Facilitated Drug Delivery into the Central Nervous System

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The emergence of peptides derived from the rabies virus glycoprotein (RVG) as targeting ligands for drug delivery to the brain, have shown promise as an effective way of non-invasively overcoming the blood brain barrier (BBB) for targeted therapy. RVG forms the part of the rabies virus which is responsible for this neural interaction and is ultimately responsible for the highly neurotrophic nature of the rabies virus itself, as it is the only surface protein expressed on the viral envelope (Yan., *et al*. 2002). (Son., *et al*. 2010) described RVG as a potential "magic bullet" for the targeting of genes to the brain. Rabies Virus-derived peptide (RDP) is a 39 amino acid derivative of RVG. RDP has been utilised successfully to deliver therapeutic payloads to mouse brain *in vivo* (Fu., *et al*. 2012), gaining effective entry into the central nervous system (CNS) and showing preferential accumulation in neural cells compared to non-neural, both *in vitro* and *in vivo* (Fu., *et al*. 2013). Likewise, it has been peripherally conjugated to gold nanoclusters for non-invasive brain screening, due to its observed ability to specifically accumulate in neurons *in vivo* (Zhang & Fu., *et al.* 2015). Another derivative of RVG, RVG-29, allowed preferential accumulation of an itraconazole payload in neural cells when conjugated to an albumin nanoparticle carrier (Chen., *et al*. 2010). Further-more, Liu., *et al*. (2009) showed how nanoparticles coated with RVG-29 exhibited higher blood brain barrier (BBB) crossing efficiency than unmodified nanoparticles.

Thus far, there has been conflicting evidence in the literature as to which receptor is utilised in these synthetic peptide-neural interactions and indeed by the rabies virus glycoprotein itself. Fu., *et al*. (2013) reported that the $GABA_{(a)}$ receptor is responsible for RDP uptake in neural cells, however RVG-29 has been linked to both the $GABA_{(b)}$ (Liu., *et al*. 2009) and the nicotinic acetylcholine receptor (Lafon., *et al*. 2005 & Kumar., *et al*. 2007). However given the abundance of recent evidence that would indicate major nicotinic acetylcholine receptor (nAChR) involvement (Sajjanar., *et al*. 2015; Vigerelli., *et al*. 2014; Zhan., *et al*. 2010), it may be possible to utilise this interaction to deliver therapeutic agents non-invasively across the Blood Brain Barrier (BBB), with a view of treating neurodegenerative processes such as Parkinson's Disease (PD). It is therefore important that the receptor interaction of these RVG-derived peptides with neural cells is considered, if they are to be brought forward as potential drug-targeting moieties, to aid modelling and optimisation for *in vivo* success.

The promise of these rabies virus glycoprotein-derived peptides for selectively targeting the CNS, could provide an exciting new way of non-invasively overcoming the challenges of the BBB and delivering a therapeutic cargo to the brain or spinal cord. Given the natural preference for neural cells *in vivo* and the lack of immune response reported thus far, the foundation for future work exists, to develop potential drug delivery systems for the fight against neurodegenerative disorders which are notoriously difficult to treat.

For a full review of this subject area please see:

Huey R & Hawthorne S. "The potential use of rabies virus glycoprotein-derived peptides to facilitate drug delivery into the central nervous system: a mini review". *Journal of Drug Targeting* (2016): 1-7. https://doi.org/10.1080/1061186x.2016.1223676

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