



## **Think Muscle Newsletter #27**

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The Think Muscle Newsletter publishes the latest news and research on exercise physiology, dietary supplements, performance enhancement, lifestyle management, health & nutrition, and bodybuilding & fitness. The newsletter is dedicated to providing accurate and unbiased scientifically based information.

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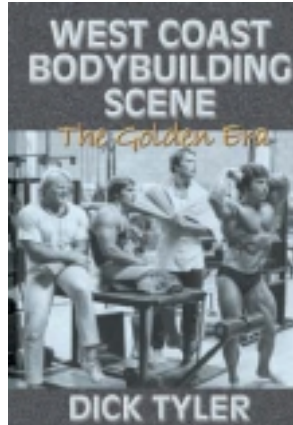
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### **Message from the Editor in Chief:**

We have some great announcements this month. First I want to thank my good friends Dave and Laree Draper for sharing a fantastic book with me, Dick Tyler's new book, "West Coast Bodybuilding Scene. The Golden Era". Who is this book for? Everyone who loves bodybuilding. Reading this book is like sitting down and hearing all the stories from the golden era of bodybuilding straight from the guys who lived it. In fact, that's exactly what this book is. It is a wonderful experience and it leaves you feeling uplifted. In a day when the bodybuilding scene is full of tuff-guy attitude, competitive isolation, name calling, and poor sportsmanship, this book breathes new hope into the possibilities of what bodybuilding once was and could be again.

The book contains 160 rare and candid photos of all the big names from that era including, Arnold, big Mike Katz, Frank Zane, Dave Draper, Sergio Oliva, Steve Reeves, Reg Park, Franco Columbu, Ed Corney, Vince Gironda, Rick Wayne, Larry Scott, Bill Pearl, and many, many more. If you love bodybuilding, or are even just curious about what it used to be like before Synthol, buy this book.

Head over to [DaveDraper.com](http://DaveDraper.com) and tell him “bryan” sent you. You wont be sorry.



We've also got a new eBook by Charles Ridgely. Charles' previous articles have been so successful that we decided to offer an entire eBook written by Charles outlining how to set up a training routine specifically to build muscle as fast as possible. This is some GREAT info. You don't want to miss it. The following is just a sample of what you'll learn from the book:

- How to select the most Efficient Mass Building Exercises
- How to select the right Volume to Maximize Gains
- How to Prevent Fatigue from Destroying your Progress
- How to use a Constant Workload throughout your Entire Cycle
- How to use Drop Sets Without Reducing Volume

These are just a few of the things you will learn. There is much, much more in the information-packed eBook. It is detailed while keeping your attention. It's scientific, yet easy to read and understand.

To learn more about Charles Ridgely's new eBook click [HERE](#). To learn more about the author, click [HERE](#).

-bryan

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**Editor's Note:** *So we already know that the FDA doesn't like ephedra. Never mind the politics involved, it is simply a part of their agenda to get herbs that actually do something to our bodies off the shelves, and according to the most recent ruling posted February 6th the sale of dietary supplements containing ephedrine alkaloids (ephedra) is officially prohibited because "such supplements present an unreasonable risk of illness or injury." So in honor of "the end of ephedra", I thought I would reprint the following article, "Pharmacological Approaches to Fat Loss: etc, etc" because it speaks directly at an issue that no one seems willing to talk about. And that is this, if an herbal supplement*

*were to actually work, the FDA will pull it off the shelves because if it has a demonstrable physiological effect, it is in fact a drug. That leaves us in an industry where effective herbal supplements are illegal to sell over the counter, and those who do sell herbal supplements ensure that they don't actually work because otherwise they would face near fatal liability risks. So without further adieu, here it is.*

## **Pharmacological Approaches to Fat Loss: Targeting Beta-Adrenergic Receptors** by Bryan Haycock M.Sc.

### **Introduction**

There are dozens of products on the market that claim to be "fat burners". There is such a demand for effective supplements and drugs to "burn fat" it has driven diet drugs and supplements into a big money industry. Amidst the clamor to try the latest drug to meet FDA approval an ancient and common remedy has been widely overlooked by the general public. Bodybuilders, on the other hand, have been using it widely for some time. What is this "ancient Chinese secret"? Ephedra of course.

Ephedra has been used in China for at least two thousand years. The most familiar form of Ephedra is the Chinese herb ma huang. Its active ingredient is ephedrine. Ephedrine is an alkaloid that acts as a sympathomimetic and has thermogenic and anorectic properties. It is commonly used as a smooth muscle dilator in the treatment of asthma, bronchitis and nasal congestion. So what does this have to do with fat loss you ask? In order to properly use ephedrine as a tool for fat loss, its mechanism of action needs to be understood. Hereafter we will explore the possible mechanism of ephedrine's thermogenic/lipolytic effects and it's potential as a fat loss agent. Then we'll take a look at human studies involving the use of ephedrine and a couple of additional compounds that seem to enhance ephedrine's fat reducing properties.

As a sympathomimetic, ephedrine acts to stimulate the sympathetic nervous system. It does this by causing pre-synaptic nerve terminals to release norepinephrine, or what is commonly called noradrenaline (NA), into the synaptic space. It also has the effect of increasing circulating adrenaline (Adr), the body's chief beta-2 agonist. Noradrenaline, once released into the synaptic space, interacts with adrenergic receptors on the surface of adipocytes (also known as plain old fat cells). This initiates a sequence of events within the adipocyte that increases lipolysis.

### **The Process of Lipolysis**

Lipolysis is the process of breaking down triglycerides into glycerol and fatty acids. This process is dependent on an enzyme called hormone sensitive lipase (HSL). Activating HSL is the last step of a chain of intracellular reactions that make up the second messenger system. It is called a second messenger system because NA acts as the first messenger and Cyclic Adenosine Monophosphate (cAMP) acts as the second.

The entire chain of events that occurs after administration of ephedrine goes as follows: 1) Ephedrine stimulates the release of NA from sympathetic nerve endings. 2) NA then binds to adrenergic receptors on the surface of all tissues that contain these receptors. Adipose tissue and skeletal muscle have abundant adrenoceptors on their surface. 3) As NA binds to beta-adrenergic receptors, stimulatory guanine nucleotide regulatory proteins(Gs-proteins) within the cell membrane activate the enzyme adenylate cyclase. 4) Adenylate cyclase then converts ATP into 3'-5' cAMP. 5) cAMP then binds to the regulatory subunit of protein kinase A. 6) Once bound by cAMP, protein kinase A releases its catalytic subunit. 7) The catalytic subunit phosphorylates HSL, thus transforming it into the active form, HSL-P. 8) HSL-P then catalyzes a three step hydrolysis reaction to reduce triglycerides into glycerol and fatty acids.

### **Step One**

Lets go back and take a closer look at these steps. In Step One, it is important to realize that ephedrine does not interact directly with adrenergic receptors. It is through its effects on the release of NA that ephedrine increases adrenergic activity.<sup>1</sup> This was determined by examining the effects of ephedrine on adipose tissue with intact sympathetic nerves or without. Once the nerves had been removed, the ephedrine had little, if any, effect at concentrations typical of oral administration. This has a number of disadvantages as well as some advantages. First the disadvantages; Ephedrine is called a non-specific adrenergic agonist because through the release of NA, it has an effect on more than one class of adrenergic receptor. NA can bind with alpha and beta-receptors alike. This produces a generalized effect because alpha-receptors, particularly alpha-2 receptors, decrease lipolysis and beta-receptors increase lipolysis. The overall lipolytic effect of ephedrine is determined by the ratio of alpha and beta-receptors on each particular adipocyte.

Another disadvantage is potency. Non-specific agonists have a far weaker effect on beta-receptors than specific beta agonists such as epinephrine, Albuterol or Clenbuterol. This is obvious once you look at the mechanism. Clenbuterol will interact directly with the beta-receptor with or without sympathetic activity in a dose dependent manner. Ephedrine is dependent on the release of noradrenaline to do the job and is only dose dependent up to a point. Continuing with the problem of potency, it is well known that the selective beta-agonist Clenbuterol, has potent anabolic activities in animal studies when used in dosages equal to about 4 mg per kg body weight for a period lasting approximately 10 days. This effect is dependent on long and steady activation of the receptor by the agonist.<sup>27</sup> Clenbuterol is the most effective anabolic beta-agonist by virtue of it's long half-life (34-35 hours). In contrast, the half-life of ephedrine is only about 3-4 hours. Contributing to Clenbuterol's long duration of action is the fact that it does not undergo first-pass metabolism like most other beta-agonists. The exception being the structurally related beta-agonist Mabutrol which has a half-life of 20-30 hours.<sup>28</sup> The vast majority of beta-agonists have half-lives of only up to 6 hours.<sup>29</sup> It should be noted however that ephedrine does show some anabolic action even with such a short half-life.<sup>14</sup> This relationship between anabolic activity and half-life of beta agonists would indicate that all beta-agonists have the potential for anabolic activity, whether or not this translates into noticeable gains in muscle size depends on how long the active form of the

drug interacts with the beta receptor on muscle tissue. The truthfulness of this statement was demonstrated in a study by Choo<sup>27</sup> which took the beta agonist Salbutamol which has not been shown to produce anabolic effects and compared it with Clenbuterol during continuous infusion in animals. Under these conditions the half-life of the substance is not a factor and the drug can bypass the liver, avoiding first pass degradation. During continuous infusion Salbutamol produced equal anabolic effects in muscle tissue as clenbuterol.

The assertion that beta-agonists such as clenbuterol and ephedrine have no anabolic effects in humans is premature. There is a large difference in the dosages normally given to animals (4 mg/kg) as compared to humans (up to 40 µg/day). Slow release Salbutamol has been shown to increase voluntary muscle strength in healthy men.<sup>30,31</sup> Research showing preservation of lean tissue and significantly improved protein deposition in response to treatment with ephedrine during caloric restriction indicates that beta-agonists are exerting an anabolic effect in humans.<sup>14</sup> More research is needed to determine the extent and most efficacious way to administer these compounds to elicit an anabolic effect in man.

The advantages to using a non-specific beta agonist are two fold. First, although ephedrine binds to other adrenergic receptors, it seems that the most beneficial adrenergic effects, such as thermogenesis, are actually enhanced after chronic use.<sup>2,3</sup> This may be explained by chronic stimulation of alpha receptors by NA and Adr. This chronic alpha-adrenergic stimulation may activate thyroxin deiodinases leading to the peripheral conversion of T4 to T3. In fact, significant increases in the ratio of T3 to T4 have been shown to occur after 4 weeks of chronic treatment of ephedrine.<sup>2</sup> Increased levels of T3 can sensitize adrenergic sensitivity to NA and Adr. It should be noted that the same study showed that this ratio decreased below initial values after week 12 of treatment.

Another explanation of its increased efficacy after chronic treatment is its interaction with the beta-3 receptor. Although the exact structure and function of this receptor is still being explored, it is almost certain that at least 40% of ephedrine's actions are due to its effect on beta-3 receptors.<sup>6</sup> A study done to explore this used a beta-1 and beta-2 antagonist called nadolol. Nadolol was administered concomitantly with ephedrine to healthy volunteers. Nadolol completely inhibited changes in heart rate and plasma glucose due to its blockade of beta-1 and beta-2 receptors. However, the thermogenic effect of ephedrine was still at about 43%. This means that at least 40% of ephedrine's thermogenic effects are due to beta-3 activation. This alone does not explain ephedrine's effects after long-term use. What does explain this is the desensitization properties of the beta-3 receptor. Beta-3 receptors lack most of the structural properties that are responsible for beta-2 receptor desensitization.<sup>7</sup> So even after ephedrine fails to have significant effects on the beta-2 receptor, it would potentially continue to stimulate adenylate cyclase activity by virtue of its effect on the beta-3 receptor.

There seems to be an impression that research with "selective" beta 3-agonists has not been promising. This may stem from earlier research done before second generation beta3-agonists were available. Rosenbaum, using a non-selective beta agonist,

isoproterenol did early research showing questionable results. (32) Newer more potent compounds such as CL316,243 and CGP12177A (beta 1- and beta 2-AR antagonist, beta 3-AR agonist) are currently undergoing safety and efficacy testing in primates. Initial indicators appear to be promising with these newer "selective" beta 3-adrenergic agonists.<sup>33,34,35</sup> This avenue of pharmacologic treatment of obesity and diabetes which includes some benefit to bodybuilders, has great potential keeping in mind that activation of the beta 3-adrenergic receptor not only increases the production of thermogenic uncoupling proteins in fat and muscle, increases brown adipose tissue differentiation and perhaps proliferation, but also increases non-oxidative glucose disposal in peripheral tissues including muscle.<sup>36,37</sup>

Concerning beta-2 receptor desensitization, the fact that ephedrine is less potent than specific beta-2 agonists decreases the amount of beta-receptor down regulation subsequent to chronic treatment. Chronic stimulation of beta2-adrenergic receptors causes a decrease in the sensitivity of tissues to beta agonists. This decrease in sensitivity involves either homologous desensitization, where the receptor's active site is translocated within the cell membrane so that the binding site is no longer positioned extra cellularly, or it involves heterologous desensitization, where the receptor is phosphorylated rendering it incapable of participating in the second messenger system.<sup>4</sup> Receptor desensitization is a complex process with several different mechanisms. This complexity allows for more control of hormone signaling. As a general rule, the more potent the stimulus, the greater and more rapid the desensitization. Clenbuterol elicits a strong thermogenic effect but only for a short period of about two weeks. The usual practice is to increase the dosage at this time. Unfortunately, this only increases desensitization further and makes catecholamine-stimulated lipolysis virtually come to a halt. Ephedrine, on the other hand, elicits a more mild response but it's thermogenic effects can be seen up to 20 weeks.<sup>5</sup>

In summary, the advantages of using a non-selective beta agonist such as ephedrine are, it has beneficial effects on thyroxin deiodinase activity thereby increasing the T3/T4 ratio, it's effect on beta-3 receptors, and it's tendency not to cause extreme desensitization of beta-2 receptors. All of this lends to the fact that the thermogenic affects of ephedrine are enhanced after chronic treatment.

## **Step Two**

Going back to the steps of ephedrine stimulated lipolysis, in step two we see that NA binds to the adrenergic receptors on the surface of tissues that contain them. By looking at all of ephedrine's side effects you get an idea of what tissues contain adrenergic receptors. In the beginning you get an increase in heart rate. This is because beta-adrenergic stimulation of the heart increases its rate, force and frequency of contraction. It also causes vasoconstriction, which leads to a decrease in blood flow to most organs including skin, eyes, kidney and gastrointestinal tract. In most all of these tissues, the sympathetic response is designed to help the body respond to perceived emergencies. You may have heard of the "flight or flight" response. By reducing blood flow to the viscera, more blood is available to be diverted to working muscles. The heart pumps more blood, the eyes dilate, the GI tract slows motility (no time for potty breaks), and

attention, or alertness, is enhanced allowing the animal (or person) to be focused on escape or capture and less focused or perceptive of pain.

Muscle and fat tissue also contain adrenergic receptors. In fat tissue there are gender specific ratios of beta to alpha-receptors on various parts of the body. This gives rise to the familiar male (android) and female (gynoid) fat patterning. Females tend to resist lipolysis on their hips, buttocks and thighs, whereas men tend to resist lipolysis on their abdomen and oblique region. This is due to a preponderance of antilipolytic alpha-receptors on the cells in these regions. Our goal in using beta agonists is to increase lipolysis in fat tissue. The effect of both alpha and beta receptors being located on fat tissue allows for more control of lipolysis. In essence it gives the body both an accelerator and a brake.

In muscle tissue, beta-adrenergic activation seems to stimulate protein synthesis rates through the same second messenger system that stimulates lipolysis in fat tissue. In studies measuring body composition as well as weight loss, ephedrine has shown the ability to prevent lean tissue loss.<sup>8</sup> In a small double blind study lasting only eight weeks, two groups of obese women were given either 20 mg ephedrine with 200 mg caffeine (E+C) or placebo (P). After eight weeks weight-loss was not significantly different between the groups, but the E + C group lost 4.5 kg more body fat and 2.8 kg less fat-free mass (FFM). That is a difference of more than six pounds in eight weeks. The expected decrease in 24-hour energy expenditure (EE) seen in the P group was 10% at day 1 and 13% at day 56, but was only 7% and 8% in the treated group. The higher EE in the E +C group was entirely covered by fat oxidation. People have speculated that beta-agonists were anticatabolic. This is disproved somewhat by the fact that 3-methylhistidine, which is used as an index for skeletal muscle breakdown, was not altered by ephedrine administration yet nitrogen balance was significantly improved during very low calorie dieting.<sup>9</sup> So although muscle tissue was being broken down at the same rate, more lean tissue was being produced.

### **Step Three**

In step three we see that G proteins play a key role in regulating fat metabolism in adipocytes. In this step NA binds to the adrenergic beta-receptor activating stimulatory G proteins (Gs). These G proteins then go on to activate adenylate cyclase. When alpha-receptors are activated, inhibitory G proteins (Gi) are activated and adenylate cyclase is not activated. This puts a halt to cAMP formation and hence a halt to lipolysis. G proteins are also involved, at least in part, in receptor desensitization. If you recall it was briefly mentioned that one of the ways beta-receptors are desensitized is called heterologous desensitization. This involves uncoupling of the receptor from stimulatory G proteins. This has the effect of stopping the message from getting any further than the receptor itself. Other mechanisms are also involved in heterologous desensitization but we will not go into it any further in this article.

### **Step Four**

In step four, ATP is converted into cAMP and inorganic phosphate (PPi) by the enzyme adenylate cyclase. cAMP contains a single phosphate group that is attached both to the 3'

carbon and the 5' carbon of the sugar ribose. This is why it is called "cyclic" AMP. Neither PPi nor cAMP is allowed to exist in these forms for very long. The PPi that is formed when ATP is converted to cAMP is hydrolyzed by inorganic pyrophosphatase to form two Pi. 3'-5'-cAMP is also quickly rendered inactive by the enzyme known as cyclic AMP phosphodiesterase (PDE). PDE breaks the bond between the 3' carbon of ribose and the phosphate group thus making 5'-cAMP. 5'-cAMP is inactive and does not bind to protein kinase A and does not lead to the activation of HSL. This is the first feedback inhibition mechanism we've discussed so far but there are others that act to shut off the original signal and slow lipolysis. As we will see later, feedback inhibition is one area we can target to increase the effectiveness of ephedrine.

### **Steps 5-8**

In steps five, six, seven and eight cAMP binds to the regulatory subunit of protein kinase A. This binding releases the catalytic subunit of protein kinase-A which then phosphorylates HSL. Once HSL is phosphorylated it can then participate in the actual process of lipolysis. This brings us to the final step. HSL-P catalyzes the breakdown of triglycerides in three steps. Each of the three steps removes one fatty acid until all that is left is glycerol and three fatty acids. Now, just because you have disassembled your stored fat does not mean it is gone for good. If you do not burn this fat it will simply be re-esterified and turned back into triacylglycerol (storable triglycerides). This process of lipolysis and lipogenesis using the same fatty acids is called a "futile cycle" for obvious reasons.

### **Feedback Inhibition**

The process of lipolysis is under feedback control which attenuates lipolysis at several levels. The chemicals involved in attenuating the effectiveness of ephedrine are phosphodiesterases, prostaglandins, and adenosine. As you might expect, these are the chemicals that we will try to minimize while using ephedrine as a fat loss agent.

### **Phosphodiesterases (PDE's)**

As with most biologically active molecules, cAMP must be rapidly inactivated in order to serve as a controllable second messenger in response to hormone activation. In target cells, phosphodiesterases (PDE's) act to hydrolyze cAMP into inactive fragments. Because of PDE's, the stimulatory effect of norepinephrine and epinephrine, which use cAMP as a second messenger, depends on continuous regeneration of cAMP and thus depends on the level of secretion of norepinephrine and epinephrine. Although it is our goal to overcome this feedback mechanism, I must emphasize its importance in physiological systems. A second messenger system with no PDE's is a messenger system that cannot be shut off. It would be like not being able to let off of the accelerator on your car once you pushed it to the floor. Feedback inhibition is about control. A switch is worthless if it cannot be turned off as well as on.

### **Prostaglandins**

Prostaglandins are produced in virtually all tissues of the body. Prostaglandins are abbreviated PG, with additional letters and numbers indicating their structure. For example, PGE2 means that it is a prostaglandin of the "E" type which designates it as a



beta-hydroxyketone. The number indicates how many double bonds it has, in our case, two. Prostaglandins (PG) come in many varieties and participate in a number of physiological responses. The ones you are probably most familiar with are pain sensitivity and inflammation. Prostaglandins are made from 20 carbon fatty acids such as arachidonic acid. In the first step of the conversion of arachidonic acid into prostaglandins, the enzyme cyclooxygenase oxygenates arachidonic acid producing the prostaglandin PGG<sub>2</sub>. Most all of your non-steroidal anti-inflammatory agents like aspirin, ibuprofen, naproxin sodium and others, work by inhibiting cyclooxygenase activity which then diminishes prostaglandin synthesis. In response to beta-adrenergic stimulation, E<sub>2</sub> prostaglandins are released into the synaptic space. These prostaglandins have receptors coupled to inhibitory G proteins (G<sub>i</sub>). These G<sub>i</sub>'s then decrease adenylate cyclase activity and thus decrease cAMP concentrations in the cell.<sup>10</sup> So the idea of using prostaglandin inhibitors seems a logical adjunct to ephedrine treatment for fat loss.

### **Adenosine**

Adenosine is somewhat more of a complicated feedback molecule that has dual roles as both an activator as well an inhibitor. Adenosine is a purine nucleoside and our concern with it is its ability to inhibit cAMP accumulation. When a fat cell is stimulated by a beta adrenergic agonist such as norepinephrine, the cell produces adenosine. Adenosine then interacts with its receptor coupled to regulatory G proteins (G<sub>i</sub>) which inhibits adenylate cyclase activity, and thus prevent the accumulation of cAMP.<sup>11</sup> It's effects in the synaptic space are similar to those of alpha-2 agonists due to receptors coupled to inhibitory G proteins. Got all that? The bottom line is that when using sympathomimetics such as ephedrine, you activate regulatory mechanisms involving adenosine.

It should be apparent by now that the reason we are talking so much about negative feedback in response to adrenergic stimulation is because we have a plan to attenuate these responses. This is where we introduce methylxanthines and prostaglandin inhibitors.

Caffeine is a methylxanthine. Caffeine possesses the ability to inhibit phosphodiesterases within the cell and has even been shown to have the ability to prevent some re-uptake of norepinephrine.<sup>12</sup> Another property of caffeine is adenosine receptor blockade. There is some question as to whether oral caffeine ingestion actually inhibits phosphodiesterases but it does seem to inhibit adenosine action in vivo. Both of these properties make it potentially useful as an adjunct to ephedrine to enhance fat loss.

Aspirin, as discussed earlier, is a prostaglandin inhibitor. It works by inhibiting cyclooxygenase activity. Because certain prostaglandins act to inhibit lipolysis and are produced in response to adrenergic stimulation, prostaglandin inhibitors have the potential to enhance ephedrine's actions on fat loss.

Now that we have discussed the mechanism of lipolysis and how ephedrine, caffeine, and aspirin might enhance lipolytic activity in fat cells, let us take a look at what studies have shown concerning the effectiveness of these compounds in combination.

### The Research Looking at Ephedrine / Caffeine / Aspirin and Weight Loss

In a double blind, placebo controlled study, caffeine alone was found to produce thermogenic and lipolytic effects in humans in a dose dependent manner.<sup>13</sup> These researchers found that the thermic effect was significantly correlated to plasma triglyceride levels, plasma lactate concentrations and vascular tone. The authors attribute the increase in lactate, triglycerides and enhanced vascular tone to the increased metabolic rate. In a study using caffeine and ephedrine researchers found no difference in the total amount of body weight that was lost over 8 weeks.<sup>14</sup> However, they did find significant differences in the source of the weight that was lost. Fourteen obese women were treated with a ~1000 kcal diet and either E + C (20mg E + 200mg C) or placebo three times per day for 8 weeks in a double-blind study. The total weight-lost was not different between groups, but the E + C group lost ~10 lbs. more body fat and ~6 pounds less fat-free mass. This is encouraging news for any bodybuilder. You must bear in mind, however, that these were obese women. Studies have shown that nutrient partitioning is determined in part by your % fat before you diet or before you over eat.<sup>15,16</sup> Nevertheless, that is a tremendous effect on fat loss and muscle retention.

Some research has shown that the anti obesity effects of ephedrine are not significant unless caffeine is used in conjunction with ephedrine.<sup>17</sup> In fact, most studies exploring the thermogenic effects of ephedrine also look at caffeine as a synergist. In a randomized, placebo-controlled, double blind study, 180 obese patients were treated by a calorie restricted diet and either an ephedrine/caffeine combination (20mg/200mg), ephedrine (20 mg), caffeine (200 mg) or placebo three times a day for 24 weeks. Average weight loss was significantly greater with the combination than with placebo from week 8 to week 24. Weight loss in both the ephedrine only and the caffeine only groups was similar to that of the placebo group. The authors conclude that the effect of either caffeine or ephedrine alone is ineffective in inducing significant weight loss.<sup>18,19</sup> Not only is it necessary to combine ephedrine and caffeine to elicit a significant fat burning effect, the two compounds exhibit synergistic effects in certain ratios. By comparing different ratios of ephedrine and caffeine, it was found that 20 mg of ephedrine and 200 mg of caffeine exhibited a supra additive or synergistic effect while no other ratio did.<sup>20</sup> This means that ephedrine and caffeine taken in a 1:10 ratio (20 mg ephedrine : 200 mg caffeine) creates effects greater than the sum of the two drugs added together. In other words, 2 + 2 = 5 in this ratio!

So what about aspirin? There has not been as much research done on aspirin in this "stack". Looking first at animals, chronic administration of aspirin to obese mice had no effect on weight loss. Ephedrine given to these mice increased energy expenditure by 9% and reduced body weight and body fat by 18% and 50%, respectively: obesity however, was reduced but the mice still were not comparable to normal controls. When given both ephedrine and aspirin, increase in energy expenditure found during treatment with ephedrine alone was doubled, and the obese group lost greater than 75% of body fat, and obesity essentially was reversed.<sup>21</sup> The research done on humans has also been somewhat promising. The effect of ephedrine (30 mg) and aspirin (300 mg) on the acute thermogenic response to a liquid meal (250 kcal) was investigated in lean and obese women (n = 10 each group). Resting metabolic rate (RMR) was measured prior to each of

the following treatments: meal only (M), meal plus ephedrine (ME) or meal plus ephedrine and aspirin (MEA). The postprandial rise in metabolic rate, following the MEA treatment compared to the ME, was significantly greater for the obese group but not the lean. It was concluded that aspirin potentiates the stimulatory effect of ephedrine on the thermogenic response to a meal in obese but not lean women.<sup>22</sup> One weakness of this study was the small number of subjects. Nevertheless, these findings are not all that surprising considering the fact that decreased thermic effect of food is often seen in the obese.<sup>23</sup> In another study,<sup>24</sup> a mixture of ephedrine (75-150mg), caffeine (150mg) and aspirin (330mg), in divided premeal doses, were investigated in 24 obese participants in a randomized double blind placebo-controlled trial. Energy intake was not restricted. Overall weight loss over 8 weeks was 2.2kg for ECA vs. 0.7 kg for placebo. Eight of 13 placebo subjects returned 5 months later and received ECA in an unblinded crossover. After 8 weeks, mean weight loss with ECA was 3.2 kg vs 1.3 kg for placebo. Six subjects continued on ECA for 7 to 26 months. Notice that there is no concern about receptor down regulation or trying useless dosing schedules like "2 weeks on and 2 weeks off". Anyway, after 5 months on ECA, average weight loss in five of these was 5.2 kg compared to 0.03 kg gained during 5 months between studies with no intervention. The sixth subject lost 66 kg over 13 months by self-imposed caloric restriction. This sixth subject lost an amazing 150 lbs. By exercising and cutting calories! Can you believe they didn't encourage the other subjects to diet and exercise? In all studies, no significant changes in heart rate, blood pressure, blood glucose, insulin, and cholesterol levels, and no differences in the frequency of side effects were found. ECA in these participants caused significant weight loss even without caloric restriction. The authors of this study go on to comment that the ECA combination might be more effective with caloric restriction. That kind of conservatism cracks me up!

In one study that really got my attention they compared the effects of ephedrine against the popular prescription drug dexfenfluramine that goes under the brand name Redux.<sup>25</sup> In order to compare the efficacy and safety of these two anorectic drugs, 103 patients with 20-80% overweight were included in a 15-week double-blind study in general practice. Patients were randomized to either 15 mg DF twice daily (n = 53), or 20 mg/200 mg ephedrine/caffeine three times a day (n = 50). Subjects went on a 1200 kcal/day diet during the treatment period. After 15 weeks of treatment, the DF group (n = 43) had lost ~15 +/- 9.46 lbs. and the EC group (n = 38) had lost ~18.3 +/- 11.5 lbs. In the subgroup of patients with BMI > or = 30 kg/m<sup>2</sup> (n = 59), the mean weight loss was 7.0 +/- 4.2 kg in the DF group (n = 29) and 9.0 +/- 5.3 kg in the EC group (n = 30), P < 0.05. Both systolic and diastolic blood pressures were reduced similarly during both treatments. Central nervous system side-effects, especially agitation, were more pronounced in the EC group, whereas gastro-intestinal symptoms were more frequent in the DF group. The side-effects declined markedly during the first month of treatment in both groups. Not only was the weight loss with ephedrine and caffeine comparable to Redux, it was probably greater! This study did not look at body composition but I bet it would have shown the E/C combination as superior in retaining lean mass.

You may have noticed that most of the studies I have cited have used obese subjects. This is understandable considering it is the obese population that is targeted for drug therapy.

It should be noted however, that the thermogenic properties of an ephedrine/caffeine mixture are also demonstrated in lean subjects as well.<sup>26</sup> You should expect increased effectiveness in obese people because of underlying problems with metabolic rate. Anytime you increase the metabolic rate in obese individuals you will see large changes in energy expenditure because the relative increase in metabolic rate is greater than in lean individuals.

### **In Conclusion**

Now let us put all of this together. First, what do we know; Ephedrine stimulates lipolysis by increasing noradrenaline (NA) release from sympathetic nerve terminals. This increase in noradrenaline activates adrenergic receptors, which increases cAMP levels in fat cells and muscle cells. This has the effect of increasing lipolysis in fat cells and increasing protein synthesis in muscle tissue. Negative feedback mechanisms are activated as well, and involve the production of phosphodiesterases, adenosine, and prostaglandins. Caffeine has the ability to inhibit phosphodiesterase activity and interfere with the adenosine receptor. This combined with its ability to prevent some NA re-uptake increase the effectiveness of ephedrine in a synergistic fashion.<sup>12</sup> Aspirin has been shown to increase the effectiveness of ephedrine in some individuals presumably by its actions as a prostaglandin inhibitor.

Maximum effectiveness is achieved when taking 20 mg ephedrine with 200 mg caffeine and 300 mg aspirin three times a day about one half hour before meals. Common side effects are associated with its sympathetic activity namely, anorexia, initial rise in blood pressure, initial tachycardia, slowed GI motility (constipation), insomnia, agitation, anxiety, nervousness and depression- like withdrawal symptoms. Most all of these symptoms exhibit tachyphylaxis after about 4-6 weeks. Thermogenic activity seems to last upwards of 20 weeks due to its low desensitization properties and beta-3 affinity. About 75% of ephedrine's effects on weight loss in the obese are due to appetite control.

Anyone considering taking ephedrine, caffeine and aspirin should educate themselves first about the potential side effects. Individuals with pre-existing high blood pressure should not use sympathomimetics such as ephedrine. When taking herbal forms of ephedrine, be sure you understand just how much is in each serving. Be aware that herbal preparations are standardized but you still can not be sure exactly how much you are taking with each capsule.

The future of fat loss for the bodybuilder will not, or should not, focus on appetite alone. It should focus on enhancing lipolysis and overcoming the regulatory mechanisms designed to prevent rapid and substantial fat loss. Ephedrine, caffeine and aspirin are effective but are still limited by inhibitory mechanisms built into our physiology. Gaining better understanding of the mechanisms involved in lipolysis and gaining funding for appropriate research is critical. The pharmaceutical industry already recognizes the profitability of weight loss agents unfortunately they are focusing at present on appetite control. Perhaps as these strategies continue to fail they will focus more on body composition instead of just "body weight". When this happens you can be sure that adrenergic receptors and the second messenger system will be the focus of attention.

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## **Stretching the truth:**

Can the benefits of stretching towards injury prevention be proven?

**Title:** The Impact of Stretching on Sports Injury Risk: A Systematic Review of the Literature

**Researchers:** THACKER, STEPHEN B.; GILCHRIST, JULIE; STROUP, DONNA F.; KIMSEY, C. DEXTER JR.

**Institution:** Centers for Disease Control and Prevention

**Source:** *Med. Sci. Sports Exerc.*, Vol. 36, No. 3, pp. 371–378, 2004.

**Summary:** We conducted a systematic review to assess the evidence for the effectiveness of stretching as a tool to prevent injuries in sports and to make recommendations for research and prevention.

**Methods:** Without language limitations, we searched electronic data bases, including MEDLINE (1966–2002), Current Contents (1997–2002), Biomedical Collection (1993–1999), the Cochrane Library, and SPORTDiscus, and then identified citations from papers retrieved and contacted experts in the field. Meta-analysis was limited to randomized trials or cohort studies for interventions that included stretching. Studies were excluded that lacked controls, in which stretching could not be assessed independently, or where studies did not include subjects in sporting or fitness activities. One author screened all articles initially. Six of 361 identified articles compared stretching with other methods to prevent injury. Data were abstracted by one author and then reviewed independently by three others. Three authors using a previously standardized instrument assessed data quality independently, and reviewers met to reconcile substantive differences in interpretation. We calculated weighted pooled odds

ratios based on an intention-to-treat analysis as well as subgroup analyses by quality score and study design.

Results: Stretching was not significantly associated with a reduction in total injuries and similar findings were seen in the subgroup analyses.

### **Discussion:**

I felt this review paper was important because I feel the world's exercise practices are steeped in tradition rather than actual knowledge of how the body responds to exercise and related practices such as stretching.

Basically this paper is a meta analysis. A meta analysis is simply a review off all the relevant research on a given question to find out if there is a consensus. The results of this review paper clearly demonstrated that there isn't sufficient evidence to believe that stretching before exercise or sport prevents injuries. However, the research *did* indicate that stretching increases temporary flexibility. Well that makes sense doesn't it? But once again, even increased flexibility has not been shown to prevent injuries. Not only that, but increased flexibility has actually been shown to decrease performance in more than one study.<sup>1,2,3</sup>

One thing this paper brought out was that "warm-up", rather than mere stretching, may indeed be useful in preventing injury. Warming up helps to increase the blood flow to muscle tissue, increase temperature of the tissue, and even increases range of motion.

Effective warm-up for weight lifting should include multiple reps on the exercise that is to be performed. Using about 50% of the maximum workload is generally effective for warm-up. Warm up for a given muscle group is not necessary after a work set has been performed. In other words, it is only necessary to warm up before your first set for a given muscle group.

Now I can hear many of you thinking, "I enjoy stretching. I don't know if I want to stop stretching." Please don't misunderstand the purpose of this article. I don't want people to stop stretching. All I want is for people to stop telling other people that stretching is required to prevent injury. There is no evidence to believe that stretching prevents injury and the ongoing belief and practice of stretching to prevent injury is just one more stumbling block preventing understanding and real progress in the practice of bodybuilding.

Stretching acts as a sort of primer or a pre-exercise ritual. It helps people get mentally prepared for maximum effort even if it doesn't do much for the muscle itself. This is important and shouldn't be abandoned simply because stretching adheres to the SAID principle (Specific Adaptation to Implied Demands) just like everything else. More detailed information on the use of "pre-exercise rituals" can be found [HERE](#)



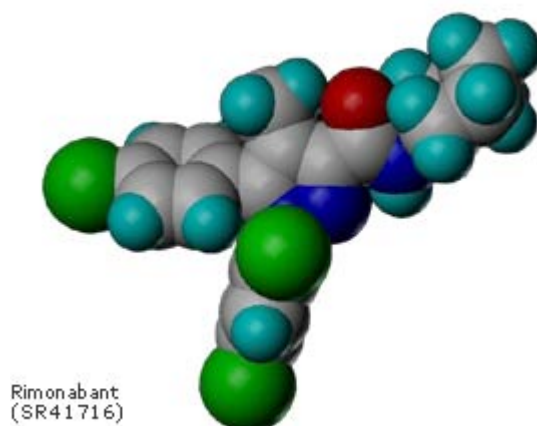
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## Rimonabant: Diet Pill Extraordinaire

**It's like willpower, but without the hassle of “self” control.**

Introducing “N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide”! Or, if you have any trouble saying that three times in a row you can just call it “Rimonabant”.



On March 9<sup>th</sup>, the French drug company Sanofi-Synthélabo, announced the early results of two Phase III studies with their new drug they call “ACOMPLIA™” (rimonabant). Rimonabant is the first in a class of drugs called Selective CB1 Blockers. They report that overweight/obese patients lost weight over 12 months while improving their lipid and glucose profiles. Not only that, but smokers who had previously unsuccessfully tried to quit smoking, were able to quit in 10 weeks *without* the usual post cessation weight gain. The results of both the RIO-Lipids (Rimonabant In Obesity) and STRATUS-US (STudies with Rimonabant And Tobacco USe) trials were presented for the first time at the American College of Cardiology annual meeting in New Orleans, LA. Rimonabant phase III programs in obesity and smoking cessation are due to be completed at the end of 2004; the product is still non-approved for marketing.

The “CB” in CB1 stands for cannabinoid receptor type-1. This receptor is the primary receptor involved in the actions of cannabis (delta 9-THC). The cannabinoid system is involved in everything from sleep/wake cycle to sexual behavior. Not only will

Rimonabant help you eat less, but it will also help you get up in the morning, stop smoking, and stop drinking. In essence, this drug takes away the brain's "reward" after ingesting/inhaling most addictive substances (including sugary-fat) and/or behaviors.

Is this type of brave new drug good for us? I mean, is it better to use a drug to control others, and our selves, or is it better to struggle and fight until we grow stronger and are able to overcome our weaknesses?

To be honest, I used to feel that people who overate themselves into the hospital from obesity, diabetes, and related complications deserved what they got. After all, no one was forcing them to eat. They knew that they were making themselves sick by eating so much and exercising so little. Over the years however, I have had a change of heart.

After working with thousands of individuals to help them improve their health, whether it was by eating better, exercising, or using medications to lose weight, I have gotten to the point where it just seems better for some people to staple their stomachs or take mind altering drugs to get them to stop eating so much. After all, I've seen many obese people spend a great deal of time and money on the best trainers and dietitians and still not overcome their devastating eating habits. In the end, what does it accomplish to keep throwing "self control" at them when it obviously doesn't work? After 10 years of struggling I would say nothing.

Write in and tell me what *you* think of the ever-increasing trend towards the use of medications to control our own behavior. I'll share some of your responses to this question in the next newsletter. So if there is something you want a lot of people to hear, write to me at (bryan at hsnhst dot com). Sorry I can't just write it out but the SPAM bots sniff out email addresses from the website and bombard me with junk...

Until next time, be healthy and be happy.

-bryan

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Reader Survey  
Tell Us What You Think?

1. Message from the Editor in Chief:

- It was good.
- It was okay.
- I didn't like it.
- I'm not interested.

2. Pharmacological Approaches to Fat Loss: Targeting Beta-Adrenergic Receptors

- It was good.
- It was okay.
- I didn't like it.
- I'm not interested.

3. Stretching the Truth-The True Benefits of Stretching: by Bryan Haycock

- It was good.
- It was okay.
- I didn't like it.
- I'm not interested.

4. Rimonabant: Diet Pill Extraordinaire: by Bryan Haycock

- It was good.
- It was okay.
- I didn't like it.
- I'm not interested.

5. What type of articles would you like to see in the future? (Check all that apply.)

- Anabolic Steroids and Pharmaceuticals
- Anti-aging medicine
- Body Transformation
- Children's Health and Nutrition
- Competitive Bodybuilding
- Diet and Nutrition Reviews
- Dietary Supplements
- Exercise Physiology
- Fitness Competitions
- Fitness Psychology
- General Health Topics
- Lifestyle Management
- Men's Health
- Powerlifting
- Seniors Health Topics
- Sports Specific Training
- Women's Health and Nutrition

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I hope you have enjoyed the latest issue of the Think Muscle Newsletter.  
Suggestions? Comments? Questions? I'd love to hear them!

Best regards,

-bryan

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