choline in a reaction catalyzed by the enzyme *choline acetyl transferase* (CAT; Figure 1, p. 73).

Acetyl-CoA comes from any of several sources, including dehydrogenation of pyruvate, end products of fatty acid metabolism, or production of coenzyme A (CoA) from vitamin B5 which is then acetylated before interacting with choline.

Pyruvate is the end product of aerobic glycolysis. It can also be converted from lactate, the end product of anaerobic glycolysis. Pyruvate can then be converted to acetyl-CoA through the action of the *pyruvate dehydrogenase complex*. Acetyl-CoA then has several potential fates, all of which demand the transfer of acyl groups, including participation in the Krebs cycle, in fatty acid synthesis, in the production of ACh, and others.[4]

Pantothenic acid (PA), vitamin B5, is the initial substrate for de novo CoA synthesis. This five-step process requires both pantothenate (ionized PA) and the sulfur containing amino acid cysteine. Pantethine is a derivative of PA and is the functional component of CoA in the carrying of acyl groups. Pantethine is composed of two pantethine molecules joined by a disulfide bond.[5]

Choline is an essential nutrient. Humans reutilize choline and synthesize it de novo, but in quantities insufficient to meet metabolic demand. Therefore, an adequate intake of choline is necessary for health.[6] The established adequate intake (AI) in adult men is 550 mg/day and in adult women is 425 mg/day unless pregnant (450 mg/d) or breast-feeding (550 mg/d). Eggs are the richest dietary sources of choline, followed by animal protein sources, leaving vegans and several other groups at routinely inadequate daily intakes.[7–10] A list of choline content in foods can be found in the Micronutrient Information Center article on choline from the Linus Pauling Institute, Oregon State University.[7]

Choline is an essential substrate in the synthesis of the neurotransmitter ACh, but is also vital in several other bodily processes. Choline is necessary: as a component of cell membranes, in cell signaling molecules, in lipid metabolism and transportation, and as a major source of methyl groups. Methylation reactions turn body processes on and off and activate and inactivate metabolic intermediates.[7]

Choline deficient states may play a part in diseases and conditions including liver disease and fatty liver infiltration, neural tube defects, methylation defects, hypertension, atherosclerosis, neurological disorders, inflammatory disorders, and cancer.[7] Population research has demonstrated that many groups do not achieve their AI of choline.[6,8–11] For instance, there is evidence that only 2% of postmenopausal women reach their choline AI on a daily basis.[11]

Research has established that genetic polymorphisms which alter choline or folate metabolism may increase an individual's dietary requirement for choline. For instance, when 5-methyltetrahydrofolate (5-MTHF) is deficient due to a polymorphism (or other reasons), the body depends on betaine from choline for the conversion of homocysteine to methionine.[12] Methionine is then converted to S-adenosyl-methionine (SAMe), the major methyl donor for one-carbon transfers in the body.[13] When choline is required as a methyl donor it is shunted away from other biochemical processes. Therefore, greater demand for dietary choline may be prevalent in the population based on genetic polymorphisms that are prevalent.[14–16]

Therapeutic Plausibility

The therapeutic plausibility of utilizing the ACh pathway in the treatment of cardiac dysrhythmias through supplementing oral precursors requires both that (1) oral supplementation be able to raise ACh levels in the neurons; and (2) those increases demonstrate clinical effects.

It is well established that the amount of ACh in the central nervous system is directly affected by the oral intake of choline. Studies and reviews which date back to the late 1970s establish that the synthesis of ACh in the brain (CNS) responds to the availability of choline in the blood and that the ability of neurons to make and release neurotransmitters, including ACh, depends directly on the concentration of amino acids and choline in the blood.[17,18]

Excellent research has been produced by Marty Hinz, MD, and his groups over the recent decades substantiating that oral supplementation of amino acid precursors can raise endogenous neurotransmitter levels. His work pertains primarily to serotonin and catecholamines, but is applicable to ACh via analogous mechanisms. More importantly, the work of Hinz et al. has established that oral precursor dosing leads to demonstrable clinical effects and improved patient outcomes.[19–22]

The half-life of ACh is very short at 2 minutes. To ensure fidelity in neuromuscular transmission, the body further enhances this breakdown of ACh enzymatically through *acetylcholine esterase* enzymes. While ACh is reclaimed by reuptake at the synaptic cleft, augmenting production and release to the extent necessary to inhibit cardiac automaticity will require the persistent availability of substrates for ACh production, a problem that we will need to address.

While we can find no evidence in the medical literature for the use of choline to address cardiac dysrhythmias, we can establish that the biochemical action of ACh exerts control over the cardiac rate and depolarization. The fact that supplementing oral choline raises levels of ACh in the CNS is long established in the medical literature, as cited.[17,18] Therefore, the biochemical and therapeutic plausibility for the choline aspect of MAP is present.

Pantethine has been reported to have antiarrhythmic action on experimental models of cardiac arrhythmias. In a study of a dog model of hypoxic cardiac perfusion, administration of pantethine was shown to significantly prolong the cardiac action potential and refractory period.[23] While the mechanism of that effect was not described, it is noteworthy that this is the same action which ACh has on the supraventricular myocardial cells, as described above.

Research on rate models of cardiac function has demonstrated that the intravenous (IV) administration of CoA results in a transient decrease in the heart rate. These studies make it appear that it is the adenosine portion of the CoA molecule which may be responsible for the decrease in heart rate rather than the pantethine, pantothenic acid, or cysteine constituents of the molecule.[24]

The accumulation of long chain acyl fatty acid intermediates promotes cardiac arrhythmias. This has been