Cumulative Brain Injury from Motor Vehicle-Induced Whole-Body Vibration and Prevention by Human Apolipoprotein A-I Molecule Mimetic (4F) Peptide (an Apo A-I Mimetic)

Ji-Geng Yan, MD, PhD,* Lin-ling Zhang, MD,* Michael Agresti, MS,* Yuhui Yan, MD,* John LoGiudice, MD,* James R. Sanger, MD,* Hani S. Matloub, MD,* Kirkwood A. Pritchard Jr, PhD,† Safwan S. Jaradeh, MD,‡ and Robert Havlik, MD*

Background: Insidious cumulative brain injury from motor vehicle-induced whole-body vibration (MV-WBV) has not yet been studied. The objective of the present study is to validate whether whole-body vibration for long periods causes cumulative brain injury and impairment of the cerebral function. We also explored a preventive method for MV-WBV injury. *Methods:* A study simulating whole-body vibration was conducted in 72 male Sprague-Dawley rats divided into 9 groups (N = 8): (1) 2-week normal control; (2) 2-week sham control (in the tube without vibration); (3) 2-week vibration (exposed to whole-body vibration at 30 Hz and .5 *G* acceleration for 4 hours/day, 5 days/week for 2 weeks; vibration parameters in the present study are similar to the most common driving conditions); (4) 4-week sham control; (5) 4-week vibration; (6) 4-week vibration with human apolipoprotein A-I molecule mimetic (4F)-preconditioning; (7) 8-week sham control; (8) 8-week vibration; and (9) 8-week 4F-preconditioning group. All the rats were evaluated by behavioral, physiological, and histological studies of the brain. *Results:* Brain injury from vibration is a cumulative process starting with cerebral vasoconstriction, squeezing of the endothelial cells, increased free radicals, decreased nitric oxide, insufficient blood supply to the brain, and repeated reperfusion injury to brain neurons. In the 8-week vibration group, which indicated chronic brain edema, shrunken neuron numbers increased and whole neurons atrophied, which strongly correlated with neural functional impairment. There was no prominent brain neuronal injury in the 4F groups. *Conclusions:* The present study demonstrated cumulative brain injury from MV-WBV and validated the preventive effects

Abbreviations: 4F, human apolipoprotein A-I molecule mimetic; DDSA, dodecenyl succinic anhydride; DSN, dark shrunken neuron; EC, endothelial circumference; EC/EM, vasodilation degree; EM, elastic membrane; HDL, high-density lipoprotein; Hz, Hertz; LM, light microscopic study; MCA, middle cerebral artery; MV, motor vehicle; NCV, nerve conduction velocity; RIU, relative intensity unit; TEM, transmission electron microscopic; WBV, whole-body vibration.

From the *Department of Plastic and Reconstructive Surgery, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin; †Department of Pediatric Surgery, Children's Hospital of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, Wisconsin; and ‡Department of Neurology & Neurological Sciences, Stanford University, Stanford University Medical Center, Stanford, California.

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Address correspondence to Ji-Geng Yan, Department of Plastic and Reconstructive Surgery, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. E-mail: jyan@mcw.edu.

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of 4F preconditioning. **Key Words:** Brain injury—neural functional impairment—whole-body vibration—neuronal atrophy.

Introduction

Modern industrial and technical developments have brought many benefits and much convenience to our daily life; however, when we enjoy these benefits, we may at times overlook insidious harm. Motor vehicles (MVs), the most common form of transportation, produce whole-body vibration (WBV). Although engineers and industrial scientists have made advances to reduce WBV, their major goal is to make drivers and passengers more comfortable sitting. WBV still exists. Hand–arm vibration syndromes and disorders induced by hand–arm vibration tools have been extensively studied, but WBV injury and treatments have not yet been investigated. In 2011, 32,367 people were killed in an estimated 5,338,000 police-reported motor vehicle accidents (MVA), and 2,217,000 people were injured. A recent study by Charlie Klauer of the Virginia Tech Transportation Institute Center for Vulnerable Road User Safety states that physical fatigue is a cause of 20% of all U.S. automobile crashes. People believe tired drivers are deadly drivers. However, our recent preliminary study results[1-3] on simulated motor vehicle-induced whole-body vibration (MV-WBV) challenge the traditional thinking; our studies suggest that "driver's fatigue" is actually brain dysfunction and brain impairment resulting from MV-WBV. Here we hypothesize that prolonged MV-WBV induces brain injuries that compromise a driver's judgment and reactive capabilities and may be one cause of MVAs. Prevention of early neural injury from MV-WBV can avert or reduce late chronic brain diseases. In our previous study on hand–arm vibration injury, human apolipoprotein A-I molecule mimetic (4F), an apo A-I mimetic, was studied, and its ability to prevent hand–arm vibration injury was validated.[4] The goal of the present study was to discover the pathological process of such brain injury, to elucidate the cellular and molecular mechanism from MV-WBV injuries, and to determine whether 4F prevents WBV injury. The rat's anatomy and physiological and biological features are similar to those of a human being.[5-8] A simulated animal study is the only way to reach these objectives.

Materials and Methods

Ethics Statement

For the care and use of laboratory animals, all protocols of the present study conformed to the National Institutes of Health guidelines and received approval from the Biomedical Resource Center and the Institutional Animal Care and Use Committee at our institution (AUA-2363). After the animals arrived, they were allowed to acclimate for 7 days before exposure. The animals were housed in a central animal care facility with 12-hour light cycles and were given food and water ad libitum.

Animal Study Model and Vibration Setup

Animal Groups

Seventy-two Sprague-Dawley male rats (weight 250-300 g) were divided into 9 groups (N = 8)[1]: the 2-week normal control group had no treatment[2]; the 2-week sham control group was restrained in the tube without vibration[3]; the 2-week vibration group was exposed to WBV at 30 Hz and .5 *g* acceleration for 4 hours/day, 5 days/week for 2 weeks[4]; the 4-week sham control group was restrained in the tube without vibration[5]; the 4-week vibration group was vibrated for 4 weeks[6]; the 4-week vibration group was treated with 4F-peptide (Ac-DWFKAFYDKVAEKFKEAF-NH2) preconditioning[7]; the 8-week sham control group was restrained in the tube without vibration[8]; the 8-week vibration group was vibrated for 8 weeks[9]; and the 8-week vibration group was treated with 4F-peptide preconditioning. At the end point, all the rats were evaluated by behavioral, physiological, histopathological, and molecular studies of the brain.

Vibration Setup

The rats in all the groups were placed individually in polyvinyl chloride tubes. Rats were given 1 day training to adapt to this small tube space, after which all the animals voluntarily entered the tubes throughout the experiment.

The rat exhibited no stress at all as seen in our previous rat experiments.[8] Actually, in all groups the rats were very still and calm for most of the time while in the tubes. The tubes were taped to a vibrating platform and the tails were taped alongside the tube on the platform (Fig 1, A). Vibration was performed without any sedative or anesthesia. The electromagnetic vibration motor (type 4809; Brüel & Kjær [B&K], Skodsborg, Denmark) was driven by a sine wave signal from a function generator (Simpson 420; Simpson Electric Co., Elgin, Illinois). The acceleration was set with a power amplifier (B&K type 2706). Frequency and acceleration was calibrated before beginning the study using an HP 1201 B oscilloscope and a B&K 4384 accelerometer connected to a B&K Integrat-