Lead Exposure and Alzheimer's Disease (grant proposal)

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Exposure to heavy metals is a major public health problem that could occur through contaminated air, food, or water, either during the course of everyday life or while working in hazardous occupations. Environmental exposure to lead (Pb) has been linked to risk of late-onset Alzheimer's disease (AD) and dementia. Although Pb has long been known as a neurotoxic agent in children, a recent and growing body of epidemiological research indicates that cumulative Pb exposure likely drives age-related neurologic dysfunction in adults. The biological mechanism underlying this link is unknown. This proposal considers the novel possibility that lead exposure causes late-life dementia via interactions between Pb-driven cerebrovascular pathology and typical AD-pathology, by examining this process in a unique mouse model. Further, this project will test an exciting new therapeutic approach that we believe could be used to treat not only this state, but general cerebrovascular complications of AD. Our preliminary data show that Pb exposure in adult mice impairs cognitive function, and causes hypertension. Further, we have shown that treatment with a low dose of the clinically approved AT1R antagonist Micardis (telmisartan) is able to ameliorate cerebrovascular disease in our mice. In specific aim 1 (SA1), we will investigate the role of Pb in neurologic disease by examining the latent effects of adult exposure as the animals develop age-related AD and CVD. In SA2, we will examine the consequences of treating our mouse line with telmisartan, and examining the effects of preventing or even reversing age-related CVD and cognitive dysfunction, with or without Pb exposure. In SA3, we will examine the interplay between lowering blood pressure, with and without Pb exposure, in our unique mouse line. Efficacy will be determined by measuring cognitive function, as well as range of immunohistochemical, molecular, and biochemical markers. These studies will be performed in a unique mouse model that develops age-related metabolic and cognitive dysfunction, amyloid and tau pathology, and severe CVD, including many small strokes and aneurysms. This novel mouse has the potential to be the basis for significant advances in our understanding of the important biological mechanisms linking environmental toxins, aging, cerebrovascular dysfunction, and AD. The strengths of this proposal are the use of an innovative mouse model, combined with an approach that explores a novel pharmacological target that has the potential to have a real world impact on the prevention or treatment of the disease. This project has the capacity to significantly improve our understanding of vascular senescence, to further our knowledge of the underlying causes of vascular dementia in the context of co-morbid AD pathology, to advance our understanding of environmental toxins in neurologic disease, and to have significant implications for the treatment and prevention of age-related complications of AD.