

TEACHERS TOPICS

Biochemistry of the Water Soluble Vitamins: A Lecture for First Year Pharmacy Students

See the next page for carbidopa binds irreversibly to B6

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This manuscript describes the lecture on vitamins contained in the core course entitled, "The Biochemical Basis of Drugs and Diseases" (Pharmacy 3050). In the first year, our curriculum is designed to focus on systems and diseases. As such, this course acts in concert with both the Anatomy & Physiology course and the Pathophysiology course to present an integrated view of human diseases and systems. The second year of our curriculum is focused on learning about drugs classes and the mechanism of action. The third year of the curriculum is focused on simulated patients, while the fourth year of the curriculum the students are presented with real patients.

The lecture on vitamins is the last topic of a course focused primarily on metabolism. Because many vitamins play major roles in metabolic cycles, this lecture allows for a brief review of much of the material covered throughout the course. Therefore, vitamin examples are primarily chosen to reinforce major metabolic cycles and also their role in human disease. There is more clinical information that is relevant to vitamins than what is presented in this lecture. However, since first year students in our curriculum have almost no knowledge of therapeutics, the focus of the lecture is on diseases and not clinical practice.

INTRODUCTION

Vitamins are a multibillion dollar industry.¹ They are readily available to the public and are the focus of the most frequently asked questions to pharmacists.² Surprisingly, most pharmacy students receive little training on the many roles of vitamins in nutrition.² Therefore, this lecture attempts to not only reinforce fundamental biochemical and metabolic pathways in the human body, but also to provide pharmacy students with practical information.

The diet is a vast source of important nutrients. These nutrients include several important classes of biomolecules such as: (1) energy yielding components (carbohydrates, lipids, and proteins), (2) essential and

nonessential amino acids, (3) essential fatty acids, (4) minerals, and (5) vitamins. Vitamins are organic substances that must be provided by the diet either because they cannot be biosynthesized or the amount that is provided through biosynthesis is inadequate for maintaining normal health. Vitamins are broadly divided into 2 classes based upon their hydrophobicity. The more hydrophilic vitamins are termed the water-soluble vitamins and are composed of the B-complex vitamins and vitamin C. The more hydrophobic vitamins, referred to as the fat-soluble vitamins, are composed of Vitamins A, D, E, and K. This article focuses primarily on the water-soluble vitamins due to their greater role in the major metabolic cycles, which are the primary focus of this course.

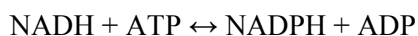
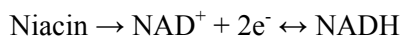
The normal North American diet is sufficient to prevent significant vitamin deficiencies and the related diseases associated with these deficiencies. However, there is increasing concern that slight vitamin deficiencies in a number of water-soluble vitamins (B1, B6, B12, folate and vitamin C) are risk factors for diseases such as

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thy, and cataract formation. Riboflavin deficiency is not normally observed in the United States; however, deficiency may be observed as part of a general case of malnutrition or in cases of chronic alcoholism.⁸ The conversion of riboflavin to FMN is required for absorption and transport into many tissues. The conversion has been shown to be inhibited by hypothyroidism and the structurally similar medications chlorpromazine, adriamycin, quinacrine, tetracycline, and tricyclic antidepressants.⁹⁻¹²

Niacin (Vitamin B₃)

The vitamin niacin (nicotinic acid) and its structural analog nicotinamide have identical function due to their facile interconversion in the body. Niacin is converted through a series of reactions to its active form nicotinamide adenine dinucleotide (NAD⁺). NAD⁺ can be converted to a reduced form NADH by gaining 2 electrons through a process similar to FAD reduction. NADH is produced in large quantities by the TCA cycle and β-Oxidation and to a lesser extent by glycolysis. Reduced NADH is returned to its oxidized form under normal cellular conditions by the electron transport chain. This newly reformed NAD⁺ can then return to other metabolic pathways to harvest more electrons. In the body the ratio of NAD⁺/NADH is approximately 1000 demonstrating the primary role of NAD⁺ in supporting cellular oxidation. NADH also can react with ATP to form NADPH. As opposed to the unphosphorylated form, the ratio of NADP⁺/NADPH is only 0.01. This ratio points to the role of NADPH in supporting reductive processes in the body.



Niacin can be found in foods such as meats, breads, and beans. Mild niacin deficiencies have similar symptoms to those observed with riboflavin, which is not surprising due to the similar roles both of these vitamins play in biochemical reactions. Niacin deficiencies are occasionally observed in alcoholics, cases of general malnutrition, and in the elderly on restricted diets. A severe deficiency of niacin is known as pellagra, which is derived from the Italian phrase meaning rough skin. Pellagra is marked by dermatitis and also is notable for causing a blackening of the tongue. Early cases of pellagra were first observed in Europe shortly after the introduction of corn from the voyages of Christopher Columbus. In these cases, poor farmers who were raising corn as animal feed were particularly susceptible. Because niacin in corn is not bioavailable unless treated with a strong

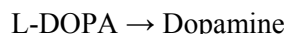
base such as lye, the farmers developed niacin deficiencies. Europeans did not know this processing method until revealed to them by Native-Americans during the early colonial period of North America. However, the connection between pellagra and niacin was not known until the early 20th century. Pellagra was a significant health issue in the United States over the period from 1900-1940 resulting in over 100,000 deaths. Today most diets are supplemented with niacin through enriched flour, which receives its name because of the added niacin.¹³

Niacin can be administered in doses of 2g to 4g to causes a decrease in circulating levels of cholesterol and LDL. While the cholesterol lowering effects of niacin are desirable there are potential side effects from such large doses of this vitamin. The most immediate reaction observed from large doses of niacin is vasodilation resulting in flushing. Over time there may be a reduction in fatty acid mobilization causing a depletion of glycogen and lipid stores in muscle tissue. Long-term exposure may also elevate blood glucose and uric acid levels, suggesting increased risk for patients who are on the borderline for diseases such as diabetes and gout. Prolonged use of high doses of niacin can lead to elevated levels of the serum enzymes alanine aminotransferase and aspartate aminotransferase, which may suggest liver damage.

Pyridoxine (Vitamin B₆)

Pyridoxine is the precursor to the active enzyme co-factor **pyridoxal phosphate (PLP)**. Pyridoxal phosphate is a critical co-factor for enzymes involved in reactions involving many amino acids. The N-terminus of the amino acid forms a covalent bond to PLP, allowing a wide variety of displacement reactions to occur at the alpha carbon. These include decarboxylations, transaminations, and transfers of side chains. Pyridoxine, therefore, plays a central role in the production of many neurotransmitters, such as serotonin, norepinephrine, and histamine. Pyridoxine also is important in the production of heme.

The PLP co-factor in several enzymes is a therapeutic target due to the ability to form **irreversible covalent bonds** with agents containing a **hydrazine moiety**, such as **carbidopa**, **isoniazid**, and **hydralazine**.¹⁴ The combination of L-Dopa and carbidopa is a widely used therapy that has a biochemical mechanism involving vitamin B6. The conversion of L-Dopa to dopamine is catalyzed by the PLP-dependent enzyme L-aromatic amino acid decarboxylase (LAAAD).



PLP = the active form of B6