

An Orthomolecular Theory of Human Health and Disease

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Abstract

Orthomolecular substances are substances normally present in the human body. Many of them (vitamins, essential minerals, essential amino acids, essential fats) are obtained only exogenously, as foods or dietary supplements, and thousands of others (coenzyme Q10, L-carnitine, apoprotein(a) and other proteins) are synthesized in the cells of the human body. Optimum health and optimum resistance to disease are achieved when all of these substances are present in the optimum amounts. The intake of most of the vitamins is less than optimum, and endogenous synthesis of many substances occurs at less than the optimum rate; the intake of supplementary amounts of these substances can lead to improvement in health. Some regulation of the rates of synthesis and the functioning of macromolecules such as proteins can also be achieved. The evidence indicates that ascorbate insufficiency is the most important cause of poor health, with the blood level of apopro-tein(a) also contributing, as well as insufficiencies in some other vitamins and some endogenous substances. Measures to achieve the optimum levels of the most important Orthomolecular substances can be taken to improve health and control disease.

Introduction

During the last half century many researchers have suggested that the usually recommended intake of ascorbate (vitamin C) is not enough to put people in the best of health. The arguments were strengthened in 1967 by the American biochemist Irwin Stone, who stated that almost all human beings suffer from the genetic disease hypoascorbemia, and that the optimum

intake of ascorbate, providing the best of health and the greatest control of disease, is 50 or more times the RDA of 60 mg/d for an adult.¹ In 1972, in his book *The Healing Factor: Vitamin C Against Disease*,² he discussed over 500 published papers in which the authors reported the value of high doses of ascorbate in preventing and treating about 100 diseases. His discussion was repeated and extended somewhat by Pauling,^{3 4} and much additional evidence about the value of a high intake of ascorbate in the prevention of disease and, as an adjunct to appropriate conventional therapy, in the treatment of disease, has been published during the last 20 years.

The recent discovery by Rath *et al.*^{5 6} that atherosclerotic plaques are formed by lipoprotein(a) [Lp(a)] rather than by low-density lipoprotein [LDL] and our recognition of the connection of Lp(a) and its apoprotein apo(a) with ascorbate⁷ have led us to investigate the evidence about the relation between the concentration in the blood of Lp(a), as well as the intake of ascorbate, to achieving the best of health, with the greatest amount of control of disease. We have reached the conclusion that the optimum intake of ascorbate and the optimum level of Lp(a) are both required for the best of health, and that the basic risk factors for nearly all diseases may well be these two substances.

The Ascorbate-Apo(a) Connection

Ascorbate is an important hydroxylating agent. It is required for the synthesis of procollagen to collagen and of proelastin to elastin, by hydroxylating prolyl and lysyl residues, and is used up in these reactions; accordingly, ascorbate deficiency results in weakness of vascular walls, which are not sufficiently strengthened by the deposition of collagen and elastin. The fact that Lp(a) is found

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in good amounts mainly in the blood of animal species that do not synthesize ascorbic acid suggested to us⁷ that apo(a) is a surrogate for ascorbate, serving to rectify some of the problems caused by ascorbate insufficiency; in particular, deposition of Lp(a) on the vascular wall can strengthen the blood vessels and stabilize connective tissue throughout the body.

The loss of the ability of primates to synthesize ascorbate occurred in the common ancestor of humans and other primates at a time about 40 million years ago, and the genetic change resulting in the synthesis of good amounts of apo(a) occurred somewhat later. Lp(a) is an unusual bodily constituent in that the concentration in the blood of a person varies 1000-fold, from less than 1 mg/dl to more than 100 mg/dl. We suggest that this great variation is the result of the short time that has passed since the need for Lp(a) developed: there has not been time enough for the evolutionary processes to occur that would stabilize the rate of synthesis of apo(a) to strengthen the blood vessels and normalize the connective tissue, whereas others overshoot the mark and deposit atherosclerotic plaques. Apo(a) is synthesized in the liver, where it attaches itself to apoB and takes up lipids to form the Lp(a) particles to be transported to the sites of requirement.

Ascorbate and Lp(a) in Relation to Health and Disease

There is now no doubt that the optimum intake of ascorbate, much greater than the RDA, leads to improved health and greater control of diseases. The relation between ascorbate intake and CVD mortality has been discussed in our earlier paper.⁸ Stone reviewed the published evidence not only for CVD but also for cancer and other diseases. Recently published epidemiological papers showing a correlation of increased mortality with decreased ascorbate intake or decreased ascorbate plasma level include not only CVD but also cancer, diabetes, and many other diseases. We shall not give references to the many papers in this field, which support the conclusions reached earlier by Stone, Pauling, and others.

There are also many published reports of studies showing that high levels of

Lp(a) are correlated with an increased risk for many diseases. An important early investigation is that by Rhoads *et al.*⁹ They found the risk for myocardial infarction to be much greater for those subjects' Lp(a) level in the top quartile (20 to 72 mg/dl) than for those in the third quartile (11 to 20 mg/dl). It is interesting that they reported also that the risk for the quartiles (0 to 11 mg/dl) was found to be larger than for the third quartile. Our interpretation of these observations is that the optimum Lp(a) level is 11 to 20 mg/dl. Persons with lower values are at increased risk because they do not have enough Lp(a) to rectify the damage done by the ascorbate insufficiency and those with the high values have too much Lp(a), causing atherosclerotic plaque formation and other deleterious consequences. In another study¹⁰ a significant association was found between high levels of Lp(a) (>17 mg/dl) and the incidence of both coronary heart disease and cerebral infarction. In a recent study of patients with angiographically documented coronary heart disease compared with control patients free of cardiovascular disease it was found that the Lp(a) level for the patients was significantly higher than for the controls.¹¹

With respect to cancer, we quote Wright *et al.*,¹² who refer to several earlier studies about cancer in relation to Lp(a). Wright *et al.* report that 48% of their sample of cancer patients had Lp(a) levels greater than 35 mg/dl, considerably higher than the 20% for normal blood donors and 29% of hospitalized control patients with cardiovascular disease.

Insulin-dependent diabetes mellitus patients are at high risk for cardiovascular disease. This fact may be explained by the observation¹³ that improved glycemic control leads to a decrease in the Lp(a) level in patients with insulin-dependent diseases. Among other diseases associated with elevated Lp(a) levels include membranoproliferative glomerulonephritis.¹⁴ Patients with chronic renal disease treated by hemodialysis tend to have much higher Lp(a) levels (>30 mg/dl) than the controls (10 mg/dl).¹⁵ These investigators mention that this fact may explain the development of atherosclerosis in these patients. The observation that the Lp(a) level increases

after an acute attack of a myocardial infarction and also after a surgical operation suggests that it is functioning as an acute-phase protein.^{16 17}

The discovery that apo(a) [not LDL] is found in sperm and other tissues suggests that this glycoprotein has functions in addition to forming Lp(a) and that the presence of some apo(a) in these tissues may contribute to good health and the control of disease by mechanisms that have not yet been discovered. We have now obtained immunological evidence that Lp(a) is present in the plasma of guinea pigs, rabbits, sheep, goats, and a few other animal species. The concentrations are, however, much lower than the average for human plasma. The fact that the presence of Lp(a) in these species escaped earlier discovery may be explained by the complication of the use of anti-human-apo(a) antibodies, complementary to the carbohydrate side chains of human apo(a), which may occur less frequently in the apo(a) of other species.

Endogenous Substances

In 1968 one of us published a detailed physicochemical analysis of the process of synthesis of endogenous substances.¹⁸ It was shown in general that the concentration that is optimum for endogenous production is less than the optimum that would be reached if the substance were provided exogenously, without the organism having to do work and use materials for its production. Accordingly an improvement in health may be achieved by supplementary intake of endogenous substances. Two examples are CoQ10 and L-carnitine, each of which, taken as an oral supplement, improves muscular strength, with special value in cardiac insufficiency.

The concentration of a protein is not easily increased, usually injection is required. The effectiveness of many enzymes can, however, be increased by increasing the intakes of the corresponding coenzymes.

The Unified Concept of Occurrence and Control of Disease

A high intake of tocopherol (vitamin E) is reported to be of value in controlling CVD and cancer, and, especially because

of its function as a fat-soluble antioxidant, probably also of other diseases. Also, niacin (vitamin B₃) in increased intake decreases the mortality from CVD and cancer. Other Orthomolecular substances in increased intake may also contribute to the improvement of health, especially those that serve as coenzymes. It is our opinion, however, that the primary cause of early incidence of and death from most diseases is the poor health that results from insufficiency of ascorbate. An example is the fact that atherosclerotic plaques usually occur at lesions in the vascular wall, and that the occurrence of these lesions can be attributed to the weakness of the wall resulting from the decreased rate of synthesis of collagen and elastin caused by an insufficiency of ascorbate. Because a high level of Lp(a) is the largest risk factor for CVD, the principal cause of death in many parts of the world, and is correlated also with mortality from other diseases, we associate Lp(a) with ascorbate in our unified concept of the occurrence and control of all diseases. The unified concept is that a low intake of ascorbate and a high level of plasma Lp(a) result in poor health of human beings and an increased incidence of nearly all diseases, and that measures to rectify these factors can contribute to the control of nearly all diseases.

Rectification of ascorbate deficiency is rather simple. It usually consists of taking ascorbate regularly by mouth in amounts of grams per day, or, in severe illnesses, intravenously administering sodium ascorbate in large amounts, as much as 200 g in 24 hours. The plasma level of Lp(a) is not so easily controlled. It is determined largely by genetic factors that regulate the rate of apo(a) synthesis in the liver. This rate is decreased, however, by an increased intake of ascorbate. Moreover, we have observed in a preliminary tissue-culture study with human liver cells that an increased concentration of niacin also decreases the rate of apo(a) synthesis, and other ways of controlling this rate may be discovered. Moreover, to the extent that a disease is related to plaque formation, much control may be achieved by the administration of inhibitors that block the binding of Lp(a) to the arterial wall, such as L-lysine.

Conclusion

There is much evidence that the optimum intake of ascorbate, the intake that would lead to the best health and the greatest effectiveness in the prevention and treatment of disease, is far greater than the recommended dietary allowance (the RDA). People receiving only the RDA have weaker blood vessels and other tissues and organs because of the inability to synthesize the proper amounts of the structural proteins collagen and elastin, to carry out other hydroxylation reactions at the optimum rates, and to provide the maximum protection that this antioxidant, the most important one in the human body, might provide. As a result of the impairment in health caused by ascorbate insufficiency, nearly every person suffers unnecessarily from premature incidence of disease and from suffering and death caused by disease. Consideration of all of the present evidence has led us to the conclusion that insufficiency of ascorbate is the principal cause of early incidence of and mortality from disease. An important contributing factor is the high concentration of Lp(a) in the blood of many people, which leads to the development of plaques and to CVD. Lp(a) and its apoprotein apo(a) are so important in relation to health and disease that we have associated them with ascorbate in our formulation of a unified concept of health and disease. Other Orthomolecular substances, such as the vitamins tocopherol and niacin and the amino acid L-lysine, may also be incorporated into our unified theory. The efforts to control disease suggested by this theory are to some extent to be considered as adjuncts to appropriate conventional methods of prophylaxis and therapeutics, and to some extent as alternatives. Since episodes of illness are known to increase the rate of aging and decrease survival time, the relation of this theory to aging and survival time is obvious.

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