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The Role of the Glyoxalase System & Reactive Metabolites in the Aging Process

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Aging is a dynamic process in which it's rate and subsequent longevity of an organism is dependent upon the balance between the reactive intermediates of normal cellular metabolism and the ability of the body to reduce these by-products through a multifaceted antioxidant defence system. Every disturbance of this balance constitutes a clear and present danger to the macromolecular integrity of the body. When defence mechanisms become diminished or impaired, the resulting imbalance results in accumulation of endogenous agents, such as reactive oxygen and carbonyl species, and a state of increased cellular stress, which can accelerate the rate of aging. Glycation is the non-enzymatic glycosylation of proteins, nucleotides and lipids by saccharide derivatives. Glucose and other reducing sugars are important glycating agents but the most reactive physiological relevant glycating agents are the dicarbonyls, in particular methylglyoxal (MG). Endogenously formed dicarbonyl compounds can react with proteins to form Advanced Glycation Endproducts (AGEs). Experimental models have recently provided evidence that reduced detoxification of AGE precursors by the glyoxalase system, engagement of the cellular receptor RAGE and RAGE dependent sustained activation of the proinflammatory transcription factor NF-κB might significantly contribute to the rate of aging and the onset of age-related neurodegenerative, musculoskeletal and vascular diseases.

To study MG and the Glyoxalase System in physiological samples, a number of assays were developed in-house, which included an analytical high-performance liquid chromatography assay for the determination of MG, Glyoxalase I & Glyoxalase II activity assay, as well as assays for total glutathione (oxidized & reduced glutathione) and D-lactate. Utilizing these assays, MG metabolism was studied in the livers of young (<8 weeks) and old (>52 weeks) wild-type old mice. It was found that both Glyoxalase I & II were significantly decreased by 42% and 76% respectively in the livers of the older mice. This was paralleled by a significant increase in plasma MG by 42%). These results showed that with increasing age, the Glyoxalase system as a whole is downregulated, leading to an increase in the concentration of circulating MG.

To establish the physiological consequences which result from elevated MG levels, the role of MG and glyoxalase I was investigated in the development of two pathophysiological conditions which are prevalent in both the elderly and in diabetic patients and contribute significantly to the rate of morbidity and mortality; the development of neuropathy and the reduction in angiogenesis potential, as exemplified by a reduced wound healing capacity. It was found that within the context of neuropathy, increased MG can lead posttranslational modification of $Na_v1.8$ and increased neuron excitability. Whereas, in the wound healing, it was found that direct interaction of MG with the subcellular environment can inhibt angiogenesis through and apoptosis-independent mechanism. Throughout this study, it was confirmed that the increase in MG formation resulting from a downregulation of Glyoxalase I play a fundamental role in the deleterious effects which are associated with the aging process and in diabetes, and that development of agents which can scavenge MG and prevent the formation of AGEs may provide a novel therapeutic strategy for the treatment of complications that are associated not only with diabetes, but also aging.