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eNOS and BH_4; endothelial function or dysfunction: Importance of tetrahydrobiopterin (BH_4)

Jennifer Gantzer
Vibrant Care, Diagnostic and Healing Center, USA

Tetrahydrobiopterin (BH_4) is a multifunctional cofactor required for vital enzyme activity in the synthesis reactions of the neurotransmitters dopamine and serotonin as well as in the synthesis of the gaseous signaling agent Nitric Oxide (NO) involved in vascular health. BH_4 must be maintained at continuously high levels including intracellular synthesis and recycling to prevent endothelial dysfunction with ongoing generation of free radicals and concomitant oxidative damage which leads to deleterious effects on the vascular wall including loss of vasodilation and protection against atherosclerotic pathogenesis. Imbalances entail a drop in BH_4 levels and occur in states of high blood sugar, high blood pressure, high blood lipids; their subsequent vascular disease states including diabetes, atherosclerosis, hypertension, hyperlipidemia and hyperhomocysteinemia induce endothelial dysfunction with negative impacts on the NOS/BH_4 enzyme system with resultant increased free radical formation, decreased NO production and concomitant reduced NO vasodilatory and signaling bioactivity. In addition to vascular effects, impaired NO production also has a role in neurodegenerative diseases including impaired cerebral blood flow and decreased BDNF secretion (important for cognition, learning and memory). Endothelial dysfunction is oxidative stress driven by low levels of BH_4 at the Nitric Oxide Synthase enzyme (NOS), called NOS-uncoupling; where NOS-uncoupling is a perpetuating cycle of superoxide (OO-) and peroxynitrite (ONOO-) free radical formation. Oxidative stress in endothelial cells depletes BH_4, switches NOS generation from NO to OO-, promotes formation of ONOO- from NO and OO-; dropping the intracellular ratio of BH_4:BH_2 inducing a feed forward cycle of more and more BH_4 depletion and NOS-uncoupling. Low levels of ONOO- exposure caused BH_4 levels to drop by 60% in 500 seconds. Vascular and cognitive health entails maintaining balanced redox ratios of BH_4:BH_2, sufficient arginine and citrulline levels for enzyme efficiency, as well as folate and antioxidants for cofactor rescue and anticipated free radical formation. Vitamin C, N-acetyl cysteine and resveratrol are free radical scavengers successfully shown to restore BH_4/NO levels, endothelial NOS function and protect against vascular and cognitive decline.

Biography

Jennifer Gantzer is an american Doctor of Chiropractic (DC) and board-certified nutritionist (DACBN) with a passion for biochemistry and neuroscience. She is pursuing her master's in nutrition from the University of Bridgeport.

dr.jen@vibrantcarecenter.com

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