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The hyperpolarizing impact of glycine on endothelial cells may be anti-atherogenic

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SUMMARY

Studies to date indicate that endothelial cells express glycine-activated chloride channels, which promote hyperpolarization of the endothelial plasma membrane. If such channels are expressed by endothelial cells lining conduit arteries, glycine is likely to have anti-atherogenic activity. This reflects the fact that endothelial hyperpolarization promotes calcium influx, activating the endothelial isoform of nitric oxide synthase, while also down-regulating the activity of the membrane-bound NADPH oxidase, chief endothelial source of superoxide. Since macrophages express glycine-activated chloride channels that suppress production of oxidants and cytokines, glycine may also oppose atherogenesis by influencing intimal macrophage function. In rats, supplemental glycine exerts anti-inflammatory and anti-angiogenic effects attributed to chloride channel activation. Administration of large daily doses of glycine would appear to be practical and safe, and has already been shown to inhibit protein glycation in human diabetics.

Endothelial cells express glycine-activated chloride channels

Bovine endothelial cells (vascular site of origin unspecified), as well as rat sinusoidal endothelial cells, have been shown to express glycine-activated chloride channels similar or identical to those which exert hyperpolarizing neuroinhibitory activity in the central nervous system; [1,2] such receptors have also been observed in Kupffer cells, alveolar macrophages, and neutrophils [3–5]. The CNS glycine receptor is composed of three alpha sub-units (of which four isoforms exist) and two beta sub-units, with three high-affinity binding sites for glycine; occupation of one or two of these sites increases the binding affinity of the remaining site(s) [6,7]. The glycine affinity of these receptors – ED50 is said to range from 20–150 μM in the CNS8 - is such that normal fasting serum levels of glycine, which are around 200 μM in rats and humans [9,10], fail to achieve full receptor activation; thus, glycine supplementation, which can readily sustain two-to-four-fold increases in serum glycine concentration [9], can be expected to promote further activation of systemic glycine receptors. Indeed, anti-inflammatory and anti-angiogenic effects of supplemental glycine in rats have been attributed to increased activation of these receptors in macrophages and endothelial cells, respectively [8,11–15].

Anti-atherogenic impact of endothelial hyperpolarization

If the endothelial cells lining human conduit arteries express similar glycine-gated chloride channels, it can be predicted that supplemental glycine will increase transmembrane potential in these cells. Two consequences are likely to flow from this: increased activation of the endothelial isoform of nitric oxide synthase (eNOS), and a down-regulation of plasma membrane NADPH oxidase activity [16]. The former effect will simply reflect increased calcium influx driven by the transmembrane potential gradient; the resulting increase in free intracellular calcium will stimulate eNOS activity [17,18]. (It should be noted that endothelial cells do not express the voltage-sensitive calcium channels that are *inhibited* by hyperpolarization) [19]. The latter effect reflects the fact that, for reasons that remain obscure, membrane potential regulates activity of the membrane-bound NADPH oxidase; hyperpolarization tends to inhibit its activity, whereas depolarization increases it [16,20–23]. Thus, the net effect of endothelial hyperpolarization should be a shift in the balance of NO and superoxide production favoring the former. This in turn would be expected to amplify the capacity of healthy endothelium to ward off atherogenesis and thrombosis.

The modest increase in serum potassium level achievable with high potassium diets tends to hyperpolarize endothelium by stimulating the activity of the electrogenic Na–K–ATPase, which expels three sodium ions for every two potassium ions imported [24]. This phenomenon is suspected to contribute to the cardiovascular protection associated with potassium-rich diets [16,22,25]. The possibility that ample dietary intakes of glycine could likewise promote hyperpolarization of vascular endothelial cells, and thereby decrease atherothrombotic risk, merits evaluation in rodent atherogenesis studies. The impact of supplemental glycine on the endothelium-dependent vasodilation of at-risk humans could also be assessed.

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Since glycine opposes the activation of Kupffer cells and alveolar macrophages, inhibiting their production of oxidants and cytokines [3,4], it is quite conceivable that glycine could likewise diminish the activity of intimal macrophages. This might represent a complementary mechanism whereby supplemental glycine could impede atherogenesis while helping to prevent plaque destabilization.

Glycine supplementation is practical

Glycine is quite inexpensive (currently around $5/kg), extremely soluble, and has a pleasant sweet flavor. Supplemental glycine intakes as high as 5 g four times daily have been used to treat human diabetics; this treatment is well tolerated and moreover inhibits protein glycation [26,27]. Acute intakes of 10 g or more can produce GI upset, so glycine is best administered in multiple daily doses of moderate size. These considerations suggest that glycine therapy would be practical and well tolerated if studies confirm that it does indeed have vasculoprotective potential.

It should be noted that taurine is also a partial agonist for the glycine receptor [28]. Nonetheless, taurine probably has less clinical potential in this regard than does glycine, in as much as sustained large increases in serum levels of taurine are less readily achieved; taurine is transported avidly into electrically active tissues, and residual serum taurine is rapidly cleared by the kidneys. Nonetheless, taurine shows anti-atherosclerotic activity in rodent models [29–31] – perhaps in part reflecting its ability to quench the oxidant hypochlorous acid [32] – and also has platelet stabilizing activity and anti-hypertensive potential [33–37]. Thus, supplemental taurine is likely to be vasculoprotective, even if activation of chloride channels is not the primary mediator of this benefit. Taurine is flavorless, and resembles glycine in its low cost and high solubility.

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