INVITED COMMENTARY

Aminoguanidine and diabetic neuropathy

Vincent M Monnier

Institute of Pathology, Case Western Reserve University, Cleveland, OH, USA

In this issue, Miyauchi and colleagues (1) present a study in which they have administered aminoguanidine orally for 16 weeks to young rats with streptozotocin-induced diabetes. Whereas motor nerve conduction velocity (MNCV) kept increasing with time in the non-diabetic control rats and reached a plateau at 16 weeks, initially no such increase was noted in diabetic rats on aminoguanidine. However, after 2 months of treatment a dose-dependent progressive increase in MNCV was noted, which, at the dose of 50 mg/kg body weight, reached almost normal levels at 16 weeks. Morphometric analysis of the sciatic nerve revealed no significant differences between diabetic animals receiving aminoguanidine and controls. The improvement in MNCV did not appear to relate to glycemic status or amelioration in body weight, both of which were unchanged at 16 weeks compared to what they were at study onset. Somewhat surprising is the fact that Na⁺, K⁺-ATPase activity in sciatic nerve was not ameliorated by aminoguanidine therapy. In effect, mean levels of both ouabain-sensitive and -insensitive forms were below those of untreated controls. This is surprising because the activity of this enzyme was found impaired in several independent studies of diabetic neuropathy in the rat and ameliorated by treatment with, for example, myoinositol or aldose reductase inhibitor (2). Thus, one has to assume that aminoguanidine corrected the defect in MNCV by a mechanism independent of Na⁺, K⁺-ATPase.

This study joins a growing number of studies showing that aminoguanidine in diabetic rodents is effective at improving diabetic neuropathy (MNCV, myelinated fiber size, nerve blood flow) as well as a host of other abnormalities, including albuminuria, mesangial expansion, formation of fluorescent products in kidney cortex, basement membrane, arterial wall and skin (3, 4), retinopathy-like changes consisting of acellular capillaries and microaneurysms (5), vascular permeability, increase in granulation tissue, retina and nerve and collagen cross-linking (3, 6, 7). Thus, aminoguanidine emerges as a drug with the potential to prevent a broad range of diabetes-induced dysfunctions that are thought to lead eventually to full-blown complications.

Aminoguanidine was initially investigated for its potential activity as an inhibitor of the advanced Maillard-glycation reaction, which is thought to play an important role in the pathogenesis of diabetic complications (8, 9). Indeed, when proteins modified by advanced glycation endproducts (AGEs) in vitro or in vivo were applied to certain culture systems or injected into animals, a number of diabetes-like changes could be reproduced, including increases in protein trapping, low-density lipoprotein oxidation, permeability of endothelium and vasculature, basement membrane thickening and mesangial matrix production, procoagulant effects and thrombotic events (9). Some of these changes may be in part related to AGE receptor-mediated effects, such as the release of cytokines and growth factors, and are preventable by aminoguanidine (9). In support of a role for AGEs in diabetic neuropathy, Miyauchi et al. presented data showing that the formation of immunoreactive AGEs was decreased in aminoguanidine-treated diabetic rats. Unfortunately, these data were obtained with proteins from renal cortex instead of nerve, and the validity of their extrapolation to diabetic neuropathy remains to be established.

Assuming that prevention of AGE formation by aminoguanidine is responsible for the amelioration of MNCV, what could be the mechanistic relationship between the two? One possibility is that aminoguanidine would trap deoxyglucosones by forming triazines (10), thereby preventing formation of pyrrole-AGEs like pyrraline (11, 12). Pyrroles have been proposed as a basis for hexane-induced neuropathy in experimental animals and humans (12). Such pyrroles could form from 3-deoxyglucosone as a metabolite of the fructose-3-phosphate pathway that has been found to be aldose reductase-dependent in the lens (13). Thus, in effect, such a mechanism would readily explain why both aldose reductase inhibitors and aminoguanidine have beneficial effects on experimental diabetic neuropathy, and why aminoguanidine is efficacious without decreasing tissue sorbitol levels, at least with regard to the kidney (4). Another AGE-dependent mechanism could involve occlusion of the vasa vasorum in nerve, resulting from the biological effects of AGEs on the anticoagulant properties of the endothelium, which, upon exposure to AGE-proteins, suppresses thrombomodulin formation and upregulates tissue procoagulant factor (8). Thus, ischemic damage to the nerve would occur that would be preventable if plasma AGE formation decreases as a consequence of aminoguanidine therapy.

Yet, aminoguanidine may act by a mechanism unrelated to AGE formation that is not mentioned in
the paper by Miyauchi et al. Corbett et al. (6) observed that aminoguanidine inhibits cytokine-induced nitric oxide synthase and normalizes albumin permeation and blood flow in several tissues, including nerve. They proposed that this could be the actual mechanism of action of aminoguanidine. In support of this proposition, they showed that N^6-monomethyl-L-arginine, which is not expected to form triazines, was equally potent at inhibiting the increase in vascular albumin clearance in granulation tissue. However, the applicability of this observation to the long-term effects of NO synthase inhibition in the context of the present study remains to be tested.

In fact, it is now recognized that there is an intricate relationship between ischemic and metabolic factors in the pathogenesis of diabetic neuropathy. Stevens and colleagues recently demonstrated that in acute diabetes the nitric oxide inhibitor L-NAME completely blocked the salutary effects of the aldose reductase inhibitor sorbinil, despite improvement in sorbitol levels, and that this effect was prevented by arginine, itself a source of nitric oxide (2). Moreover, they showed that chronic administration of L-NAME to normal rats impaired NCV and suppressed Na^+.K^+-ATPase. Thus, one has to conclude that because Miyauchi and colleagues observed a beneficial effect of aminoguanidine on NCV without improvement of ATPase activity, this effect is most likely unrelated to either inhibition of NO synthase or aldose reductase activity. Thus, AGE formation and perhaps other factors, such as pseudohypoxia (17) and oxygen free radicals (7), may be involved in ways that are not yet fully understood.

Perhaps one of the most important findings in the study by Miyauchi is that of a delay of 8 weeks in the action of aminoguanidine on NCV. The finding is important because several studies found no effect of AG therapy at 8 weeks on albuminuria (15), neurotransmission (16) or retinopathy (17), but a significant beneficial effect on similar endpoints at or beyond 16 weeks (4). Thus, it appears more and more that there are two components in the pathogenesis of diabetic complications in the diabetic rat. The first is dominant soon after diabetes onset and appears to be highly responsive to aldose reductase inhibition but refractory to aminoguanidine. In contrast, the second, later component, corresponds to an abnormality that is improved by aminoguanidine in spite of elevated sorbitol levels. Distinction between these two components is important because it may lead to the erroneous conclusion that aminoguanidine is not efficacious as an antidiabetic drug when therapeutic trials are interrupted prematurely.

The future of aminoguanidine as an antidiabetic agent (trade name “pimagedine”) will depend on three factors: whether it will be efficacious in the diabetic human: whether the side effects will be acceptable: and a deeper knowledge of its mechanism of action. The first two aspects are currently being investigated in clinical trials by the company Alteon Inc., and published data are not expected to be available before 2 years from now. As to the third, the study by Miyauchi has revealed a novel and important aspect of aminoguanidine in chronic diabetes. It is now becoming urgent to conceive long-term intervention rather than prevention trials in experimental models of diabetes, and to compare the effects of aminoguanidine with those of inhibitors of NO synthase that are not anti-glycating agents.

References

15. Way KJ, Reid JF. Effect of aminoguanidine on the impaired nitric

Vincent M Monnier, Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA

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