The therapeutic potential for RVG9RÐp137 in a disease relevant model of Parkinson’s dementia

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Research Abstract

There is a major clinical need for neuroprotective therapies in Parkinson’s Disease (PD). While many experimental therapeutic agents focus on the dopaminergic motor-related symptoms, little is oriented towards dementia which can be a debilitating complication of PD. We have recently demonstrated that a novel RVG9R-p137 treatment is neuroprotective against rotenone and 6-OHDA insults in both in vitro and in vivo models of PD, respectively (Kuan et al, 2012). The RVG9R peptide is derived from the rabies virus glycoprotein, which transports its RNA cargo

across the blood-brain barrier and specifically targets acetylcholine receptor-expressing neural cells whilst the active agent is a small non-coding RNA (p137) that selectively binds to complex 1 and rescues its function. The RVG9R system can effectively deliver the p137 RNA into neurons of both dopaminergic and non-dopaminergic systems upon transvascular administration. The mechanism of p137-mediated neuroprotection involves protecting mitochondrial complex I activity as well as restoration of mitochondrial membrane potential and ATP production. Mitochondrial dysfunction and complex I impairment has been implicated in the pathogenesis of PD and causes cell loss to develop over years. This protracted degenerative process, however, is very different to the traditional acute lesioning models. Furthermore, the formation of alpha-synuclein inclusions – the defining pathology of PD – are not seen in models generated by 6-OHDA. Recently in our lab we have established a rat model of PD involving the overexpression of alpha-synuclein using viral vectors. This model offers a slower, more disease-related neurodegeneration. Given that alpha-synuclein has been shown to inhibit mitochondrial complex I function and compromise cell viability, we believe that this model also provides a better means of evaluating the efficiency of the RVG9R-p137 treatment. We aim to test the RVG9R-p137 treatment in alpha-synuclein overexpression models focusing on dementia related symptoms with a view towards clinical translation.

Further information available at:

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