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**NUTRITIONAL
PHARMACOLOGY**

**Gene A. Spiller
EDITOR**

NUTRITIONAL PHARMACOLOGY

Editor

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Preface

This book gathers under one cover current information on the pharmacological uses of some nutrients and other compounds derived from foods: nutrients and compounds that may be in their natural form or chemically modified. Some of the compounds described are in the early stages of clinical investigation, others have already found a place in clinical practice.

After the first chapter, which defines nutritional pharmacology, topics covered include the pharmacological uses of choline and lecithin, plant and marine sterols, branched-chain amino acids, and plant fibers, as well as vitamin D metabolites, modified retinoids, and lactulose.

Each topic is covered in depth by well-established investigators and the option is available to read the entire chapter or to go directly to the aspect of specific interest to the reader, whether it is chemical, nutritional, pharmacological, or clinical. In addition to the direct clinical implications of each chapter, it is hoped that reading this entire volume will stimulate interest in new ways to develop beneficial pharmacological agents of nutritional origin.

This book should help to establish nutritional pharmacology as the link between the the nutritional and pharmacological health sciences and the application of both to medicine.

Gene A. Spiller
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Contents

Contributors	vii
Preface	
Gene A. Spiller	ix
1. Defining Nutritional Pharmacology	
Gene A. Spiller	1
2. Lecithin, Choline, and Cholinergic Transmission	
Madelyn Hirsch Fernstrom	5
3. Plant and Marine Sterols and Cholesterol Metabolism	
George V. Vahouny and David Kritchevsky	31
4. The Pharmacology of Branched-Chain Amino Acids	
Ronald J. Amen and Norman N. Yoshimura	73
5. Dietary Fiber and Other Antinutrients: Metabolic Effects and Therapeutic Implications	
David J. A. Jenkins	117
6. Modified Vitamin D Compounds in the Treatment of Certain Bone Diseases	
Russell W. Chesney	147
7. Retinoids and Carcinogenesis	
Hugh James Freeman	203
8. The Use of Lactulose in the Treatment of Portal-Systemic Encephalopathy	
Fredrick L. Weber, Jr.	217
Index	255

1

Defining Nutritional Pharmacology

Gene A. Spiller

In nutritional pharmacology, nutrition becomes an instrument of pharmacology. Nutritional pharmacology is the study of the use of nutrients, essential or nonessential, either in their natural chemical form or in a chemically modified form, to achieve a pharmacological effect rather than a nutritional effect. Therefore, it is important to begin by emphasizing that it is not nutrition per se in a classical sense but a part of pharmacology. Certainly some of the chapters of this book come closer to classical nutrition than do others, which have a more definitely pharmacological approach; but no definition or line of demarcation is perfect.

Historically, the nutritionist's interest has been the study of the effects of various components and compounds in food on the biochemical and physiological function of humans and animals. The nutritionist searches for ways in which proper or specialized diet can help in the maintenance of health, the prevention of disease, the correction of nutritional deficiencies and resulting pathologies, and the special needs of patients in such circumstances as postsurgical stress and chemotherapy for cancer.

On the other hand, the pharmacologist is concerned with the use of chemical entities, natural or synthetic, that can modify an individual's physiological and biochemical condition. Such agents might be used to alter a normal physiological state; as therapeutic agents to treat disease or pain; or to bring back to normal an abnormal biochemical condition that, even though not disease per se at the time, might, if left unchecked, lead to a disease at a later stage.

This collection of discussions has been limited to those entities that have or might some day have useful applications in clinical medicine for therapeutic use, since this is the most immediate application of nutritional pharmacology. To try to gather all the possible applications of nutritional pharmacology would be presumptuous; the science is yet adolescent. We can hope that this book will

help to establish for it a special niche in the vast structure of pharmacology. Perhaps even more important, the clinician and the research scientist may see in it an incentive to study further a potentially fruitful source of therapeutic agents.

To aid in clarifying the scope of nutritional pharmacology, I recently suggested a definition [1] that I am expanding and improving here: "Nutritional pharmacology is the study of substances found in foods that might have a pharmacological effect when fed in higher concentrations than normally found in the diet and/or chemically modified form. These compounds might not be essential nutrients per se."

Hence, the therapeutic use of diet should not be part of nutritional pharmacology, nor should special enteral nutrition, such as the use of predigested proteins or of a vitamin supplement in the RDA range. These fields belong to therapeutic nutrition. Debate may arise as to whether parenteral feeding of nutrients intended to replace enteral nutrition should be included in nutritional pharmacology. I suggest that such parenteral feeding should not be included, as the goal is nutritional rather than pharmacological despite the therapeutic goal.

This definition has some weaknesses as have many biological definitions. Controversy may arise, for instance, regarding nutrients that might be present in large amounts in the diet of certain populations and extremely low in the diet of others. An example is plant fiber, which is very low in typical Western diets, while high in some primitive diets. Is, then, the use of a "fiber supplement" in a Western country a part of nutritional pharmacology or is it simply a nutritional supplementation such as the addition of a vitamin in tablet form? Certainly, the use of large amounts of a specific fiber, e.g., guar gum (Chapter 5), that would not be normally part of the diet, can be considered nutritional pharmacology.

Fernstrom emphasizes in Chapter 2 an important concept in nutritional pharmacology. Her example can be expanded to many other substances: "When used therapeutically, choline and lecithin are administered in large amounts, not in amounts obtainable from the diet. . . . it is important to emphasize that choline and lecithin do not correct a nutritional deficiency. Rather, they act . . . to raise (*beyond normal limits*) serum choline levels resulting in elevated brain choline and ACh concentrations." In the pharmacological approach, we are not replenishing a missing nutrient with a concentrated form of the same (e.g., an iron supplement in the RDA range) but either feeding quantities abnormal in a regular diet or modifying the nutrient to achieve effects not possible with diet alone.

In the various chapters, the authors show how a wide spectrum of food components can be used pharmacologically. These range from choline and lecithin (Fernstrom, Chapter 2) and plant and marine sterols (Vahouny and Kritchevsky, Chapter 3) to branched-chain amino acids (Amen and Yoshimura, Chapter 4) and plant fibers (Jenkins, Chapter 5). These are all chemically unchanged from their state in nature. However, chemical modifications of the molecule have

yielded other compounds that are closely related to the original substances and, because of the modification, either bypass some metabolic problem in the handling of the original compound by the body or avoid toxicity stemming from intake of large amounts of the natural compounds. Vitamin D metabolites (Chesney, Chapter 6) and modified retinoids (Freeman, Chapter 7) are examples of these compounds. Finally, lactulose, a synthetic disaccharide, is an example of the use of a molecule synthesized from sugars normally found in foods to create a new compound with specified properties. When this compound reaches the colonic microflora, the desired pharmacological effects are achieved (Weber, Chapter 8). However derived, all these compounds originate in foods.

Conceptually, "pure" nutrition changes gradually to "pure" nutritional pharmacology. Somewhere between lies pharmacological nutrition. Here, "nutrition" is the substantive rather than the qualifier, while in "nutritional pharmacology" the reverse is true. Such niceties might appear precious to some, but exactness can only help in the coherent development of a science.

Let us keep in mind that this is a book on pharmacology where the compounds described are of nutritional origin. We hope that it will serve a threefold purpose: to help directly the clinician involved in the diseases described, to stimulate more research in pharmacology with food-derived compounds, and finally to establish this young discipline in its proper place in the sciences of health.

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2

Lecithin, Choline, and Cholinergic Transmission

Madelyn Hirsch Fernstrom

I. Introduction	6
II. Synthesis of ACh: Control by Precursor Availability	6
A. Acetyl Coenzyme A	8
B. Choline	8
III. Sources of Brain Choline: Availability of Choline to Cholinergic Neurons	10
A. De Novo Synthesis	11
B. Phospholipid Degradation	11
C. Hydrolysis of ACh Released Into the Synaptic Cleft: High-Affinity Uptake of Choline	12
D. Uptake From the Systemic Circulation	12
E. Dietary Sources of Choline	13
1. Ingestion; 2. Absorption of lecithin; 3. Absorption of choline.	
F. Liver Sources of Choline	15
1. Synthesis; 2. Degradation.	
IV. Acetylcholine Levels and Cholinergic Neurotransmission	16
V. Clinical Application of Precursor Therapy Using Choline and Lecithin	19
A. Tardive Dyskinesia (TD)	20
B. Huntington's Disease (HD)	21
C. Memory Disorders: Alzheimer's Disease and Aging	22
D. Psychiatric Disorders	23
E. Ataxia	23
VI. Summary and Conclusions	23
VII. References	24

I. INTRODUCTION

This chapter will review the evidence describing how and why the availability of choline (and its naturally occurring dietary form, lecithin) can affect the level and rate of synthesis of acetylcholine (ACh) in brain neurons and in peripheral synapses. Increases in ACh level can reflect, under certain conditions, enhanced cholinergic neurotransmission. Because precursor-induced rises in transmitter level are accompanied by increases in its release into the synaptic cleft, choline and lecithin have been tested as a treatment for several neurological diseases associated with insufficient cholinergic tone in brain. While substantial clinical improvement occurs when these precursors are administered in large, pharmacological amounts, it is important to emphasize that choline and lecithin do not correct a nutritional deficiency. Rather, they act as they do in rats: to raise (beyond normal limits) serum choline levels resulting in elevated brain choline and ACh concentrations. Thus, among the complex mechanisms controlling the rate of synthesis and release of ACh in brain, precursor availability has emerged as a reliable and specific means of altering cholinergic neurotransmission.

II. SYNTHESIS OF ACh: CONTROL BY PRECURSOR AVAILABILITY

ACh is synthesized from acetyl coenzyme A (AcCoA) and choline in a reaction catalyzed by choline acetyltransferase (CAT) [1]. This enzyme, confined to cholinergic terminals [2,3], is normally unsaturated with both of its substrates: rat brain CAT has a K_m of 400 μ M for choline and 18 μ M for AcCoA [4], while brain concentrations of these substrates range between 37 and 100 and 8 and 9 μ M, respectively. Because ACh is synthesized within nerve terminals, where only small amounts of free choline are present, the choline utilized for ACh synthesis must be obtained from the extracellular fluid (ECF). The major source of the brain's ECF arises from its uptake into brain from the systemic circulation. This process is mediated by a transport system which is normally unsaturated and of low affinity (choline's transport from the ECF into the pre-synaptic cholinergic terminal also occurs primarily through a low-affinity mechanism [5]) (Fig. 2-1) (see later discussion). Since choline can be readily taken up from blood into the brain's ECF, and then into the presynaptic cholinergic neurons, it seems reasonable to predict that raising serum choline levels could produce elevations in intraneuronal choline content. This, coupled with the low affinity of CAT for choline (and AcCoA) suggests that increases in brain choline could increase the rate of ACh formation.

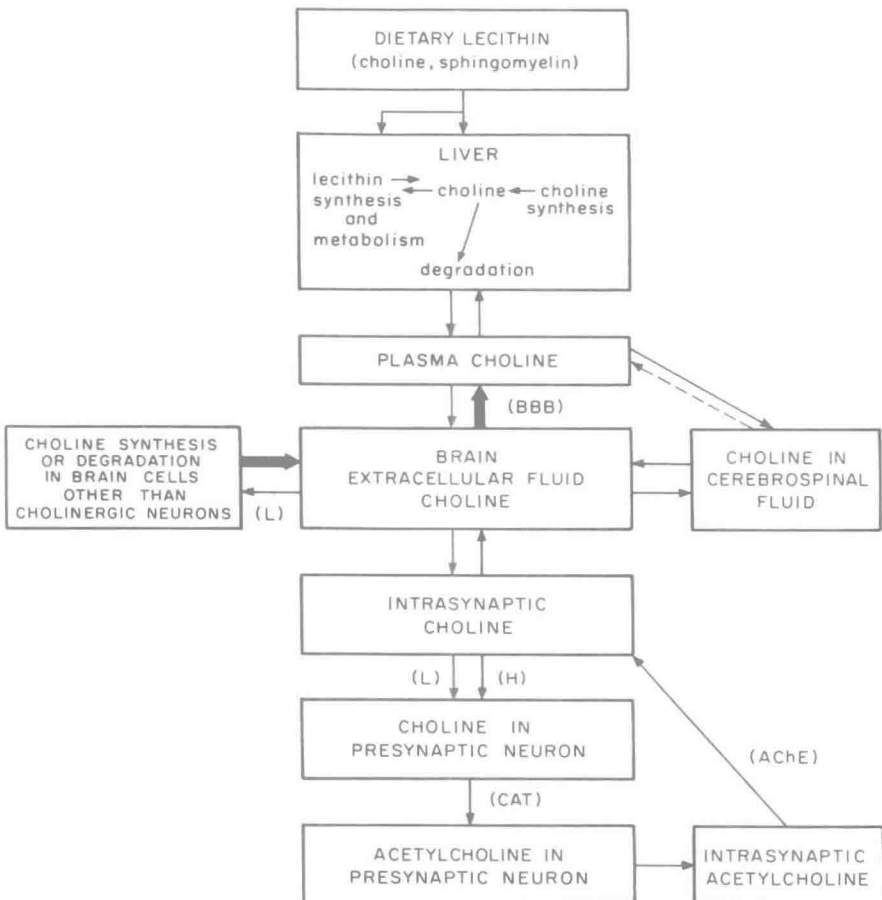


Fig. 2-1. Sources of choline for brain acetylcholine synthesis. The blood obtains choline from dietary sources (primarily lecithin) or hepatic synthesis. A low-affinity transport system (L) located within the capillary endothelium of the blood-brain barrier (BBB) transports the choline into the brain's extracellular fluid. It can then be (1) taken up within terminals of cholinergic neurons by either a high-affinity (H) or low-affinity (L) system; (2) be taken up within other brain cells by a low-affinity mechanism; or (3) pass into the cerebrospinal fluid or back into the bloodstream. Within nerve terminals, the choline is converted to acetylcholine by the action of choline acetyltransferase (CAT); ACh released into the synaptic cleft is hydrolyzed to choline by the enzyme acetylcholinesterase (AChE) following which the choline can again enter the presynaptic neuron by the high-affinity (H) transport system. Cholinergic nerve terminals also possess a low-affinity system which under certain circumstances may participate in choline uptake. In addition, a portion of the choline taken up presynaptically may be used for functions other than acetylcholine synthesis; for example, the synthesis of lecithin for incorporation into membranes.

A. Acetyl Coenzyme A

Glucose and pyruvate are the primary sources of AcCoA [6,7]. Pyruvate dehydrogenase, the enzyme catalyzing the conversion of pyruvate to AcCoA, is part of a thiamine-dependent enzyme system [8]. About 40 years ago, Mann and Quastel [9] found that brain slices obtained from thiamine-deficient pigeons synthesized ACh at a slower rate than slices from normal pigeons. In thiamine-deficient rats, large reductions in brain AcCoA levels were observed; this fall was accompanied by a 35% decrease in brain ACh concentration [10]. Reducing AcCoA availability by insulin-induced hypoglycemia or hypoxia decreases the incorporation of $^2\text{H}_4$ -choline into ACh in brain [11]. The kinds of changes in ACh synthesis observed in AcCoA-deficient states may explain in part some of the central nervous system dysfunctions observed in thiamine deficiency [8,12]. That these kinds of changes occur when the availability of AcCoA is reduced indicates the sensitivity of the ACh-synthetic pathway to this precursor, since less than 1% of the AcCoA generated by the brain is used for ACh synthesis.

Brain ACh is not the only pool affected by thiamine deficiency: rat superior cervical ganglia obtained from thiamine-deficient rats (with neurologic dysfunction), showed no change in actual transmitter content, although synthesis rate was reduced, and less ACh was released upon stimulation of the ganglia when compared with release from normal tissue [13].

B. Choline

The low-affinity, high-capacity systems mediating the uptake of choline from blood to brain, coupled with the low affinity of the synthetic enzyme for choline, raises the possibility that increasing circulating choline levels might alter brain ACh synthesis. The most rapid and direct way to raise serum choline levels is to administer free choline to animals. When choline is given to rats by injection [14,15], by stomach tube [16], or by direct addition to the diet [17], sequential elevations in serum choline levels, and brain choline and ACh concentrations are produced. Injection of physostigmine (blocking the metabolism of ACh) with choline produced an additive effect, suggesting that the ACh-synthetic rate had actually increased [14]. Other groups of cholinergic neurons are responsive to precursor availability. For example, choline and ACh levels in the terminals of preganglionic sympathetic neurons innervating the adrenal medulla increase following intragastric choline administration, an effect abolished by the transection of the splanchnic nerve (innervating the adrenal medulla) [18].

However, less than 1% of the choline normally present in the diet occurs as the free base, and is ingested in the form of lecithin (phosphatidylcholine). Thus, it was of particular interest to us to examine the effects of lecithin consumption on serum and tissue choline and ACh levels. When rats consume a single meal

TABLE 2-I
Effects of Lecithin Consumption on Brain Choline and Acetylcholine Concentrations

Group	N	Choline nmole/g	ACh nmole/g
Experiment 1, single meal			
Control	21	36.5 $\pm$ 2.9	21.5 $\pm$ 0.8
Lecithin	22	54.3 $\pm$ 3.8*	25.6 $\pm$ 1.0**
Experiment 2, three days			
Control	8	38.5 $\pm$ 4.6	20.2 $\pm$ 0.9
Lecithin	12	66.1 $\pm$ 7.1**	24.2 $\pm$ 0.3**

*P < 0.02.

**P < 0.01 differs from controls.

Note. Rats consumed a single meal containing lecithin granules (50% by dry weight) for 2 hr, (Experiment 1) or for 3 days (Experiment 2); they were killed 10 hr after access to the single meal (Experiment 1) or on the morning of Day 4 (Experiment 2). Fasting control rats in the 2-hr study were killed at 0 time; control rats in the 3-day study ate a 50% neutral fat diet. Data are expressed as means $\pm$ SE. From [19].

containing amounts of lecithin not markedly larger than those which they might normally consume within 24 hr, ACh levels increase both in brain (Table 2-I) and in adrenal glands (Figure 2-2) [19]. These increases occur after only a doubling in serum choline levels. Furthermore, the fatty acid composition of the ingested lecithin (which differs in egg- and soy-derived lecithins) had no effect on the brain's response: both types elevated serum and brain choline levels and brain ACh concentration [20]. Taken together, these studies also indicate that serum choline levels seem to be an accurate predictor of brain choline and ACh levels, an observation of great utility when testing the efficacy of choline and lecithin in the treatment of neurological disease, as will be discussed later.

When choline is administered acutely by stomach tube, large and prolonged (up to eight hours) increases in brain ACh occur [16]. Of particular interest is the fact that increases in brain ACh level produced by intragastric choline caused no simultaneous reduction in CAT activity, as might result from allosteric changes in the enzyme, or from end-product inhibition. Moreover, no reduction in CAT was noted 24–48 hr after choline administration, a time when a choline-induced decrease in enzyme synthesis, if actually occurring, might be expected to cause such a reduction to become apparent. Our inability to demonstrate such negative feedback control suggests that even after repeated administrations of choline (as is used in the treatment of disease), increases in brain choline will continue to accelerate ACh biosynthesis. This appears to be the case, since patients treated with lecithin for up to 1 year still show improvement in their symptoms.