Medical Hypotheses

Plasma Amino Acids and the Insulin/Glucagon Ratio as an Explanation for the Dietary Protein Modulation of Atherosclerosis

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Abstract — The amino acid composition of the diet influences the postprandial levels of plasma amino acids along with the hormones insulin and glucagon in humans fed single test meals identical in composition except for protein source. Soy protein (hypocholesterolemic), vs. casein (hypercholesterolemic), contains a higher amount of arginine and glycine and induces an increase in postprandial arginine and glycine. Soy protein induces a low postprandial insulin/glucagon ratio in both hypercholesterolemic and normocholesterolemic subjects. Casein induces a high postprandial insulin/glucagon ratio among hypercholesterolemic subjects. Amino acids such as arginine and glycine are associated with a decrease, while lysine and branched-chain amino acids are associated with increased serum cholesterol levels. Our data are consistent with the hypothesis that the control of cholesterol by insulin and glucagon is regulated by dietary and plasma amino acids. From this hypothesis the insulin/glucagon ratio is proposed as an early metabolic index of the effect of dietary proteins on serum cholesterol levels, a risk factor and a common mechanism through which dietary and lifestyle factors influence cardiovascular disease.

Introduction

Dietary plant proteins, in comparison to animal proteins, tend to decrease serum cholesterol levels, and this is associated with a subsequent reduction in the development of atherogenesis in animals (1–4). This lowering of serum cholesterol is apart from that previously demonstrated for unsaturated lipids or high fiber levels in the diet (5–8), since diets have been controlled for fat, cholesterol and fiber content (1–4). The dietary protein effects in humans have not been found by some (9, 10, 11) although others have reported these effects (12–16). These contradictory re-

sults in humans can be explained on the basis that high saturated fat or cholesterol diets can block the dietary effect of plant protein on serum cholesterol (4, 17). Given the similarity of metabolism between humans and animals and the metabolic interrelationship between nutrients, it seems untenable that dietary proteins would affect serum cholesterol levels in animals only, but not humans. Indeed, a review of the literature does not support this dichotomy (1–4). We explain (4) the negative results (9, 10, 11) on the basis of inadequate experimental design.

The amino acid composition of different proteins must be the cause of the different dietary pro-

tein effects on serum cholesterol and atherogenesis (1–4). A high dietary lysine/arginine ratio has been directly associated with an increase in serum cholesterol and atherogenesis in animals (18, 19). A high plasma ratio of lysine/arginine, is also directly associated with the level of serum cholesterol in humans (20–23). The plasma leucine/arginine, branched-chain amino acids/arginine and aromatic amino acids/arginine ratios may be more metabolically related to hypercholesterolemia and atherosclerosis than the lysine/arginine ratio (4).

The mechanism for the effects of dietary protein on serum cholesterol is unknown, although various hypotheses, in addition to the one we are proposing, have been proposed including differential rates of dietary protein absorption, differential steroid excretion and various metabolic effects (1–4, 24–28). The effect of differential absorption of protein on serum cholesterol levels does not appear to be of major importance (28).

High insulin levels are directly associated with mortality from cardiovascular disease (29) and constitute a sensitive indicator of increased risk to cardiovascular disease (30, 31, 32). The insulin/glucagon ratio is responsive to dietary and plasma amino acid levels (33, 34). Also, soy protein of plant origin is hypocholesterolemic and decreases the insulin/glucagon ratio while casein of animal origin is hypercholesterolemic and increases the insulin/glucagon ratio. These relationships provide the basis for a unifying hypothesis relating dietary and plasma amino acids, insulin, glucagon and serum cholesterol with atherosclerotic cardiovascular disease.

The hypothesis

The insulin/glucagon (hormones) ratio controls the rate limiting enzyme synthesizing cholesterol and is sensitive to postprandial plasma amino acid levels which are responsive to the amino acid content of dietary proteins (see Fig.). This implies that plasma amino acids and the insulin/glucagon ratio are among the earliest indicators of the effects of dietary protein on serum cholesterol levels.

This hypothesis provides the framework for further study of other hormones such as thyroxine (35) and other amino acids than those already known to be associated with serum cholesterol levels.
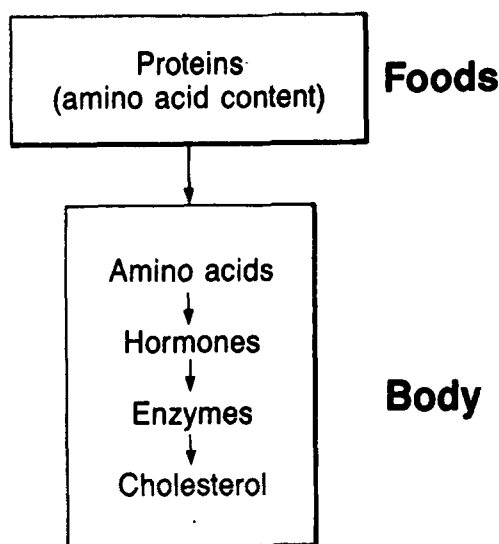

Fig. A hypothesis depicting the integrated metabolic effect of dietary proteins on serum cholesterol levels.

Basis for the hypothesis

Dietary protein and the insulin/glucagon ratio. Insulin is a key factor in the risk of cardiovascular disease (29–32). Among its metabolic functions are lowering blood glucose by facilitating the entry of glucose into the cells, increasing its utilization including glycolysis, activating enzyme systems in the de novo formation of lipids by way of acetyl CoA, storing fat by way of esterifiation (36), and activation of the rate limiting enzyme, HMG CoA reductase, in cholesterol biosynthesis (37–40). Insulin also facilitates the entry of amino acids into the cell and increases protein synthesis (36). Insulin is associated directly with total and low density lipoprotein cholesterol and with triglycerides and inversely with high density lipoprotein cholesterol (30, 31) showing that increased insulin results in a significantly increased atherogenic index in humans (31). These associations are with increased levels of insulin both during fasting or after a meal (30). Insulin is also associated with lipogenesis and smooth muscle cell proliferation in the arterial wall (32) as seen in atherosclerosis. These effects of insulin demonstrate its predictive value in

the incidence and mortality from cardiovascular disease.

Insulin does not work alone; it functions in concert with glucagon. Glucagon counteracts the metabolic effects of insulin, and is gluconeogenic. Glucagon enhances the breakdown of proteins to amino acids and organic acids, degradation of amino acids for making glucose and energy, mobilization and utilization of body fat, the activity of lipoprotein lipase in muscle, and the release of cholesterol from lipoproteins (36). Glucagon opposes cholesterol biosynthesis by inhibiting the activity of HMG CoA reductase (37–40). We propose that the insulin/glucagon ratio (33, 34) is far better than insulin levels alone (29–32) in predicting atherosclerotic cardiovascular disease.

The secretions of insulin and glucagon are closely coordinated (41, 42) and appear to be under amino acid control (42) in additoin to glucose. We find in humans (33, 34, 43, 44, 45) that soy protein, known to be hypocholesterolemic (1–4, 12, 46, 47, 48), is associated with a lower postprandial insulin/glucagon ratio than casein, known to be hypercholesterolemic (1–4, 12, 46, 47, 48). In rats, casein causes a higher serum insulin/glucagon ratio (49) and an increased activity of lipogenic enzymes in liver (50), compared to rats fed soy protein. Until proven otherwise, any metabolic process that favors lipogenesis and cholesterol esterification must be considered atherogenic (51), and thus a risk factor in cardiovascular disease. This suggests that high ratios of insulin/glucagon following casein feeding enhance atherogenesis. On the other hand, low insulin/glucagon ratios following soy protein feeding are consistent with enhanced gluconeogenesis and a decrease in cholesterol biosynthesis and/or increased catabolism.

We conclude that, especially among hypercholesterolemic subjects, the insulin/glucagon ratio is an early and sensitive indicator of the effects of different dietary protein on serum cholesterol and an indicator of risk to cardiovascular disease (33, 34). These conclusions are consistent with increased risk (30, 31, 32) and mortality (29) from coronary artery disease in humans with increased fasting and postprandial insulin levels, and with the known lipogenic (50) and hypercholesterolemic effects of the elevated insulin/glucagon ratio (49).

Dietary and plasma amino acids and the insulin glucagon ratio. Soy protein has over twice the amount of arginine or glycine compared to casein. Humans receiving a single test meal containing soy protein have significantly higher postprandial plasma levels of arginine and glycine and lower tyrosine (22) associated with a lower insulin/glucagon ratio (33, 34) compared to the same individuals fed the casein test meal. Humans receiving a diet high in soy protein have elevated fasting concentrations of plasma arginine and glucagon (14). Humans fed a plant protein diet in contrast to their usual American diet have significant increases in fasting plasma arginine, glycine, serine and threonine (20). These changes in free amino acids are associated with highly significant decreases in serum cholesterol and triglyceride levels (21). We now have evidence in hypercholesterolemic men (34) that supplementation of casein with arginine and glycine in amounts found in soy protein elevates plasma arginine and glycine and lowers the high postprandial serum insulin/glucagon ratio. This decreased insulin/glucagon ratio is similar to that observed in humans after feeding a single meal of soy protein (hypocholesterolemic) (33).

The association between amino acids and serum cholesterol suggests that certain amino acids like arginine and glycine in the diet and plasma have a hypocholesterolemic effect; others such as lysine, branched-chain and aromatic amino acids are hypercholesterolemic (20, 21, 22, 34, 44). The dietary lysine/arginine ratio known to be hypercholesterolemic and atherogenic (18, 19) is significantly lower in fasting plasma of humans on a continuous plant protein diet (20) or after a single meal of soy versus casein test meal (22). The plasma branched-chain/arginine and the aromatic amino acids/arginine ratios (22, 44) may be equal or more directly associated with hypercholesterolemia and atherosclerosis than the lysine/arginine ratio. Thus, the hypocholesterolemic amino acids are related to low and hypercholesterolemic amino acids to high ratios of insulin/glucagon (44, 45).

There is evidence showing an association between amino acids and the secretion of insulin and glucagon (insulin/glucagon ratio), hormones known to control cholesterol biosynthesis (36–41). Lysine, leucine and phenylalanine stimulate the release of insulin (52, 53, 54). High doses of arginine increase both insulin and glucagon secretions (55, 56, 57). However, at levels found in dietary proteins, arginine is associated with a decrease of insulin and the insulin/glucagon ratio (33, 34, 49). Our data (20, 21, 22, 33, 34, 44, 45) are consistent with the general hypothesis that the amino acid content of dietary proteins affects the level of serum cholesterol by the action of plasma amino acids on the insulin/glucagon ratio.

*The insulin/glucagon ratio as a common estimate of
dietary and lifestyle risk factors in cardiovascular
disease*

The insulin/glucagon ratio is a major determinant
of the metabolic directions in lipogenesis/lypolisis,
glycogenesis/glycogenolisis and glycolisis/glygluco-
neogenesis and is thereby a major contributor to
metabolic homeostasis. Our data in humans fed a
single meal with soy protein versus casein (33, 34,
43) and the association of insulin with cardiovascu-
lar disease (29) suggest that decreased serum choles-
terol levels are favored by low insulin/glucagon ra-
tios, while chronically high insulin/glucagon ratios in-
crease lipogenesis and thereby (51) the risk of cardio-
vascular disease.

In addition to dietary protein effects, the utilization
of insulin is influenced by other dietary factors. A
recent review (58) shows that unsaturated fatty acids
increase the sensitivity of cells to insulin. A high fiber
diet lowers serum cholesterol (8) and the need for
insulin among diabetics (59), and is associated with
reduced risk of cardiovascular disease (60). Insulin
is a metabolite associated with these diverse dietary
components.

Another line of evidence for the association of the
insulin/glucagon ratio with atherogenesis is exercise
which is associated with a decreased risk to cardio-
vascular disease (61). Recent data shows an increase
of high-density lipoproteins (29, 61) and a decrease
of insulin with exercise. Exercise also increases the
sensitivity of the insulin receptor sites (62).

The proportion of insulin to glucagon is a common
metabolic control mechanism by which diet and exer-
cise affect serum cholesterol metabolism. We believe
the insulin/glucagon ratio, which is sensitive to amino
acids, to be the mechanism by which dietary proteins
influence the risk to cardiovascular disease.

Conclusion

Blood insulin levels are a key risk factor in mortal-
ity from cardiovascular disease. The insulin/glucagon
ratio controls cholesterol metabolism and is respon-
sive to the plasma amino acid levels which are in-
fluenced by the amino acid content of dietary pro-
teins. While it is too early to categorize all amino
acids as to their specific effects on serum cholesterol,
arginine and glycine are implicated with hypocholes-
terolemia and lysine, branched chain and aromatic
amino acids are hypercholesterolemic. Among hyper-
cholesterolemic subjects, the insulin/glucagon ratio is
lower immediately after a meal containing a hypoc-
holesterolemic protein (soy) compared to a hyper-

cholesterolemic protein (casein). Plant proteins, un-
saturated fats, fiber, and exercise, all function to lower
blood insulin or increase its efficiency. In contrast,
feeding hypercholesterolemic proteins leads to lipo-
genesis associated with a high insulin/glucagon ratio
and atherogenesis.

The insulin/glucagon ratio is a common metabolic
mechanism for the effect of various dietary and
lifestyle risk factors in cardiovascular disease. It is
among the earliest and most sensitive metabolic esti-
mates in hypercholesterolemic subjects of the subse-
quent effects of dietary proteins on serum cholesterol.

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