Beta-Adrenergic Receptors and Fat Loss

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Pharmacy Creations

This review of basic pharmacology using ephedrine as an active medication is provided by Bryan Haycock, MS, CSCS, founder of HSN. As a sympathomimetic, ephedrine acts to stimulate the sympathetic nervous system. It does this by causing presynaptic 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 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 the second messenger system because NA acts as the first messenger and cyclic adenosine monophosphate (cAMP) acts as the second.

After administration of ephedrine, the following chain of events occurs: (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 adrenoreceptors on their surface. (3) As NA binds to beta-adrenergic receptors, stimulatory guanine nucleotide regulatory proteins (Gs proteins) within the cell membranes 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 3-step hydrolysis reaction to reduce triglycerides into glycerol and fatty acids.

Step 1: Ephedrine stimulates the release of NA from sympathetic nerve endings

Let's 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.[1] 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 receptors. 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.

Although ephedrine binds to other adrenergic receptors, it seems that the most beneficial adrenergic effects, such as thermogenesis, are actually enhanced after chronic use.[2,3] 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.[2] 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 ephedrine's 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,[6] which means that at least 40% of ephedrine's thermogenic effects are due to beta-3 activation. This alone does not explain ephedrine's continued effects after long-term use. Also contributing is the desensitization properties of the beta-3 receptors, which lack most of the structural properties that are responsible for beta-2 receptor desensitization.[7] So even after ephedrine fails to have significant effects on the beta-2 receptor, it may continue to stimulate adenylate cyclase activity by its effect on the beta-3 receptor.

Because ephedrine is less potent than specific beta-2 agonists, beta receptor downregulation decreases with chronic treatment. Chronic stimulation of beta-2 adrenergic receptors decreases the sensitivity of tissues to beta agonists. This decrease in sensitivity in-

volves either homologous desensitization, where the receptor's active site is translocated within the cell membrane so that the binding site is no longer positioned extracellularly, or it involves heterologous desensitization, where the receptor is phosphorylated, rendering it incapable of participating in the second messenger system.[4] Receptor desensitization is a complex process with several different mechanisms. This complexity allows for greater control of hormone signaling. Ephedrine elicits a milder response, but its thermogenic effects can be seen for up to 20 weeks.[5]

In summary, the advantages of using a nonselective beta agonist such as ephedrine are its beneficial effects on thyroxin deiodinase activity, which increases the T3/T4 ratio; its effect on beta-3 receptors; and its tendency not to cause extreme desensitization of beta-2 receptors. Thus, the thermogenic effects of ephedrine are enhanced with chronic treatment.

Step 2: NA then binds to adrenergic receptors

Fat tissue also contains adrenergic receptors, with gender-specific ratios of beta to alpha receptors in various parts of the body, giving 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 in fat tissue allows for greater control of lipolysis. In essence it gives the body both an accelerator and a brake.

Step 3: Gs proteins in the cell membranes activate adenylate cyclase

In step 3, G proteins play a key role in regulating fat metabolism in adipocytes. 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.

Step 4: Adenylate cyclase converts ATP into 3'-5' cAMP

In step 4, 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 can 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. The 3'-5'-cAMP is also quickly rendered inactive by the enzyme cAMP phosphodiesterase (PDE). PDE breaks the bond between the 3' carbon of ribose and the phosphate group to form 5'-cAMP, which is inactive, does not bind to protein kinase A, and does not lead to the activation of HSL.

Steps 5-8

In steps 5 to 8, 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 3 steps, with each step removing one fatty acid until all that is left is glycerol and 3 fatty acids. Now, just because the stored fat is broken down does not mean it is gone for good. If this fat is not burned, it will simply be re-esterified and turned back into triacylgylcerol (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, PGs, 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 (PDEs)

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 (PDEs) act to hydrolyze cAMP into inactive fragments. Because of PDEs, 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.

Prostaglandins (PGs)

PGs are produced in virtually all tissues of the body, with additional letters and numbers indicating their structure. For example, PGE2 is a prostaglandin of the "E" type, which designates it as a beta-hydroxyketone. The number indicates how many double bonds it has, in this case, 2. PGs 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. PGs are made from 20-carbon fatty acids such as arachidonic acid. In the conversion of arachidonic acid into PGs, the enzyme cyclooxygenase oxygenates arachidonic acid, producing PGG2. Most nonsteroidal anti-inflammatory agents, such as aspirin, ibuprofen, naproxin sodium, and others, work by inhibiting cyclooxygenase activity, which then diminishes PG synthesis. In response to beta-adrenergic stimulation, PGE2s are released into the synaptic space. These PGs have receptors coupled to inhibitory G proteins (Gis). These Gis then decrease adenylate cyclase activity and thus decrease cAMP concentrations in the cell.[10] So, using PG inhibitors as an adjunct to ephedrine treatment for fat loss seems logical.

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 with the 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 (Gi) which inhibits adenylate cyclase activity, and thus prevent the accumulation of cAMP.[11] Its effects in the synaptic space are similar to those of alpha-2 agonists due to receptors coupled to inhibitory G proteins. When using sympathomimetics such as ephedrine, regulatory mechanisms involving adenosine are activated.

Caffeine,a methylxanthine, is able to inhibit phosphodiesterases within the cell and has even been shown to prevent some re-uptake of norepinephrine.[12] Another property of caffeine is adenosine receptor blockade. It is not known if 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 PG inhibitor, which inhibits cyclooxygenase activity. Because certain PGs inhibit lipolysis and are produced in response to adrenergic stimulation, PG inhibitors have the potential to enhance ephedrine's actions on fat loss.

In Conclusion

So, what do we know? Ephedrine stimulates lipolysis by increasing NA release from sympathetic nerve terminals. This increase in NA activates adrenergic receptors, which increases cAMP levels in fat cells and muscle cells. This, in turn, increases lipolysis in fat cells and increases protein synthesis in muscle tissue. Negative feedback mechanisms are activated, as well, and involve the production of phosphodiesterases, adenosine, and PGs. Caffeine inhibits phosphodiesterase activity and interferes with the adenosine receptor. This, combined with ephedrine's ability to prevent some NA re-uptake,[12] increases the ephedrine's effectiveness synergistically. Aspirin has been shown to increase the effectiveness of ephedrine in some individuals, presumably by its actions as a PG inhibitor.

Current Medications Used in Mesotherapy for Adrenergic Receptor Stimulation:

AMINOPHYLLINE

Aminophylline is FDA approved as an asthma medication. On the surface of fat cells are alpha and beta receptors. Beta receptors burn fat, and alpha receptors cause fat storage. Above the waist, the number of alpha and beta receptors occurs in an equal 1:1 ratio in both women and men. However, below the waist, women have approximately 6 to 8 alpha receptors to every beta. This is why it is so incredibly difficult for women to lose weight in this area. Alpha receptors are stimulated by carbohydrates, fat ingestion, amino acids, and alcohol. In mesotherapy, aminophylline allows beta receptors to burn fat more efficiently. To burn fat, beta receptors first create cAMP, which allows a second step to occur. Without mesotherapy, beta receptors cannot proceed to the second step because of a chemical called phosphodiesterase, which breaks down cAMP and stops fat burning. Aminophylline inhibits phosphodiesterase, preventing it from interfering with cAMP and the breakdown of fat. (from website: www.mesotherapy.com)

Isoproterenol – stimulates beta receptors, inhibits alpha receptors, indicated for localized obesities below waist

Yohimbine – blocks alpha receptors

Caffeine – increases cAMP

Silicea – increases cAMP

Adenosine – directly increases cAMP

References

1. Dulloo AG, Seydoux J, Girardier L. Peripheral mechanisms of thermogenesis induced by ephedrine and caffeine in brown adipose tissue. Int J Obes. 1991;15(5):317-326.
2. Astrup A, Lundsgaard C, Madsen J, Christensen NJ. Enhanced thermogenic responsiveness during chronic ephedrine treatment in man. Am J Clin Nutr. 1985 Jul; 42(1): 83-94.
3. Astrup A, Madsen J, Holst JJ, Christensen NJ The effect of chronic ephedrine treatment on substrate utilization, the sympathoadrenal activity, and energy expenditure during glucose-induced thermogenesis in man. Metabolism. 1986 Mar;35(3):260-265.
4. Sibley DR, Daniel K, Strader CD, Lefkowitz RJ. Phosphorylation of the beta-adrenergic receptor in intact cells: relationship to heterologous and homologous mechanisms of adenylate cyclase desensitization. Arch Biochem Biophys. 1987 Oct; 258(1): 24-32.
5. Toubro S, Astrup AV, Breum L, Quaade F. Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture. Int J Obes Relat Metab Disord. 1993 Feb;17 Suppl 1:S69-S72.
6. Liu YL, Toubro S, Astrup A, Stock MJ. Contribution of beta 3-adrenoceptor activation to ephedrine-induced thermogenesis in humans. Int J Obes Relat Metab Disord. 1995 Sep;19(9):678-685.
7. Nantel F, Bonin H, Emorine LJ, et al. The human beta 3-adrenergic receptor is resistant to short term agonist-promoted desensitization. Mol Pharmacol. 1993 Apr;43(4):548-555.
8. Astrup A, Buemann B, Christensen NJ, et al. The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. Metabolism. 1992 Jul;41(7):686-688.
9. Pasquali R, Casimirri F. Clinical aspects of ephedrine in the treatment of obesity. Int J Obes Relat Metab Disord. 1993;17 Suppl 1:S65-S68.
10. Kather H, Simon B. Biphasic effects of prostaglandin E2 on the human fat cell adenylate cyclase. J Clin Invest. 1979;64(2):609-612.

11. Lonnqvist F, Arner P. Interactions between adenylate cyclase inhibitors and beta-adrenoceptors in isolated human fat cells. Biochem Biophys Res Commun. 1989 Jun 15;161(2):654-660
12. Kalsner S, Frew RD, Smith GM. Mechanism of methylxanthine sensitization of norepinephrine responses in a coronary artery. Am J Physiol. 1975 Jun;228(6):1702-1707.
13. Astrup A, Toubro S, Cannon S, et al. Caffeine: a double-blind, placebo-controlled study of its thermogenic, metabolic, and cardiovascular effects in healthy volunteers. Am J Clin Nutr 1990 May;51(5):759-767
14. Astrup A, Buemann B, Christensen NJ, Toubro S, et al. The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. Metabolism 1992 Jul;41(7):686-688
15. Girardier L, Control systems in the defense of body fat stores. Int J Obes Relat Metab Disord 1993 Feb;17 Suppl 1:S3-S8
16. Dulloo AG, Jacquet J, Girardier L, Autoregulation of body composition during weight recovery in human: the Minnesota Experiment revisited. Int J Obes Relat Metab Disord 1996 May;20(5):393-405
17. Dulloo AG, Miller DS, The thermogenic properties of ephedrine / methylxanthine mixtures: Human studies. Int J Obes 1986; 10: 467-81
18. Astrup A, Breum L, Toubro S, Hein P, Quaade F, The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial. Int J Obes Relat Metab Disord 1992 Apr;16(4):269-277
19. Toubro S, Astrup AV, Breum L, Quaade F. Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture. Int J Obes Relat Metab Disord 1993 Feb;17 Suppl 1:S69-S72
20. Astrup A, Toubro S, Cannon S, Hein P, Madsen J. Thermogenic synergism between ephedrine and caffeine in healthy volunteers: a double-blind, placebo-controlled study. Metabolism 1991 Mar;40(3):323-329
21. Dulloo AG, Miller DS., Aspirin as a promoter of ephedrine-induced thermogenesis: potential use in the treatment of obesity. Am J Clin Nutr 1987 Mar;45(3):564-569
22. Horton TJ, Geissler CA., Aspirin potentiates the effect of ephedrine on the thermogenic response to a meal in obese but not lean women. Int J Obes 1991 May;15(5):359-366
23. de Jonge L, Bray GA, The thermic effect of food and obesity: a critical review. Obes Res 1997 Nov;5(6):622-631
24. Daly PA, Krieger DR, Dulloo AG, Young JB, Landsberg L Ephedrine, caffeine and aspirin: safety and efficacy for treatment of human obesity. Int J Obes Relat Metab Disord 1993 Feb;17 Suppl 1:S73-S78
25. Breum L, Pedersen JK, Ahlstrom F, Frimodt-Moller J, Comparison of an ephedrine/caffeine combination and dexfenfluramine in the treatment of obesity. A double-blind multi-center trial in general practice. Int J Obes Relat Metab Disord 1994 Feb;18(2):99-103
26. Astrup A; Toubro S; Cannon S; Hein P; Madsen J Thermogenic synergism between ephedrine and caffeine in healthy volunteers: a double-blind, placebo-controlled study. Metabolism 1991 Mar; 40(3):323-9
27. Choo J, Horan M, Litlle R, and Rothwell N. Anabolic effects of Clenbuterol on skeletal muscle are mediated by beta2-adrenoreceptor activation. Am J Physiol 1992; 263:E50-E56.
28. Guentert TW, Buskin JN, Galeazzi RL Single dose pharmacokinetics of mabuterol in man. Arzneimittelforschung 1984;34(11A):1691-1696
29. Morgan J. Clinical Pharmacokinetics of Beta-Agonists. Clin Pharmacokinet 1990 Apr;18(4):270-294
30. Martineau L, Horan MA, Rothwell NJ, Little RA. Salbutamol, a beta 2-adrenoceptor agonist, increases skeletal muscle strength in young men. Clin Sci (Colch) 1992 Nov;83(5):615-621
31. Caruso J, Signorile J, Perry A, et al. Time Course Changes in Contractile Strength Resulting From Isokinetic Exercise and Beta2 Agonist Administration. J. Strength Condition. Res. 1997; 11(1):8-13
32. Rosenbaum M, Malbon CC, Hirsch J, Leibel RL. Lack of beta 3-adrenergic effect on lipolysis in human subcutaneous adipose tissue. J Clin Endocrinol Metab 1993 Aug;77(2):352-355
33. MacIntyre DE. Human Beta-adrenergic receptor agonists: identification and in vivo evaluation in the rhesus monkey. Proceedings of the 1996 International Congress on Anti-Obesity Drug Targets, Cambridge, MA, 9-11 December. Little Falls, NJ: International Quality and Productivity Center.
34. Meyers DS, Skwish S, Dickinson KE, et al. Beta 3-adrenergic receptor-mediated lipolysis and oxygen consumption in brown adipocytes from cynomolgus monkeys. J Clin Endocrinol Metab 1997 Feb;82(2):395-401
35. Danforth E, Himms-Hagen J. Obesity and diabetes and the beta-3 adrenergic receptor. Euro J Endocrin 1997; 136:362-365
36. Yoshida T, Umekawa T, Kumamoto K, et al. Beta 3-Adrenergic agonist induces a functionally active uncoupling protein in fat and slow-twitch muscle fibers. Am J Physiol 1998 Mar;274(3 Pt 1):E469-E475
37. Abe H, Minokoshi Y, Shimazu T. Effect of a beta 3-adrenergic agonist, BRL35135A, on glucose uptake in rat skeletal muscle in vivo and in vitro. J Endocrinol 1993 Dec;139(3):479-486