Introduction

Ephedra, also known under the Chinese name of Ma Huang, is an herbal remedy that has been used in China for over 5000 years. It was the first herb discovered that led to an active constituent, ephedrine (an alkaloid), being incorporated into Western medicine. Ephedra became known in the United States during the 1920's when researchers at a university in China wrote a series of papers that detailed the effects of the alkaloid. American researchers took note and eventually started to use Ephedra in the treatment of bronchial asthma and nasal congestion (1). To date, there are close to forty different species of Ephedra, which are categorized based on their five geographic locations. The Asiatic species of Ephedra is well known for its alkaloid content, which includes ephedrine and pseudoephedrine. However, the North American varieties contain no useful alkaloids, and thus cannot be used in the treatment of bronchoconstriction (2,3). The bronchodilatory effects of Ephedra are due to the interaction between the alkaloid and the adrenergic receptors in our bodies.

Today, Ephedra is sold as a dietary supplement under the labeled pretense of weight loss, performance enhancement (body-building), increased sexual drive, increased alertness, and enhanced energy levels. However, these claims should be considered unsubstantiated since they have not been proven through rigorous and impartial clinical testing (4). With the supposed promises of increased energy, weight loss and performance enhancement, consumers are driven to increase their intake amount of ephedrine-containing products in hopes of hastening the results. This type of behavior has led to current health problems with this dietary supplement. To this date, research is sparse regarding ephedrine abuse, but it is rising proportionately with the increased commercialization of the drug, and subsequently, the increased number of people suffering from its adverse side effects.

The mechanism behind ephedrine's action

The active constituent of Ephedra is ephedrine. Ephedrine and its associated alkaloids (pseudoephedrine, norephedrine, and N-methyl ephedrine) are structurally similar to amphetamines and act by stimulating adrenergic receptors. Ephedrine acts to release norepinephrine from the sympathetic nerves, stimulating adrenergic activity at the level of the a1, a2, b1, and b2-receptors.(2) The symptoms caused by ephedrine consumption are the direct results of receptor stimulation and most commonly include palpitations, vomiting, nausea, tingling, increased blood pressure, and numbness of the extremities. (5)

Each receptor is responsible for a specific set of reactions. a1-receptors are located on the vascular smooth muscle of the skin and in the splanchnic region, as well as the gastrointestinal sphincter. Excitation of the a1-receptors leads to contraction and constriction of the vascular smooth muscle and the splanchnic region. This ultimately leads to increased blood pressure by the constriction of blood vessels. a2-receptors are located in the walls of the gastrointestinal tract, and binding to theses receptor causes constriction, leading to decreased gastrointestinal motility and secretory activity. (6)

By mimicking b1-agonist activity, ephedrine also increases heart rate via the receptors located in the sinoatrial node, the atrioventricular node and the ventricular muscle of the heart. Receptor binding causes excitation, with an increase in heart rate, conduction velocity, and contractility. These combined effects, much like binding to the a1-receptors, ultimately leads to increased

blood pressure. Lastly, b2-agonist activity of ephedrine occurs at the level of vascular smooth muscle of the skeletal muscles and of bronchial smooth muscles. Receptor binding causes relaxation and dilatation of those muscles.(6) The latter effect is what led the Chinese to use Ephedra as a bronchodilator.

The mechanism by which receptor binding leads to the physical change is through a complex cascade involving G-proteins. "G-proteins influence membrane-associated enzymes that control the concentration of second messengers, thereby affecting the activity of enzymes and ion channels."(7) In particular, a2, b1, and b2 receptors affect change via cyclic AMP. In the case of the beta-adrenergic receptors, the G-protein activates the adenylate cyclase reaction. cAMP activates protein kinase A (PKA), which leads to a decrease in Ca2+ levels and subsequent muscle relaxation (b2 receptors) or nerve stimulation (b1 receptors). On the other hand, binding to a2-receptors inhibits the G-protein, and therefore the adenylate cyclase reaction. The a1-adrenergic receptor also interacts with a G-protein, but it is regulated by the activity of phospholipase C. This enzyme produces two second messengers which eventually cause Ca2+ levels to be released from intracellular stores, leading to vasoconstriction (8)

Ephedrine used to be isolated from Ephedra, but the process was time consuming and the yield relatively low. Most of the ephedrine found in today's dietary supplements is produced through chemical synthesis, and is therefore not derived from the herb. (2)

Acute use of ephedrine leads to cardiovascular complications

Ephedrine related cardiovascular toxicity includes hypertension and tachydysrhythmias. (8) Published reports on ephedrine are few but usually include a case report of a patient with cardiovascular problems after ingestion of ephedrine related products. In one report, a patient was brought in to the emergency department with a blood pressure of 220/110 mmHg. The patient had ingested four gelatin capsules of "herbal ecstasy" (dosage amount could not be obtained from the patient) and started to develop multiple ventricular ectopic beats and left ventricular hypertrophy after 2 hours. He was treated with lidocaine, an drug that inhibits ionic fluxes needed for the initiation and conduction of impulses, and with sodium nitroprusside, an antihypertensive medication. His symptoms resolved in 9 hours. (10)

Another report, an epidemiological study conducted by the CDC, reports 500 adverse reactions from people who consumed ephedrine in a dietary supplement. The range in the severity of the symptoms went from trembling, headaches, vomiting, nausea, dizziness, chest pain, to myocardial infarctions. Eight of these 500 reports were fatalities, seven of which died from a myocardial infarction or cardiovascular problem. The medical records of these fatalities showed patients presenting with irregular and increased heart rates, and increased blood pressure. (11)

Of particular interest is the possibility that people who are adversely affected by ephedrine (i.e. suffer from a myocardial infarction or stroke) are predisposed to its effect because of existing risk factors (i.e. high blood pressure). However, one study showed that people with risk factors, and those with no risk factors were both adversely affected by the use of ephedrine. (12) Moreover, not only do large doses of ephedrine have serious health risks, but most dietary supplements with ephedrine also include caffeine as an additional dietary ingredient. Studies have shown that ephedrine and caffeine together are more potent and lead to more serious health risks including, stroke secondary to intracranial hemorrhage, seizures and psychosis. (13)

Chronic abuse of ephedrine can lead to renal toxicity

Another health problem seen, this time with chronic ephedrine abuse, is a renal toxicity aptly named ephedrine nephrolithiasis. It is a relatively new problem that has arisen in chronic abusers of ephedrine who take more than the recommended dose. Ephedrine elimination from the body is primarily through the renal system, with 70- to 80% excreted unchanged in the urine. Excess ephedrine will precipitate in the urine, and some chronic ephedrine abusers will develop kidney stones made up primarily of ephedrine. (14) Normally, kidney stones are made up of uric acid, calcium oxalate compounds, calcium phosphate compounds, and other compounds. However, ephedrine does not occur naturally in our body or diet and should not be one of these substances. This has led researches to believe that chronic ephedrine abuse can lead to ephedrine nephroliathisis. (14,15)

Events that led to these health problems

The regulation of dietary supplements falls under the Dietary Supplement Health and Education Act of 1994 (DSHEA) signed into law on October 25, 1994. This law defines what is considered a dietary supplement, describes dietary ingredients, and the proper use of statements of nutritional support.(16) That is, a dietary manufacturer can make claims about how the product affects the structure or function of the body, but it cannot claim to prevent, treat, cure, or diagnose a disease without prior FDA approval.

The following is an example of how an internet dietary supplement manufacturer, D&E Pharmaceuticals, can go about describing its product: "Whether you are looking to lose weight, rev up your sex life or end fatigue: Nature's Ultra Boost 1700mg. A Blast Of Herbal Dynamite! Each compact tablet is an explosion of pure hebal (sic) dynamite. Nature's Ultra Boost combines impressive doses of the two strongest natural energizers [ephedrine and caffeine] available without a prescription. Each one is a potent boost on it's own." (17) The Dietary Supplement Health and Education Act of 1994 also require manufacturers of dietary supplements to give the Federal Drug Administration (FDA) a 75-day notice of any new dietary ingredient prior to its marketing. Once this is done, dietary supplements manufacturers can market the supplements without any prior premarket safety evaluation. They are not required to submit any evidence of its safety, only that there is a "reasonable expectation that use of the supplement will be safe." (16) Moreover, it is the FDA's responsibility for testing the dietary ingredient in the supplement and to research the accuracy of the dietary supplement labeling in terms of weight, composition, and claims.(16) Given that the dietary manufacturing industry has grown to a $12 billion a year business, with new products continuously being put on the market, the FDA cannot keep up with adequate product testing.

Another interesting twist to DSHEA deals with the date a dietary ingredient is put on the market. If the dietary supplement had an ingredient that was used prior to October 1994, as is the case with many products containing ephedrine, there is no FDA review required. The FDA reviews only dietary ingredients that were added after October 1994. This loophole is one of the reasons why in 1995, the FDA warned against certain ephedrine-containing products as it received more and more reports of adverse reactions, and finally started to actively research and analyze dietary supplement containing ephedrine. (18)

Conclusion

Ephedrine is an herbal stimulant that has been traditionally used in the treatment of bronchoconstriction and nasal congestion. However, because of its effects on adrenergic receptors, it has recently been touted as a method for promoting weight loss, increasing energy levels, sex drive, and improving body-building results. Because of the unregulated dietary supplement market, many manufacturers have played into Americans' insecurities and have touted ephedrine-containing products as a panacea for these problems, with minimal regulatory constraints from the US government. From the consumer perspective, this was the miracle natural solution: an herb that could restore all vital activities. And since it is only an herb, why not take more to get the results faster? These events are what led to what we are seeing today; consumers that take larger doses of chemically formulated ephedrine and end up with serious and potentially fatal health problems.

One obvious solution to this problem is to increase the FDA's authority over this industry. A recent bill was introduced into Congress called the "Neutraceutical Research and Education Act" (HR 3001) to create an oversight committee within the FDA that would solely focus on dietary supplement evaluation and regulation.(4) This oversight committee is desperately needed to stop these preventable deaths. However, it appears as though it will be a difficult battle to win given the new level of lobbying power the dietary supplement industry has achieved.

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