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APOLIPROTEIN MIMETIC D-4F PRECONDITION EFFECTS TO PREVENT VIBRATION INJURY

---- experiment in rats

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INTRODUCTION

Our previous studies demonstrated that the ventral artery in the rat-tail exposed to short-term vibration shows vasoconstriction and endothelial-cell damage. The present study investigated whether pretreatment with D-4F, an apolipoprotein A-1 mimetic with known antioxidant and vasodilatory properties¹⁻³, prevents vibration-induced vasoconstriction, endothelial-cell injury and protein nitration

MATERIALS AND METHODS

Male adult SD rats weighing between 250g-300g were used, randomly assigned to 9 groups (n=8 per group, detail, See Table 1) Vibration treatment for rats' tails were 4 hours per day continuously at 60 Hz, 49 m/s² r.m.s. acceleration for either 1 or 3 consecutive days. The vibration platform was vertically accelerated by a Brüel and Kjær motor. Vibration parameters were set and rechecked with a Brüel and Kjær Integrating Vibration Meter. D-4F, the ApoA-I mimetic peptide, was synthesized by the Protein and Nucleic Acid Shared Facility of the Medical College of Wisconsin and the BloodCenter of Wisconsin. All rats received intraperitoneal injections one hour prior to the initiation of the vibration experiment protocol. The rats in Groups 3, 5, 7, and 9 received an intraperitoneal injection of D-4F (3mg/kg). All other rats received intraperitoneal injection of sterile saline. One-day groups received a single injection, and the 3-day groups received three injections. The rats were then anesthetized with intraperitoneal sodium pentobarbital. The arteries in tail segments C5 and C6 were dissected under the microscope for paraffin embedding. Arteries from the C7 and C8 segments were dissected under the microscope and postfixated and embedded in epoxy resin as performed previously. Paraffin sections were cut at 6 µm for immunohistochemistry. Staining for nitrated tyrosines by incubating with rabbit anti-nitrotyrosine (1:250, Upstate Biotechnology, Lake Placid, NY) followed by goat anti-rabbit IgG. To quantify immunoperoxidase staining, sections from all group arteries were incubated together and photographed digitally at the same exposure and light intensity setting and X20 magnification. Optical density of staining was analyzed using MegVue 5.0r7 software (Universal imaging Corporation, Downingtown, PA), with four regions positioned at 3, 6 and 9 and 12 o'clock sampled per artery. The values from the four regions were averaged to derive the mean optical density for the artery.

Semithin, epoxy cross sections stained with toluidine blue and digitally imaged for computer-assisted measurement of the artery lumen circumference and length of the internal elastic membrane. The degree of vasoconstriction was defined as the lumen circumference divided by the length of the internal elastic membrane times 100.

RESULTS

Lumen size

The decrease in lumen size was prevented by 1 and 3 days of D-4F treatment. D-4F treatment of the sham vibration groups (Groups 2 and 6) produced no detected difference in lumen size when compared with the control group (Group 1). Vibration-induced cellular damage was similar to that described previously in constricted arteries; endothelial cells were severely compressed and protruding into the lumen.

Nitrotyrosine immunoperoxidase staining Intense immunostaining for nitrotyrosine was present in the walls of the arteries of the 1- and 3-day vibration groups. D-4F treatment prevented vibration induction of nitrotyrosine (Fig. 2). Sham vibration groups (Groups 2 and 6) and sham vibration with D-4F injection groups (Groups 3 and 5) exhibited little or no immunostaining.

Optical density quantitation revealed that vibration for 1-day produced darker staining of the tunica media compared to that in the sham vibration groups. D-4F treatment blocked nitration in the vibration groups. Staining of the 1-day Vibration+D-4F group was not different from that of the Shams or Vibration. The 3-day vibration group exhibited greater staining than the 3-day sham vibration group. The 3-day vibration group also exhibited greater staining than the 1-day vibration group. The 3-day vibration with D-4F group showed significantly lighter staining than 3-day vibration group.

DISCUSSION

What attributes of D-4F are postulated to counter vasoconstriction, cell damage and nitration? D-4F has been shown to improve acetylcholine mediated eNOS dependent vasodilation and restores a safe balance of nitric oxide and superoxide anion generation in endothelial cells². With preservation of eNOS function and without superoxide excess, peroxynitrite is not generated to exacerbate endothelial cell damage. Our research indicates that vibration can trigger an intense vasoconstriction, which is a major early contributor for the development of vascular dysfunction in HAVS. The present study shows that D-4F prevents vasoconstriction, which appears to work by preserving NO mediated vasorelaxation. The ability of D-4F to minimize oxidative stress and endothelial cell injury makes it a superb antidote for vibration induced endothelial cell injury^{1,3}. Further studies are needed to determine which of the manifold protective actions of D-4F are actively protecting arteries from vibration injury in the rat-tail model. The knowledge gained from these studies may prove to be useful in the prevention of HAVS

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