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Bqca, a highly specific M1 muscarinic receptor allosteric modulator, reduces native and misfolded prion protein in a prion-induced neurodegenerationmouse model

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It has been predicted that by 2030, 65million people would suffer from some form of neurodegeneration-induced dementia, such as Alzheimer's disease. At the moment, there are no treatments available that could prevent or even slow down the progression of neurodegeneration. G-protein coupled receptors are cell surface receptors whose activities regulate virtually all-physiological processes including the function and plasticity of neuronal circuits. The five GPCR-subtypes of the muscarinic receptor family (M1-M5), which are responsible for the transduction of many of the important physiological functions of the neurotransmitter Acetylcholine, have already been validated as important pharmacological targets for neurological and neuropsychiatric diseases. We have previously demonstrated that prion disease shows features very similar to Alzheimer's pathology including memory deficits associated with the disruption of the hippocampal cholinergic innervation. In addition, prion murine disease is a terminal neurodegenerative disease induced by the accumulation of misfolded prion protein, similar to the misfolded beta amyloid and tau pathology of Alzheimer's disease. Remarkably, our recent studies have shown that increases in the M1 muscarinic receptor signalling, via positive allosteric modulators including BQCA, restores memory loss in prion disease. Here we extend these studies by investigating the neuroprotective mechanism observed following the BQCA treatment of mice inoculated with prion infected brain homogenates (RML). In particular, we show that the chronic treatment with BQCA, a highly selective positive allosteric modulator of M1 receptor, increases the survival ($p<0.001$) of prion diseased mice and reduces native (about 35%, $P<0.001$) and scrapie (about 80%, $P<0.05$) forms of prion. Moreover, we are setting up a new approach to regulate prion protein levels within the neurones. Briefly, by using the von Hippel-Lindau protein (VHL), which is part of the ubiquitination machinery complex of the cell, fused with a nano-body that recognizes and therefore targets prion protein, we would be able to induce prion specific protein degradation, in-vitro and in vivo. This new approach may elucidate the effects of the prion protein itself on neuronal functions. In conclusion, we present here the effects of the positive M1-muscarinic receptor allosteric modulator, BQCA on prion protein levels, in vivo, and preliminary data about an novel approach to target prion protein.