

Progress report for the Fisher Center for Alzheimer's Research Foundation - Svenningsson

Several important diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are characterized by slow degeneration. A component of the cell called p11 has been discovered in the Greengard lab in 2006 as a key regulator of brain signaling and initially in the context of depression. Currently we are evaluating the role of p11 in the context of degeneration. We found that p11 is less present in several brain regions of patients such as PD patients. We have also found that mice completely lacking p11 have a lower response to L-dopa, the golden standard therapy for PD. We are currently pursuing studies on memory functions in p11 KO mice addressing the role of p11 in AD. Supported by the Fisher Foundation we have generated unique mice which lack p11 specifically in some neurons and we are studying how the signaling of these neurons is affected. More clinically relevant, we are also studying how these neurons lacking p11 respond to environmental toxins, like rotenone, known to induce PD-like symptoms in mice and also in humans. Moreover, we are studying responses to rivastigmine, a commonly used agent in AD, in the p11 KO mice. Since 80% of the PD patients develop dementia at later disease stages, it is plausible that p11 levels might be correlated with cognitive performance. We are therefore currently studying whether changes in p11 in the blood may predict the development of PD-associated dementia. We are also studying the levels of p11 in samples from AD patients. If the P11 hypothesis was confirmed, this work could lead to novel therapeutic avenues such as gene therapy.

Green H, Zhang X, Tiklova K, Volakakis N, Brodin L, Berg L, Greengard P, Perlmann T, Svenningsson P. Alterations of p11 in brain tissue and peripheral blood leukocytes in Parkinson's disease. *Proc Natl Acad Sci U S A*. 2017 Mar 7;114(10):2735-2740.

Schintu N, Zhang X, Alvarsson A, Marongiu R, Kaplitt MG, Greengard P, Svenningsson P. p11 modulates L-DOPA therapeutic effects and dyskinesia via distinct cell types in experimental Parkinsonism. *Proc Natl Acad Sci U S A*. 2016 Feb 2;113(5):1429-34.

Svenningsson P, Kim Y, Warner-Schmidt J, Oh YS, Greengard P. p11 and its role in depression and therapeutic responses to antidepressants. *Nat Rev Neurosci*. 2013 Oct;14(10):673-80.