Jack Rogers et al., J Psychol Psychother 2018, Volume 8
DOI: 10.4172/2161-0487-C4-032

RNA driven improved iron homeostasis in neurons exposed to parkinsonian manganese stress

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Manganese (Mn) toxicity is poorly understood and yet Mn is known to cause occupational movement disorders resembling Parkinson's disease (PD) and PD-like syndromes. We demonstrated that Mn dose- and time-dependently blocked translation of amyloid precursor protein (APP) and heavy-chain Ferritin (H-Ferritin), each known to be iron homeostatic proteins with neuroprotective features. APP and H-Ferritin are post-transcriptionally regulated by iron-responsive proteins (IRPs), which bind to homologs iron-responsive elements (IREs) located in the 5'-untranslated regions (5'-UTR) within their mRNA transcripts. We (Venkataramani et al, in revision) demonstrated Mn exposure repressed the 5'-UTR-activity of APP and H-Ferritin via increased IRP-IRE binding, thus blocking their protein translation. Loss of the protective axis of APP and H-Ferritin resulted in an unchecked accumulation of redox-active ferrous iron ($Fe2^{+}$) fueling neurotoxic oxidative stress. Enforced APP expression partially attenuated Mn-induced generation of cellular and lipid reactive oxygen species (ROS) and neurotoxicity. We validated the Mn-mediated suppression of APP and H-Ferritin in two rodents *in vivo* models mimicking acute and chronic Mn exposure. Our results indicated Mn-induced neurotoxicity is partly attributable to the translational inhibition of APP and H-Ferritin with impaired iron metabolism and exacerbated neurotoxic oxidative stress. The novel benzimidazole "BL-1" was found to exert a therapeutic profile to avert Mn neurotoxicity and this agent was diversified. We discovered, by secondary Western blot assays, that BL-1 activated translation of the ferritin light and heavy chains to safely store iron and prevent a toxic buildup of iron-catalyzed oxidative radicals. BL-1's protective activity in conditions of iron overload was specific to neurons. This agent exhibited little or no off-target induction of ferritin in monocytic (THP-1) or in cervical cancer (Hela) cell lines. BL-1 did not induce ferritin expression in oligodendroglia, which exhibited constitutively high expression of this iron storage protein. These results serve as further proof of BL-1's iron-mediated selectivity to neuronal lineages when promoting safe storage of intracellular Fe likely to prevent ferroptosis and slow down cellular aging. In neurons, BL-1 was highly selective to IRE-like targets and did not change the expression of a battery of metabolic proteins (i.e., GAPDH, LDH, and cis-aconitase) and beta-actin and beta-tubulin levels were unchanged). To address therapy to thwart Parkinsonian Mn toxicity to neurons, we designed fifteen novel analogs of BL-1 (K.H.), four of which were tested for neuroprotective action to shield neurons from manganese (Mn) toxicity. We observed Mn caused 30-70% reduction in cell viability by MTS assays (250 micromolar for 48 h). Our BL-1 analogs protected SH-SY5Y cells from Mn-dependent loss of viability in a dose-dependent manner (e.g., 4-methoxy =494, the 4-H = 495, and pyridyl-analogs = 498 and 499). In particular, the 494-specific analog of BL-1 offset neurotoxicity by increasing viability by 75% compared to untreated cells at 0.05 micromolar concentrations of Mn exposure. BL-1-494 is more metabolically stable than BL-1 (e.g., no oxidation of the thiomethyl group). We will medicinally diversify BL-1 as our lead small molecule activator of ferritin translation into a drug that will combat iron overload in the brain including in AD/PD.

Biography

Jack Rogers, PhD. is an authority on the role that RNA plays in the maintenance of iron homeostasis and metal toxicities related to the blood (anemia) and in Alzheimer's disease, and more recently in Parkinson's disease. Director of the Neurochemistry Laboratory in the Psychiatry/Neuroscience Department at Massachusetts General Hospital and an Associate-Professor at the Harvard Medical School, Jack has a well-funded track record in established scientific journals (Cell, J. Biol. Chem. including cover issue, J. Neurochem, and PNAS). His peer-review publications won him a Zenith award from the Alzheimer's Association on the subjects of iron metabolism and translational control related to disease progression. Jack has a track record on the novel iron metabolic approach to AD and Parkinson's disease. His integrative program has used RNA based therapeutic strategies to ameliorate the progression of the AD (2002-2018), and PD disease in partnership with the Michael J-Fox Foundation (2009-2019). He is a mentor of postdoctoral fellows and helped teach the molecular biology of disease at the Harvard Med. students. Dr. Rogers gives a creative approach to gene based therapies and basic science, and serves on several scientific advisory Boards. He and his family live in Arlington, Massachusetts.

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