# Pantethine: A Review of its Biochemistry and Therapeutic Applications

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## Abstract

Pantethine is the stable disulfate form of pantetheine, the metabolic substrate which constitutes the active part of coenzyme A (CoA) molecules and acyl carrier proteins. Because pantethine is located nearer to CoA than is pantothenic acid in the biosynthetic pathway of CoA, it has been suggested it will have clinical benefits in conditions where pantothenic acid is not effective, and clinical trials with pantethine appear to prove this argument. Oral administration of pantethine has consistently shown an ability to favorably impact a variety of lipid risk factors in persons with hypercholesterolemia, arteriosclerosis, and diabetes. Pantethine administration positively affects parameters associated with platelet lipid composition and cell membrane fluidity. In several animal models, preliminary studies have indicated pantethine can inhibit cataract formation. Pantethine is capable of lipotropic activity, and in experimental models exerts hepato-protective action and impacts adrenal cortex function. The intravenous administration of pantethine has been shown to impact several central nervous system neurotransmitters and hormones; however, oral doses of pantethine have not demonstrated a similar action, suggesting cysteamine, a metabolite of pantethine, is responsible for these actions.

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## Introduction

As the stable disulfate form of pantetheine, pantethine is the metabolic substrate which constitutes the active part of coenzyme A (CoA) molecules and acyl carrier proteins (ACP). The reactive component of both CoA and ACP is not the pantothenic acid molecule but rather it is the sulfhydryl (SH) group donated from cysteine. Although pantothenic acid is commonly known as Vitamin B5, pantethine, or its reduced-SH form pantetheine, contain the SH molecule required for enzyme activity. Pantethine, as opposed to pantothenic acid, bypasses the cysteine reactions required to form pantetheine from pantothenic acid, providing a more metabolically active form of the vitamin. See Figure 1 for the chemical composition of CoA, pantethine, pantetheine, and pantothenic acid.

The metabolic activity of Vitamin B5 is due to its role in the synthesis of CoA and ACP. CoA is a cofactor in over 70 enzymatic pathways, including fatty acid oxidation, carbohydrate metabolism, pyruvate degradation, amino acid catabolism, heme synthesis, acetylcholine

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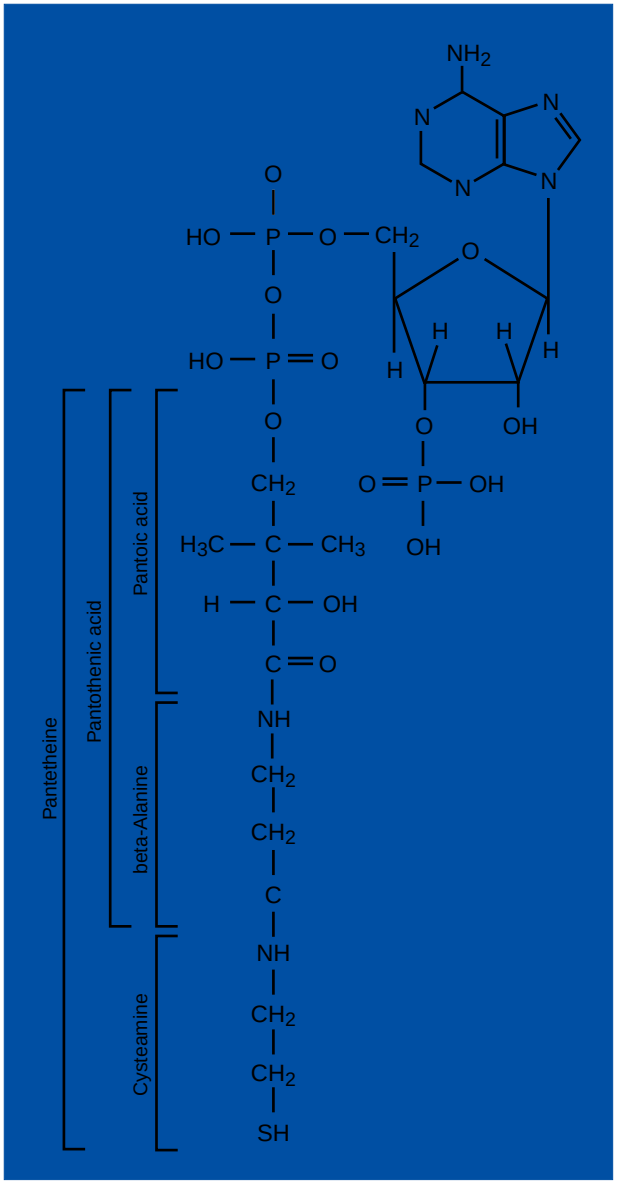
**Figure 1.** Chemical composition of CoA and its constituents: pantetheine and pantothenic acid.




synthesis, and phase II detoxification acetylations. ACP is an essential component of the fatty acid synthase complex required for fatty acid elongation.

## Biosynthesis of Pantetheine and Related Compounds

Biosynthesis of pantothenic acid can be accomplished by most plants and microorganisms by enzymatically combining pantoic acid with b-alanine. Mammals lack the enzyme for this synthetic step, so are unable to synthesize pantothenic acid.

Although foods contain CoA, ACP, pantetheine, and pantethine, as well as pantothenic acid, endogenous synthesis of both CoA and ACP can begin with pantothenic acid in humans. After pantothenic acid is absorbed and transported into cells, it can be converted to either CoA or ACP by a synthetic process requiring several enzymatic steps. Described below is the most common biosynthetic pathway; however, the initial phosphorylation reaction can also occur after pantetheine, the reduced form of pantethine, is formed or provided exogenously.

The first step is a phosphorylation reaction catalyzed by pantothenate kinase, a magnesium-dependent enzyme, resulting in the formation of 4'-phosphopantothenic acid (4'-PPA). High levels of CoA can inhibit this enzymatic step; however, carnitine has been shown to reverse the inhibitory action under experimental conditions in rat hearts.[1]

The next step in CoA or ACP biosynthesis is a condensation reaction with cysteine, producing 4'-phosphopantothenoyl cysteine. The enzyme needed for this synthetic step is also magnesium dependent. In the absence of cysteine, 4'-PPA will accumulate, suggesting, in biological systems, an absence of cysteine as a substrate is the limiting factor in biosynthesis of pantothenic acid's down-line metabolites.

4'-phosphopantetheine (4'-PP) is then formed by a decarboxylation reaction. The reaction rate of this enzymatic step is increased by the availability of protein-SH compounds, such as cysteine, suggesting the importance of these compounds for the activity of this decarboxylase enzyme.[2]

The final two steps in the synthesis of CoA involve the addition of an adenosyl group derived from ATP and the phosphorylation of this molecule. Both of these enzymatic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reactions require magnesium as a cofactor. See Figure 2 for the synthetic pathway for CoA.

Although degradative enzymes exist for the breakdown of CoA, the scattered location of these enzymes within the cell appear to indicate the cell is geared to minimize degradation of CoA once it has been formed.[3]

While CoA accounts for a large proportion of cellular pantothenic acid, ACP also contains the pantothenic acid molecule. The synthesis of ACP is not completely elaborated; however, as in CoA, 4'-PP has been identified as the prosthetic group.[3] Evidence suggests ACP, in addition to its role in fatty acid synthase, might be associated with a number of protein complexes. Observations also indicate ACP levels are maintained at the expense of CoA in bacteria;[3] however, it is unclear whether this is also the case in mammals.

Several hormones might impact the synthesis of pantothenic acid-dependent enzymes. In experimental models, glucagon increases, while insulin decreases, the incorporation of pantothenic acid into CoA. Glucocorticoids appear to potentiate the effects of glucagon.[3] Hyperthyroidism is also reported to increase CoA synthesis.[4]

## Metabolism of Pantethine

The metabolic fate of an oral dose of pantethine in humans has not been clearly described. However, because pantethine is closer to CoA than is pantothenic acid in the biosynthetic pathway of CoA, it has been suggested that pantethine will have clinical benefits in conditions where pantothenic acid is not effective. Based on clinical trials with pantethine, this theoretical argument appears to be true.

It is generally accepted that a portion of pantethine is hydrolyzed to pantetheine and a portion is degraded to pantothenic acid prior to intestinal absorption. The pantetheine can then be phosphorylated to provide the active 4'-PP moiety of CoA and ACP.[5]

Ono et al have suggested pantethine is more readily absorbed than calcium pantothenate, a commonly-used form of Vitamin B5 supplementation, when given orally to rats. In these animals, pantethine was hydrolyzed to pantetheine and pantothenic acid prior to absorption.[6] Shigeta et al have also

**Figure 2.** Coenzyme A biosynthesis.

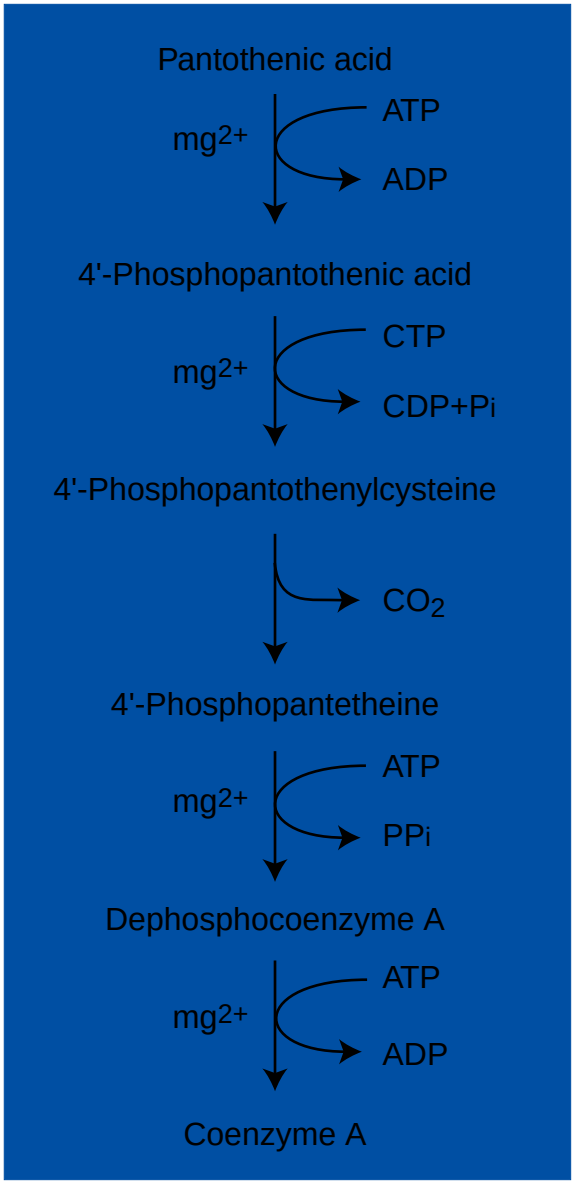




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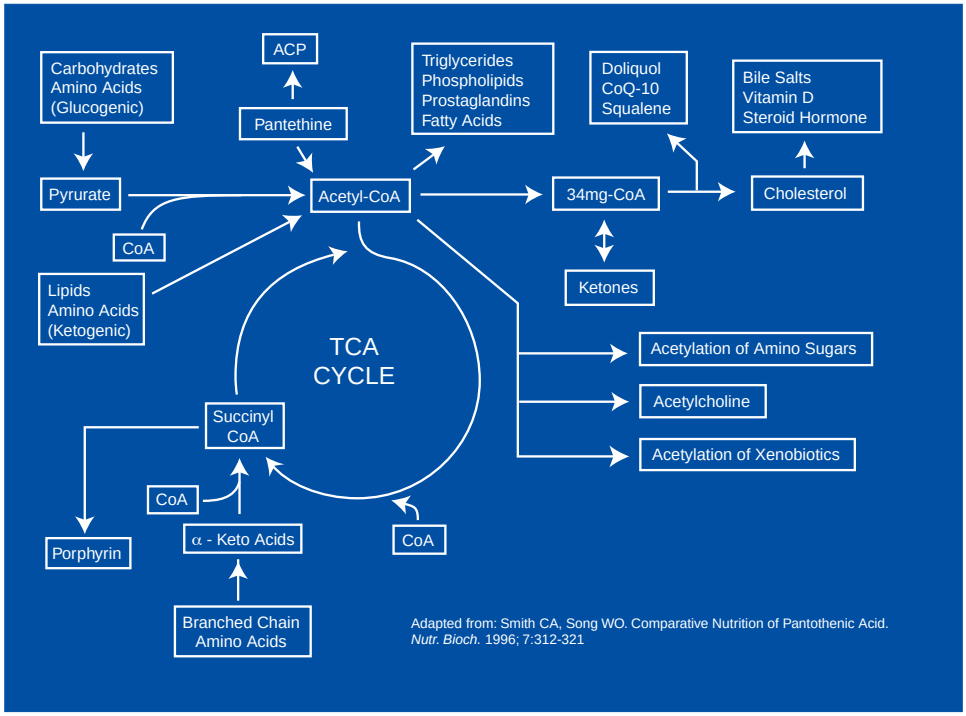
**Figure 3.** CoA and ACP dependent pathways




suggested pantethine, following intramuscular injection in healthy subjects, is retained longer in the blood and has more tissue affinity than pantothenic acid.[5]

## Biochemical Functions of Pantethine and CoA

The biological functions of pantethine as an enzyme component is dependent on its degradation to pantetheine and its subsequent incorporation into CoA or ACP. Both CoA and ACP function as acyl or acetyl carriers. CoA performs this function by forming thioester linkages between its sulfhydryl group and available acyl or acetyl groups. In this manner, CoA facilitates the transfer of acetyl groups from pyruvate to oxaloacetate in order to initiate the tricarboxylic acid (TCA) cycle. Before pyruvate can be used in the TCA cycle, it must be converted to acetyl-CoA by oxidative carboxylation. Coenzyme A, as well as thiamine, lipoic acid, riboflavin, niacin, and magnesium are all required.

Directly or indirectly, CoA is involved in the breakdown of the carbon skeleton of most amino acids. Alanine, cystine, cysteine, glycine, serine, threonine, and hydroxyproline are metabolized to pyruvate and then enter the TCA cycle with the help of CoA. CoA is directly involved with the breakdown of leucine, lysine, and tryptophan. The degradation of the pyrimidine bases, cytosine, uracil, and thymine, is also dependent on CoA.

CoA can direct acetyl groups into the formation of all the polyisoprenoid-containing compounds, which include dolichol, ubiquinone (CoQ10), squalene, and cholesterol. Dolichol is a sugar carrier used in the synthesis of glycoproteins. In addition to this indirect role in the formation of glycoproteins, CoA is also used in the formation of N-acetylated derivatives of amino sugars, including N-acetylglucosamine, N-acetylgalactosamine, N-acetylmannosamine, and N-acetylneuraminic acid. Because of the involvement of CoA in the initial steps of cholesterol synthesis, all down-stream metabolites of cholesterol, including steroids, Vitamin D, and bile acids, are indirectly impacted by CoA.

CoA is required for the acetylation of choline to form the neurotransmitter acetylcholine. It is also used for acetylation conjugations of phenol amines, sulfur amino, aliphatic amines, and hydrazines. The biosynthetic pathway of melatonin also requires an acetylation reaction.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Pantetheine has a wide array of functions which interact with fat metabolism, including synthesis, degradation, and transportation of fatty acids. The formation of fatty acids from excess amounts of glycogen involves CoA. In the first step in the synthesis of fatty acids, malonyl-CoA is formed by the carboxylation of acetyl-CoA. Fatty acid chain elongation is also dependent on CoA. The cytoplasmic fatty acid synthesizing system uses ACP, a protein analog of CoA derived from pantetheine to bind intermediates in the synthesis of long-chain fatty acids. CoA is also needed for the transport of long chain fatty acids into the mitochondria, a critical component of beta-oxidation, the process of converting fats to energy.

Before fatty acids can be attached to a glyceride backbone (e.g., triglycerides) they must first be converted to a CoA thioester. The acyl groups can then bond with the hydroxy group of glycerol. Additionally, the biosynthesis of phospholipids (phosphatidylcholine, ethanolamine, serine, inositol, cardiolipin), as well as plasmalogen, sphingenin, and ceramide, require CoA. Figure 3 provides a schematic diagram of several of the physiological functions of pantethine.[7]

## Pantothenic Acid Deficiency

Because pantothenic acid and its derivatives are so widespread in foods, it is generally considered a dietary deficiency in humans is unlikely; however, symptoms of deficiency have been produced in both animals and humans using a pantothenic acid agonist. Pantothenic acid deficiency has also been produced in persons fed a semisynthetic diet virtually free of pantothenic acid. Subjects typically complain of headache, listlessness or fatigue, and a sensation of weakness. Other symptoms can include personality changes, depression, sleep disturbances, and impaired motor coordination.[3] Sleep disturbances, frequent infections, postural hypotension, rapid heart beat on exertion, epigastric distress, anorexia, constipation, numbness and tingling of the hands and feet, parethesis ("burning feet syndrome"), hyperactive deep tendon reflexes, and weakness of finger extensor muscles have also been reported. More severe deficiency in some animals results in impaired glucocorticoid production and adrenal cortex failure.[8] In animals, other deficiency symptoms include dermatitis, graying hair, loss of hair, hemorrhage, neurological lesions, inflammation of nasal mucosa, corneal vascularization, and sexual dysfunction.

## Clinical Applications of Pantethine

### Hyperlipidemia

The majority of human research on pantethine has focused on its role as a therapeutic agent in the treatment of dyslipidemia. Oral administration of pantethine has consistently shown an ability to favorably impact a variety of risk factors in persons with hypercholesterolemia, arteriosclerosis, and diabetes.

Arsenio et al concluded that oral supplementation with pantethine results in a "clear tendency towards normalization of the lipidic values." They administered 600 mg/day of pantethine to 37 hypercholesterolemic and/or hypertriglyceridemic patients for a three-month period. Twenty-one of these patients were also diabetic. Administration of pantethine resulted in a quick and progressive decrease in total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol and apolipoprotein B (Apo-B), and an increase in high density lipoprotein (HDL) cholesterol and apolipoprotein A (Apo-A) in all groups. After suspending the treatment, a reversal of the improvement of these parameters was observed.[9] Arsenio et al subsequently conducted a one-year clinical trial with pantethine in 24 patients with established dyslipidemia of Fredrickson's types IIa, IIb, and IV, alone or associated with diabetes mellitus. Blood lipid assays revealed consistent reductions in total



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cholesterol, LDL-cholesterol, and Apo-B, along with an increase of HDL-cholesterol and Apo-A in individuals with types IIa and IIb dyslipidemia. The results were equally good in patients with uncomplicated dyslipidemia and in those with associated diabetes mellitus. A marked reduction in triglycerides was observed in the patients with Fredrickson's type IV dyslipidemia.[10] Seghieri et al similarly reported a decrease in triglycerides in uremic patients on hemodialysis with type IV dyslipidemia.[11]

Maggi et al investigated the effect of 900 mg per day of pantethine on 30 patients with dyslipidemia. The six patients in the subgroup of type IIa dyslipidemia decreased total cholesterol by 26%, triglycerides by 28%, LDL-cholesterol by 38%, very low density lipoprotein (VLDL) cholesterol by 28%, and Apo-B by 16%. HDL-cholesterol increased by 34%. The nine patients with type IIb dyslipidemia experienced decreases of 25% for total cholesterol, 49% for triglycerides, 33% for LDL-cholesterol, 44% for VLDL-cholesterol, and 11% for Apo-B. An increase in HDL-cholesterol of 43% was observed. The 15 individuals with type IV dyslipidemia decreased total cholesterol by 13%, triglycerides by 68%, VLDL-cholesterol by 53%, and Apo-B by 18%. HDL cholesterol increased by 25%.[12]

Gaddi et al gave pantethine (900 mg/day) to 11 patients with type IIb and 15 patients with type IV dyslipidemia. The patients with type IIb dyslipidemia experienced reductions in total cholesterol, LDL-cholesterol, and triglycerides, and an increase in HDL-cholesterol. In type IV patients, a clear decline in triglycerides was demonstrated. The variation in total, LDL-, and HDL-cholesterol in these individuals was not significant.[13]

Bertolini et al treated a series of seven children and 65 adults suffering from hypercholesterolemia alone or associated with hypertriglyceridemia (types IIa and IIb of Fredrickson's classification) with pantethine (900 mg daily (children and young boys) and 1200 mg daily (adults)) for 3–6 months. In the pediatric group they reported a 20% reduction of total cholesterol and a 27% decrease in LDL-cholesterol. In adult patients with type IIa hyperlipoproteinemia, a 25% decrease in total cholesterol, a 39% decrease in LDL-cholesterol, a 34% decrease in Apo-B, and a modest increase in HDL-cholesterol were observed. In adult patients with type IIb hyperlipoproteinemia, total cholesterol was reduced by 19.8%, LDL-cholesterol by 37%, triglycerides by 31%, and Apo-B by 6%. In this subgroup, a 23% increase of HDL-cholesterol and a 15% increase in apolipoprotein A-I were also observed.[14]

Donati et al tested the effectiveness and tolerability of pantethine in the treatment of 31 patients with dyslipidemia undergoing chronic hemodialysis. The mean duration of treatment was nine months, with an oral dose of between 600–1200 mg of pantethine daily. A significant improvement in total blood cholesterol was noted in the patients with basal hypercholesterolemia, and a highly significant reduction of serum triglycerides was observed for the entire group. Significant variations of HDL-cholesterol or total Apo-A were not detected.[15]

Murai et al administered 1000 mg of pantethine orally daily for three months to 12 male survivors of cerebral infarction. A tendency toward a decrease in plasma concentrations of total cholesterol, triglyceride, phospholipid, and VLDL- and LDL-cholesterol was observed. HDL-cholesterol concentration, especially HDL2, and the HDL:LDL ratio improved significantly.[16]

Binaghi et al treated 24 hypercholesterolemic perimenopausal women with 900 mg/day of pantethine. After 16 weeks of treatment they reported an efficacy rate of about 80% with significant reductions in total cholesterol, LDL-cholesterol, and LDL/HDL ratios.[17]


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**Table 1.** Pantethine's reported impact on lipid parameters in patients with Fredrickson's type IIa, IIb, and IV dyslipidemia

| Type | Clinical Definition | Pantethine's Impact |
|---|---|---|
| IIa | total cholesterol elevated<br>LDL elevated<br>triglyceride normal | decrease total cholesterol<br>decrease LDL-cholesterol<br>decrease VLDL-cholesterol<br>decrease triglyceride<br>decrease Apo-A<br>increase HDL-cholesterol<br>increase Apo-A |
| IIb | total cholesterol elevated<br>LDL elevated<br>VLDL elevated<br>triglyceride elevated | decrease total cholesterol<br>decrease LDL-cholesterol<br>decrease VLDL-cholesterol<br>decrease triglyceride<br>decrease Apo-B<br>increase HDL-cholesterol<br>increase Apo-A |
| IV | total cholesterol normal<br>VLDL elevated<br>triglyceride elevated | mixed results with total cholesterol<br>mixed results with LDL-cholesterol<br>decrease VLDL-cholesterol<br>decrease triglyceride<br>decrease Apo-B<br>mixed results with HDL-cholesterol |

Atherosclerotic manifestations are not only common in individuals with diabetes but also result in significant long-term complications. Correspondingly, lipoprotein disorders must be managed in diabetics. Tonutti et al reported that pantethine was effective in lowering triglyceride levels in diabetic patients with dyslipidemia.[18] Hiramatsu et al reported oral administration of pantethine to 31 diabetic patients with hyperlipidemia decreased cholesterol from a mean value of 236 mg/dl to 217 mg/dl, and increased HDL-cholesterol from a mean value of 40 mg/dl to 43 mg/dl.[19] Donati et al conducted a clinical study on 1045 hyperlipidemic individuals; 57 with insulin-dependent and 241 with non insulin-dependent diabetes. Oral administration of pantethine (900 mg/day) resulted in improved lipid metabolism in patients with and without diabetes.[20] Miccoli et al observed a decrease in total cholesterol, LDL-cholesterol, and Apo-B in diabetics following administration of pantethine. No variations were observed in other lipid parameters.[21]

Pantethine administration has been shown to favorably affect parameters associated with platelet lipid composition and cell membrane fluidity. Prisco et al observed a significant decrease of total cholesterol and total phospholipids in plasma and in platelets following pantethine supplementation. A relative increase of omega-3-polyunsaturated fatty acids both in plasma and in platelet phospholipids, and a decrease of arachidonic acid in plasma phospholipids was also observed.[22]



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Gensini et al studied the effect of oral treatment with pantethine on platelet lipid composition in 20 patients with dyslipidemia. In addition to a reduced phospholipid and cholesterol content, treatment resulted in a reduction of saturated and mono-unsaturated, and a relative increase of polyunsaturated fatty acid content of platelet phospholipids. An increased content of eicosapentaenoic and docosahexaenoic acid, and a concomitant decrease of arachidonic acid content was also noted.[23]

In diabetic patients, composition of platelets is characterized by a derangement in a wide variety of lipid concentrations and a higher microviscosity than in healthy platelets. Administration of pantethine is reported to normalize these values of fatty acids to control levels, and result in a concomitant reduction in experimentally induced hyperaggregation. The volume of platelets and the microviscosity were also lower following oral administration of pantethine.[19] Oral administration of 1200 mg/day of pantethine is very effective in lowering elevated levels of beta-thromboglobulin, a marker associated with increased platelet activation and release in diabetes.[24]

While the exact mechanism of action of pantethine in normalizing parameters associated with dyslipidemia is unknown, several explanations have been proposed. Some authors have suggested pantethine might be capable of directly modulating the action of several enzymes. The addition of pantethine to cultured cells has been shown to cause an 80% inhibition in cholesterol synthesis.[25] Experimental evidence suggests pantethine is effective at inhibiting cholesterol synthesis when levels of the cholesterol precursor mevalonate are elevated. Under this circumstance, an increased incorporation of the substrate into cholesterol is progressively reduced and an increased incorporation of the substrate into precursors of cholesterol (methyl sterols and squalene) occurs.[26] *In vitro* and cell culture experiments suggest pantethine can inhibit the activity of HMG-CoA reductase.[27] Administration of pantethine has been shown to increase lipoprotein lipase activity in adipose tissue of rats.[28] Pantethine is also capable of inhibiting total fatty acid synthesis.[25]

Although the efficacy of pantethine in normalizing parameters of dyslipidemia has been attributed to its ability to increase CoA levels, this relationship has never been demonstrated. Theoretically, if pantethine enhances the formation of CoA, the additional CoA might then combine with free acetyl groups to form acetyl-CoA. The acetyl-CoA could then be directed into the TCA cycle or beta-oxidation of fats at the expense of cholesterol formation. Enhanced formation of CoA could also impact cholesterol levels since the CoA molecule is important in the formation of bile salts.

Wittwer et al have proposed the action of pantethine might be a result of its hydrolysis product, cysteamine. *In vitro* experiments have shown modulation of cholesterol and methyl sterol synthesis by pantethine, cysteamine, or cystamine (the disulfide of cysteamine), while pantothenic acid had no effect. *In vivo* experiments have also shown oral pantethine or equimolar cystamine can lower plasma cholesterol, while pantothenic acid does not.[29]

## Cataract Protection

In several animal models, preliminary studies have indicated pantethine can inhibit cataract formation. Administration of pantethine (820 mg/kg) inhibits selenite-induced opacification in rats. The effect of pantethine was most significant when it was administered within six hours following selenite injection. Administration of pantethine 10–17 hours after selenite injection was not protective.[30] Other experimental results suggest protein aggregation and lens opacification associated with a variety of physiological


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and biochemical mechanisms, including radiation, selenite, galactose, and streptozotocin can be delayed or inhibited by the systemic administration of pantethine.[31] The pattern of proteins in animal lenses protected from selenite-induced protein aggregation and opacification by administration of pantethine is reported to resemble the pattern for proteins from transparent lenses of normal untreated animals.[32] While it appears pantethine might be active in preventing cataract formation in these animal models, reversal of existing opacities has not been observed with the use of pantethine.

## Central Nervous System Impact of Pantethine

Cysteamine, a cysteine derivative formed from the degradation of pantethine, is known to cause depletion of somatostatin, prolactin, and noradrenaline in the brain and peripheral tissues. Similarly, pantethine has been shown to deplete somatostatin, prolactin, and noradrenaline, although with lower efficacy compared to cysteamine.[33] The actual clinical relevance of pantethine's impact on the central nervous system in humans has not been explored. In animals, the effect on somatostatin, prolactin, and noradrenaline has been demonstrated following intraperitoneal and intravenous administration of pantethine; however, the effect does not appear to occur after an oral dose.

Ong et al reported intraperitoneal injection of pantethine depleted somatostatin and prolactin levels in experimental animals.[34] Vecsei et al also observed decreased concentrations of striatal somatostatin following administration of high doses (1.95-3.90 mM/kg SC) of pantethine. This effect was attenuated 24 hours after treatment.[35] Both intraperitoneal and intravenous administration of pantethine can deplete prolactin from plasma; however, oral administration of pantethine does not seem to be capable of influencing plasma prolactin concentrations.[36]

The effects of pantethine on central neurotransmissions was investigated in rats. Pantethine administered in low doses (0.48-0.96 mM/kg SC) induced a decrease of the hypothalamic noradrenaline level without influencing the concentrations of dopamine and dihydroxyphenyl acetic acid (DOPAC). When pantethine was injected in higher doses (1.95-3.90 mM/kg SC), a marked depression of noradrenaline and an increased concentration of dopamine and DOPAC was observed in the hypothalamus. This effect was attenuated 12 hours following administration of pantethine, and disappeared after 24 hours.[35] While pantethine consistently reduces the noradrenaline and increases the dopamine and DOPAC concentrations in the hypothalamus,[37,38] pantothenic acid does not appear to influence hypothalamic catecholamine concentrations.[38]

Detoxification and Liver Protection

Acetylation reactions are an important component of the hepatic phase II detoxification system. Although species variation in acetylation reactions appear to occur, in all acetyltransferase reactions the donor of the acetyl group is acetyl-CoA. Acetylation reactions primarily metabolize $NH_2$ groups. Acetylation reactions of OH and SH groups are known but uncommon. The compounds typically metabolized by acetylation reactions include aliphatic amines (such as histamine and mescaline), aromatic amines (such as sulfonamide), hydrazine and hydrazide, and certain amino acids (such as phenylcysteine). Because of its biochemical position as the most stable supplemental form of an immediate precursor to CoA, pantethine might be able to play an important role in the metabolism of some xenobiotic compounds.

Ligas et al have reported lipotropic activity of a preparation combining pantethine and a calcium salt of phosphorylcholine chloride.[39] Pantethine should also be useful in the treatment of hepatitis A. Calcium



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pantothenate (300 mg and 600 mg daily) and pantetheine (90 mg and 180 mg daily) were administered orally for 3-4 weeks as combined therapy in 156 patients with hepatitis A. A favorable clinical effect, as well as an enhanced immunomodulatory action, a beneficial effect on the level of blood serum immunoglobulins, and an increased phagocytic activity of peripheral blood neutrophils were reported. Pantetheine provided the most pronounced therapeutic effect.[40]

Pantethine, as well as other derivatives of pantothenic acid, can decrease acute toxicity of acetaldehyde in mice. The duration of the narcotic action of ethanol in mice and rats is also decreased by administration of pantethine. The anti-toxic effect of pantethine and other pantothenic acid derivatives did not appear to be mediated by CoA-dependent acetylation reactions of detoxification,[41] so the protective effect is probably related to pantethine's capability to decrease the rate of ethanol oxidation.[42]

Daily intraperitoneal administration of pantethine (500 mg/kg) has been shown to offer significant protection against carbon tetrachloride-induced liver damage in a rat model. Hepatotoxicity and peroxidative damage were prevented, and increases in serum ALT were lessened. Pantethine also prevented the development of hepatic steatosis caused by the halocarbon.[43] Pantethine and other pantothenic acid-related compounds have been shown to protect cell membranes against damage by oxygen free radicals. Slyshenkov et al suggest pantethine's ability to increase cellular levels of CoA is probably responsible for the observed protection. It is presumed CoA can diminish propagation of lipid peroxidation and promote repair mechanisms by enhancing phospholipid synthesis .[64] Hiramatsu et al have reported a diet with an excess of pantethine protects the drug-metabolizing system of the rat liver, and increases the survival rate of animals against exposure to autoxidized linoleate.[45] In a subsequent report, they suggest this activity might be due to decreased lipid peroxidation resulting from the reducing property inherent in pantethine's SH group.[46]

Pantethine's ability to decrease lipid peroxidation is likely to provide clinical benefits in other tissues as well. Kobayashi et al note pantethine, glutathione, and ascorbic acid are effective in controlling chronic urticaria. They suggest a relationship exists between peroxidation of serum lipids and fatty acids, and the pathogenesis of chronic urticaria.[47]

## Impact on Adrenal Function

The administration of pantethine appears to exert an influence on some indicators of adrenal function. Several animal experiments have indicated a deficiency of pantothenic acid adversely affects adrenal cortex function.[48-50] The pantothenate derivatives (pantethine, 4'-PPA, and CoA in particular) injected into animals have a marked steroidogenous effect.[51] Administration of pantethine to 20 humans with a variety of clinical conditions was reported to buffer the increase in 24-hour urinary 17-hydroxycorticosteroids and plasma 11-hydroxycorticosteroids stimulated by a loading dose of adrenocorticotropic hormone.[52] While these reports are interesting, the clinical relevance of pantethine supplementation on adrenal function remains largely unexplored.

## Toxicology and Dosage

Animal studies have documented the low toxicity and safety of pantethine.[53,54] Although digestive disturbances have occasionally been reported in the literature, the majority of researchers have commented on the complete freedom from side-effects and subjective complaints experienced by individuals taking pantethine.

The most common oral dosage used


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in the treatment of dyslipidemia has been 300 mg three times per day. Higher dosages can be utilized; however, in the majority of individuals this seems to be unnecessary. When utilizing pantethine for other clinical conditions, although information on dosage is limited, a similar schedule is advised.

## Conclusion

Pantethine is a metabolically active substrate for CoA and ACP. Because it bypasses several of the enzymatic reactions required for incorporation of pantothenic acid into these molecules, pantethine is capable of exerting a therapeutic effect in conditions where pantothenic acid is ineffective. Pantethine contains a sulfhydryl (SH) group from a cysteine derivative, while pantothenic acid must be supplied with this SH group prior to having vitamin activity. *In vivo*, availability of cysteine and SH groups is probably the limiting factor preventing biosynthesis of coenzymes from pantothenic acid. Pantethine offers a significant biochemical advantage by avoiding the need for this endogenous supply of cysteine.

Pantethine has consistently demonstrated an ability to favorably impact lipid parameters in a wide variety of clinical situations. Pantethine administration has been shown to favorably affect platelet lipid composition and cell membrane fluidity. Although supplementation with pantethine should not be expected to reverse existing opacities, administration has successfully prevented experimentally-induced cataract formation. Evidence suggests pantethine might be beneficial in the treatment of hepatitis A. In addition to having lipotropic activity, pantethine seems to be very effective in reducing peroxidative damage and enhancing hepatic enzyme function. Pantethine might be capable of enhancing the function of the adrenal cortex; however, more research is needed to ascertain the exact nature of its impact on the adrenal gland and glucocorticoid production in humans. Clinical results of pantethine supplementation are impressive, and because the coenzymes which utilize pantethine for their metabolic activity are utilized in over 70 biochemical reactions affecting a wide variety of cellular functions, it is very likely that only the tip of the iceberg of the therapeutic potential of pantethine has been discovered.

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