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THE ROLE OF ENZYME AND SUBSTRATE DEPENDENCE IN NO-MEDIATED VASCULAR DYSFUNCTION WITH AGING

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Abstract

The process of aging affects the vasculature, resulting in remodeling and dysfunction in both the macro- and microvascular systems. A marker of vascular health is the production and, ultimately, the bioavailability of nitric oxide (NO), which is recognized to be antiatherogenic. NO synthesis predominantly depends upon the extracellular levels of L-arginine and the efficacy of endothelial nitric oxide synthase (eNOS), while reactive oxygen species can negatively impact both eNOS activity and NO directly leading to a decrease in NO bioavailability and vascular endothelial dysfunction. Tetrahydrobiopterin (Bh4), a cofactor which recouples eNOS, and chronic L-Citrulline (L-Cit), which increases plasma L-arginine, both by independent mechanisms, may increase NO bioavailability. Therefore, this study sought to evaluate the role of eNOS activity and/or L-arginine concentration in the NO-mediated vascular dysfunction associated with advancing age. Eight old subjects (73 ± 6 yr; ht: 168 ± 12 cm; wt: 84 ± 33 kg) received Bh4 acutely and underwent a 1 week supplementation of L-Citrulline (8 g per day). Vascular function was assessed by brachial artery flow mediated dilation (FMD: %) and passive leg movement (PLM: blood flow ΔPeak and AUC) with or without Bh4, both before and after L-Citrulline supplementation (Ctrl; Bh4; L-Cit; L-Cit + Bh4). PLM ΔPeak increased ≈35% and ≈27% in the Bh4 and L-Cit + Bh4 conditions, respectively ($p < 0.05$). PLM AUC increased ≈114% ($p < 0.05$) in the L-Cit + Bh4 condition. There were no significant intervention-induced changes in FMD. With advancing age, vascular function, as assessed by PLM, which may be more NO mediated than FMD, appears to be more limited by eNOS function than NO substrate. However, these findings also suggest that the combination of increased eNOS coupling and eNOS substrate most consistently enhances vascular function in the elderly, as assessed by the total (AUC) PLM response.