DIETARY POLIPHENOLS AGAINST BRAIN AGEING

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Protein quality control is a critical feature of intracellular homeostasis. In particular, unfolded or misfolded proteins resulting from environmental stresses or free radicals are rapidly degraded via the ubiquitin–proteasome pathway[1]. In addition, modulation of endogenous cellular defense mechanisms via the stress response signaling represents an innovative approach to therapeutic intervention in diseases causing chronic tissue damage, such as neurodegeneration and cancer[1]. Protein thiols play a key role in redox sensing, and regulation of cellular redox state is crucial mediator of multiple metabolic, signalling and transcriptional processes. Under optimal conditions long-term health protection is accomplished by protein homeostasis, a highly complex network of molecular interactions that balances protein biosynthesis, folding, translocation, assembly/disassembly, and clearance[2,3]. Efficient functioning of maintenance and repair processes is crucial for both survival and physical quality of life. This is accomplished by a complex network of the so-called longevity assurance processes, which are composed of several genes termed vitagenes[4-8]. The term vitagenes refers to a group of genes which are strictly involved in preserving cellular homeostasis during stressful conditions. The vitagene family is actually composed of the heat shock proteins (Hsp) Hsp32, Hsp70, the thioredoxin system and the sirtuin system[9]. Dietary antioxidants, such as polyphenols and L-carnitine/acetyl-L-carnitine, have recently been demonstrated in vitro to be neuroprotective through the activation of hormetic pathways, including vitagenes[10-12]. Over the past decade there has been a remarkable increase of interest in hormesis as a result of more significance being given to low dose effects and the use of more powerful study designs which have enabled to identify rational approaches to detect hormetic biphasic dose responses in the low dose zone. The hormetic dose–response, challenging long-standing beliefs about the nature of the dose–response in a lowdose zone, has the potential to affect significantly the design of pre-clinical studies and clinical trials as well as strategies for optimal patient dosing in the treatment of numerous diseases, including oxidant disorders. Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing stress responses. We have recently focused our research on the role of acetylcarnitine in the defense mechanisms against cellular stress and neurodegeneration. In addition, with a redox proteomics approach, we identified mitochondrial oxidatively modified proteins as a function of brain aging, specifically in those brain regions, such as cortex and hippocampus, that are commonly affected by the aging process. In all brain regions examined, many of the identified proteins were energy-related, such as pyruvate kinase, ATP synthase, aldolase, creatine kinase, and a-enolase. These alterations were associated with increased expression of Hsps, as well as carnosinase and thioredoxin reductase and with significant changes in both cytosolic and mitochondrial redox status in all brain regions analyzed. This findings are relevant to potential pharmacological interventions in healthy medicine strategy, pointing to maximize cellular stress resistance of the brain thus providing neuroprotection[9-12], and will be extended to other systemic oxidant disorders such as diabetes or cancer.

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