Phenethylamines, Free Radicals, and Antioxidants

By Brian Leibovitz, Ph.D.

THIS INFORMATION is for those who experiment with phenethylamines as well as those with patients who use these compounds. Phenethylamines are a class of compounds chemically, and functionally, related to adrenaline — the fight or flight neurotransmitter made from the amino acid tyrosine. Phenethylamines all contain a benzene (C_6H_6) ring linked to an ethyl-amine ($-CH_2-CH_2-NH_2$) group, and include: amphetamine (a stimulant), ephedrine (a naturally-occurring decongestant), and methylenedioxymethamphetamine (MDMA, a psychotherapeutic agent that facilitates communication).

If one takes phenethylamines, it would be prudent to take supplemental antioxidants as well.

STUDIES in the last few years have established that phenethylamines can undergo "redox cycling," a ping pong-like process that liberates copious quantities of oxygen free radicals. Free radicals are substances with extra, unpaired electrons, whose characteristic is reactivity, and whose hallmark is cell biochemical and cellular damage. Indeed, oxygen radicals are linked to a wide variety of diseases and conditions, including: heart disease, stroke, cancer, emphysema, and neurologic disorders.[1] While our body has mechanisms to protect against the steady-state levels of radicals, excessive amounts overwhelm the protective systems and damage ensues.[2] Incidentally, free radicals are not *always* the bad guys; our white blood cells produce, and use, free radicals as the primary means of killing bacteria, viruses, and other microbial invaders.

Phenethylamines are stored in highest concentrations in the brain and nervous system. Not surprisingly, these tissues are at the greatest risk for being harmed by free radicals (and associated oxidants) formed during the redox cycling of phenethylamines. Moderate intakes appear to be handled well. Excessive quantities of phenethylamines, however, may cause oxidative damage as the protective mechanisms just can't handle the load.[2] It is the overproduction of radicals that causes, in large part, the fatigue and mental dysfunction associated with sustained amphetamine abuse.[3]

The key, as always, is protection, and knowing the mechanism of action can only yield one conclusion: those who take phenethylamines should also take antioxidant supplements. All phenethylamines are prooxidants by nature, and can redox cycle. This means that there will be a dose-dependent increase in free radical production, so even at a low dose there will be free radical generation to some extent. Therefore, if one takes phenethylamines, it would be prudent to take supplemental antioxidants as well. This includes both the water-soluble (e.g., vitamin C and glutathione) as well as fat-soluble (e.g., vitamin E) antioxidants. Other important antioxidants include: selenium (the coordinating mineral for the enzyme glutathione peroxidase) and beta-carotene (a quencher of "singlet oxygen" — a non-radical form of activated oxygen). Bioflavonoids are also indicated, not only for their direct antioxidant effects, but because they are good metal-chelating agents (and so prevent iron from catalyzing reactions that generate free radicals). Studies in both animals and (to a lesser extent) humans document the protective effects of antioxidants against the radical-mediated, untoward side-effects of phenethylamines.[2,4,5]

I suggest that the combination of vitamins, minerals, and non-vitamin nutrients listed in **Table 1** would be valuable for the prevention and/or

treatment of the adverse effects that may result from phenethylamine overdose or overuse. There is nothing magic about the doses listed; it is my best estimate based on present knowledge in nutrition. Note that N-acetyl cysteine (NAC) is recommended instead of glutathione as it is more effective in raising tissue glutathione levels; in addition, it is less expensive than preformed glutathione. L-Carnitine and CoQ_{10} have also been included, as both are known to increase cellular energy (adenosine triphosphate, or ATP) generation, thereby enhancing cellular integrity.

The bottom line is that, by using an appropriate combination of antioxidants and other nutritional supplements, one can ameliorate the prooxidant, and potentially harmful, side-effects of high-dose phenethylamines.

I would also like to mention my new journal, The *Journal of Optimal Nutrition* (JON). JON's focus is on supplements of macronutrients and micronutrients for the prevention and treatment of disease as well as for the maintenance of optimal health. An enormous, and ever-increasing, volume of data supports the concept that increased dietary levels of nutritional factors are effective against a wide variety of ailments.

JON is the first journal specifically dedicated to the study of optimal nutrition — and to the most crucial question of modern nutrition: the elucidation of optimal nutrient intakes. JON's Editorial Board includes Drs.: Linus Pauling, Jeffrey Blumberg, Mohsen Meydani, Karl Folkers, Mark Levine, Richard Kreider, and many (75+) other distinguished nutritional scientists and physicians. JON is published quarterly; the subscription rate is $75 per year ($25 for students). ■

For more information, contact:
Jennifer Ann Mueller, Managing Editor,
The Journal of Optimal Nutrition,
2552 Regis Dr., Davis, CA 95616.
Phone (916) 756-3311. Fax (916) 758-7444.

Journal of Optimal Nutrition ***is the first journal specifically dedicated to the study of optimal nutrition***

Table 1: Nutrients For Blocking Phenethylamine Damage

Nutrient	Preventive Dose	Therapeutic Dose	Form
β-Carotene	5 mg	15 mg	Consider supplements of other carotenoids (e.g. lycopene) as they become available
Bioflavonoids	2 grams	6 grams	Mixed bioflavonoids from a variety of sources
Coenzyme Q_{10}	100 mg	300 mg	Only one form available
L-Ascorbic acid	2-4 grams	6-12 grams	Free acid or calcium magnesium salt
L-Carnitine	1 gram	3 grams	L-Carnitine HCl or, if possible, less hygroscopic salts (e.g., L-carnitine magnesium citrate)
N-Acetylcysteine (NAC)	2 grams	6 grams	Only one form available; do not use L-cysteine
Selenium	250 mg	500 mg	Form not critical – inorganic (e.g., selenite) as effectiveand less expensive than organic forms (e.g., selenomethionine)
Vitamin E	1,000 IU	3,000 IU	Available data indicate that form is not critical

1 Marx JL. Oxygen free radicals linked to many diseases. Science 235: 529-31, 1987.
2 Bindoli A, Rigobello MP, Deeble DJ. Biochemical and toxicological properties of the oxidation products of catecholamines. Free Radical Biol & Med 13: 391-405, 1992.
3 Caldwell J. (editor) Amphetamines and related stimulants: chemical, biological, clinical, and sociological aspects. CRC Press, Inc., Boca Raton, FL, 1980.
4 Wagner GC, Carelli RM, Jarvis MF. Ascorbic acid reduces the dopamine depletion induced by methamphetamine and the 1-methyl-4-phenyl pyridinium ion. Neuropharmacology 25: 559-61, 1986.
5 Wagner G, Carelli R, Jarvis M. Pretreatment with ascorbic acid attenuates the neurotoxic effects of methamphetamine in rats. Res Comm Chem Path Pharm 47: 221-8, 1985.