolism, LPL (fat storage enzyme) or HSL activity. What this means is that you have to keep your sympathetic nervous system fired up to prevent future weight gain and lose body fat.

On adipose cells, drugs that stimulate  $\beta$  receptors enhance fat loss. Most thermogenic supplements on the market target fat cells by stimulating the production of catecholamines, norepinephrine and epinephrine. Researchers have discovered that if adipose cells are exposed to norepinephrine, fat cells won't proliferate and form new fat cells. But if the fat cells are exposed to drugs like propranolol, which blocks the actions of norepinephrine, new fat cells are created.<sup>15</sup>

Trying to get ripped for a competition or for personal goals can be an extremely difficult feat to accomplish. Everyone wants to have that ripped look where your skin is paper-thin and veins pop out everywhere, but achieving that look takes an extreme amount of willpower, guts and dedication in the gym. Your body doesn't understand the mind of a bodybuilder so it thinks, "I'm starving, there's a drought, calories are insufficient, I'm losing body fat...slow down all metabolic systems until body fat returns to normal." Your own body tries to sabotage your competition goals of losing fat by slowing down your metabolism and breaking down lean muscle mass as an energy source. During a calorie-restricted diet the sympathetic nervous system is decreased. This decrease in sympathetic nerve activity results in a reduction in lower metabolic rate, thus conserving reserves of nutrients. During fasting or calorie restriction, adipose tissue readily releases stored energy. That's where thermogenic supplements come in handy because they increase sympathetic nervous system activity and restore sympathetic tone.

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