Proteomic alterations after chronic treatment of the TgF344-AD rat model of Alzheimer's disease with the neuroprotective compound P7C3- S321

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The absence of treatment options for patients suffering from neurodegenerative disease highlights the need for discovery and development of neuroprotective drugs. The P7C3 class of neuroprotective compounds has demonstrated efficacy in a wide variety of preclinical models of neurodegeneration, including Alzheimer's disease (AD), Parkinson's disease, peripheral neuropathy, and traumatic brain injury. A major mode of P7C3's action is to help neurons preserve levels of nicotinamide adenine dinucleotide (NAD+) under times of otherwise overwhelming energetic stress. To further elucidate related neuronal events and modes of action, we have implemented a non-biased proteomic discovery approach in brain tissue from the TgF344-AD rat model of AD, as well as wild type (WT) littermates, as a function of treatment with vehicle or P7C3-S321. P7C3-S321 was previously shown to reduce neurodegeneration and neuropsychiatric deficits in this model. We have identified protein expression patterns in both male and female rats that indicate involvement of molecular pathways related to metabolism, cellular function, chaperone activity, neuronal vitality, and cytoskeletal maintenance, which are now undergoing validation. The goal is to identify both new mechanistic aspects by which P7C3 achieves its neuroprotective efficacy, and also to identify pathways important in neuronal survival in aging or AD that would not otherwise have been predicted.