Gene Therapy Targeting Striatal cGMP signaling in experimental parkinsonism

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Principal Investigators

WEST, ANTHONY R

Institution

ROSALIND FRANKLIN UNIV OF MEDICINE & SCI

Contact information of lead PI
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USA

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Research Abstract
? DESCRIPTION (provided by applicant): Available dopamine (DA)-based drug therapies help to subdue motor symptoms associated with Parkinson’s disease (PD), but lose effectiveness with time and produce debilitating side effects such as dyskinesias. Therefore, our long-term goal is to identify new gene therapy-based strategies which can offer more selective symptomatic, and potentially, disease modifying treatment for PD by targeting non-

dopaminergic signaling pathways. One relatively understudied yet promising candidate for second messenger-based therapies is the soluble guanylyl cyclase (sGC)-cGMP-protein kinase G (PKG) signaling cascade. Converging evidence from animal models indicates that dysregulation of striatal cGMP synthesis and metabolism is likely to contribute to pathophysiological changes observed in PD. In addition, striatal DA denervation leads to a robust upregulation of sGC expression and cGMP synthesis. This phenomenon is also observed following acute D2 (but not D1) receptor antagonism, thereby indicating that loss of DA tone results in preferential upregulation of cGMP synthesis in D2 receptor-expressing striatopallidal neurons. Therefore, our primary objective is to use gene therapy approaches to assess whether an enduring reversal of abnormalities in striatal sGC-cGMP-PKG signaling and PD-like pathology can be achieved in DA-depleted rats. Similar approaches will also be utilized to determine if upregulation of cGMP-PKG signaling is sufficient to recapitulate a parkinsonian-like state in naïve animals. Our central hypothesis is that sustained downregulation of sGC-cGMP-PKG signaling in the DA-depleted striatum is sufficient to rescue motor impairments observed following DA depletion. In support of this, our preliminary studies show that acute and chronic pharmacological inhibition of sGC induced an enduring improvement in forelimb akinesia in PD models. We also expect that chronic downregulation of cGMP-metabolizing PDEs together with enhancement of PKG activity in striatopallidal MSNs is sufficient to produce a PD-like state in D2- (but not D1-) Cre-transgenic mice. Thus, the rationale for the proposed work is that genetic manipulations of striatal sGC-cGMP-PKG signaling may be a powerful approach for restoring the striatal dysfunction induced by chronic DA depletion and for treating motor deficits associated with PD. We will test our hypotheses via two specific aims. Aim 1 will determine the utility of gene therapy-induced downregulation of striatal sGC-cGMP-PKG signaling for reversing experimental parkinsonism in a rat model of PD. Aim 2 will determine whether upregulation of striatal sGC-cGMP-PKG signaling is sufficient to produce a parkinsonian-like state in naïve animals. The approach is innovative, because it focuses on an entirely different target for regulating synaptic and motor dysfunctions associated with PD, i.e., intracellular sGC-cGMP-PKG signaling cascades. The proposed research is significant because results from these studies could reveal that targeting sGC-cGMP-PKG signaling in striatopallidal MSNs using gene therapy represents a promising disease modifying strategy for treating patients with PD.

Further information available at:

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