Ephedrine; Pathways and Side Effects

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Biochemistry 471

Ephedrine, also known as ephedra, is a stimulant, both in the literal sense and the metaphorical sense. In the metaphorical sense it is the source of massive controversy and disagreement. It is used as an ingredient in diet pills, illegal recreational drugs, and legal over-the-counter medications to treat nasal congestion and asthma. Legitimately, ephedrine is used to treat asthma and is absorbed by the body almost immediately whether it is taken orally or intravenously.\(^1\) Debate arises because the FDA cannot regulate the compound because it is considered to be a dietary supplement and is therefore protected under the Dietary Supplement Health & Education Act of 1994. Only drugs that are seen as “unsafe” can be taken out of this protection. Since ephedrine is closely related to amphetamines both in structure and in mode of action, it can be associated with “speed,” which is a common element in many illegal street drugs. Drug companies use this image to produce seemingly harmless alternatives to illegal drugs and try to take advantage of the market that would partake in such activity. Other drug companies attempt to go the other route and advertise that their product is “all natural” and contains nothing harmless like ephedrine. However, more often than not, on the back of that same bottle you might see that the product contains “Ma Huang,” or “the extract of a plant from the genus *Ephedra.*” The FDA released a report in the mid 90’s that stated that the ephedrine alkaloid (the active element of the extract) does indeed carry several adverse side effects. Regardless of the number of injuries this drug has caused it can still be bought today.\(^2,3\)

The stimulating effects that ephedrine has on the central nervous system and the heart are cause for concern due to the fact that the outcome of misuses can be lethal. The FDA has received over 800 reports of side effects since 1994. Some of the side effects reported are hypertension, tachycardia, nerve damage, psychosis, stroke, memory loss, heart rate irregularities, insomnia, nervousness, tremors, seizures, heart attacks, and death.\(^4\)

Ephedrine acts on the β-agonist system in the body. The β-agonist system works to control the fat stores in the body as well as muscle growth, the body’s response to exercise, even the very type of muscle fiber produced. The receptors on the muscle and fat tissues are β-receptors which bind to β-agonists, such as adrenaline, epinephrine and norepinephrine. Ephedrine also indirectly stimulates the release of norepinephrine from within the body.

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When binding occurs, the receptor starts a cascade of several chemical reactions that eventually result in the production of c-AMP (cyclic adenosine monophosphate). The c-AMP then goes on to activate enzymes that phosphorylate proteins. In fat tissues the enzymes that are activated induce lipolysis, or fat break down.

In muscle tissue, the enzymes that are activated increase metabolism and cause other reactions to occur that control muscle growth and muscle fiber type.5, 6, 7

Ephedrine alone is not very effective. When combined with caffeine and aspirin, in what body builders call a “stack,” the effects are maximized. As ephedrine enhances β-agonist production of c-AMP, caffeine is used in the mix in order to inhibit the breakdown of c-AMP and aspirin inhibits the negative feedback loop. Caffeine is an inhibitor of an enzyme called phosphodiesterase (PDE). PDE lowers the c-AMP levels in the cell and caffeine in turn, inhibits this action and c-AMP rise. Caffeine itself is also capable of releasing norepinepherine from peripheral storage sites. (Structure: Fig 1) Aspirin inhibits adenosine receptors that if able to bind with adenosine then norepinepherine would not be released. Therefore when aspirin is taken with these other two compounds there is an even greater release in norepinepherine.8 (Structure: Fig 2)

7 Reference at University of Guelph Ontario Veterinary College. Accessed: 4/19/03. URL: http://www.ovc.uoguelph.ca/BioMed/Courses/PublicPharmacology/pharmsite/98-309/ANS/Adrenergic_Agonists/adrenerg_agon.html
The basic premise for the support of ephedrine is theory that the user can gain positive results whether they exercise or not, unlike steroids where the user has to exercise frequently and aggressively or the steroids will have more severe adverse effects such as fat growth. The ideal design is to induce a higher metabolism and burn more fat than what is being taken in. The three compounds taken together effectively amplify the production of c-AMP and as a result increase the stimulation of the sympathetic nervous system as well as metabolism.8 (Pathway: Fig 3)

Figure 3
Pathway of ephedrine, caffeine and aspirin indicating the production of higher levels of c-AMP, thermogenesis which results in burning calories.

Figure 1
Caffeine

![Caffeine Structure](image)

Figure 2
Aspirin

![Aspirin Structure](image)

Figure from A. G. Dullo, Int J Obes Relat Metab Disord. 1993 Feb;17 Suppl 1:S35-40.
β-receptor activation also affects several other aspects of the body besides the heart like the liver, skeletal muscle, fat cells and peripheral vasculature. The activation of β-receptors in skeletal muscles activates glycogenolysis, which is the break down of glucose into simple sugars so the body can use them to fuel muscle contraction. The same kind of thing occurs in the liver where the β-receptor agonist instigates glycogenolysis and gluconeogenesis, which both contribute to elevating blood sugar levels. The action of the receptors also stimulates the surface of fat cells which results in the activation of the enzyme known as hormone sensitive lipase. This enzyme propagates fat break down of a cell and also allows the fat to be released into the blood stream and used as fuel. This movement into the blood stream is vital since those muscle groups that are most active are going to be the muscles that actually burn the fat off from other parts of the body. This can explain how you lose weight, or “inches”, from your body as a whole and not just in one particular place.

One of the more serious side effects of ephedrine is increased heart rate. Cyclic AMP increases the inflow of calcium into the cardiac muscle cells and norepinephrine as well. These are the main inducers of increased heart rate due to ephedrine. It does this by activating beta receptors in the myocardial cells, which increases the force of contraction. The beta receptors in the “pace maker” cells in the SA (sinoatrial) node in the heart are also activated resulting in the increased rate of contraction, as well as an increased rate of myocardial relaxation which is the increased (diastolic) filling of the heart with blood. Since systole is shorter than diastole, the time spent in diastole is longer, leading to more blood being in the heart at the time of the next contraction. All of these things lead to an aggressive amount of cardiac out put and if the user has a heart that is subject to arrhythmia then there is a very good chance that the user might experience chest pain, PVC’s or in some cases, myocardial infarction.

Provided here is a table indicating those over-the-counter (OTC) drugs that contain ephedrine and pseudoephedrine. (Table 1) While the FDA attempts to harness the control over this controversial drug, it lies between

<table>
<thead>
<tr>
<th>OTC products containing ephedrine</th>
<th>OTC products containing pseudoephedrine</th>
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<tbody>
<tr>
<td>Bronkaid®</td>
<td>Actifed®</td>
</tr>
<tr>
<td>Bronkotabs®</td>
<td>Afrinol®</td>
</tr>
<tr>
<td>Ephedrol®</td>
<td>Dimacol®</td>
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<tr>
<td>Quibron Plus®</td>
<td>Sudafed®</td>
</tr>
<tr>
<td>Tedral®</td>
<td>Common side effects of pseudoephedrine</td>
</tr>
<tr>
<td>Common side effects of ephedrine</td>
<td>agitation, insomnia</td>
</tr>
</tbody>
</table>

nervousness, headache, rapid heartbeat


10 Prevost, Mike Ph.D. “Can Athletes Favorably Alter Body Composition With Ephedrine, Caffeine and Aspirin?” Accessed: 4/19/03. URL: http://members.tripod.com/JPE_Sportscience/ephedrine.html
two different sides of the argument. One side suggests that there are needless deaths associated with ephedrine and there are other means of attaining the same desired affect. On the other hand, there is that proposition that if taken correctly there is no real danger involved, and it is only a handful of the extreme cases that are directing the nation’s perception of ephedrine. It is too difficult to establish a proper usage regimen or develop some method of excluding certain potential users from using this drug due to both inadequate testing and taking into account the wide variety of side effects that react under a myriad of situations. There have been so many cases of adverse effects that come from healthy adults that there doesn’t seem to be any place to start, not to mention what might happen when the user stops taking the drug as some of the more serious side effects could occur at any time.