TACSM Abstract

Transiently Silencing Genes Associated with Voluntary Physical Activity Using Intravenous Injection of Vivo-morpholinos

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ABSTRACT

Physical inactivity has been associated with several diseases and conditions with multiple candidate genes proposed to regulate voluntary physical activity. However, there has not been a reliable method to silence candidate genes in vivo to determine causal mechanisms of physical activity regulation. The novel molecular biology tool, Vivo-morpholinos, is a potential method to transiently silence specific genes. Thus, the aim of this study was to validate the use of Vivo-morpholinos in a mouse model for voluntary physical activity with several sub-objectives. We observed that Vivo-morpholinos achieved between 60 – 97% knockdown of Drd1-, Vmat2-, and Glut4-protein in skeletal muscle, the delivery moiety of Vivo-morpholinos (scramble) did not influence physical activity and that a cocktail of multiple Vivo-morpholinos can be given in a single treatment to achieve protein knockdown of two different targeted proteins in skeletal muscle simultaneously. Knocking down Drd1, Vmat2, or Glut4 protein in skeletal muscle did not affect physical activity. Vivo-morpholinos injected intravenously alone did not significantly knockdown Vmat2-protein expression in the brain ($p=0.28$). However, the use of a bradykinin analog to increase blood-brain-barrier permeability in conjunction with the Vivo-morpholinos significantly ($p=0.0001$) decreased Vmat2-protein in the brain with a corresponding later over-expression of Vmat2 coincident with a significant ($p=0.0016$) increase in physical activity. We conclude that with appropriate research design, Vivo-morpholinos can be a valuable tool in determining causal gene-phenotype relationships in whole animal models.