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New hope for devastating neurodegenerative disease

This scientific commentary refers to 'Insulin resistance and exendin-4 treatment for multiple system atrophy', by Bassil *et al.*, (doi:10.1093/brain/awx044).

When a credible new idea emerges for repositioning a diabetes drug for devastating brain disorders, it is essential to give that idea attention. In this issue of *Brain*, the team led by Dr Meissner provide such a possibility (Bassil *et al.*, 2017). More specifically, they provide a solid rationale for considering an FDA approved drug, exendin-4, as an entirely new approach for treating multiple system atrophy (MSA).

MSA is a rare, adult onset, fatal neurodegenerative disease presenting with autonomic failure, parkinsonism, and cerebellar ataxia in variable combinations, with an average survival time from diagnosis of 6–9 years. The leading pathological hallmark of MSA is glial cytoplasmic inclusions, which are formed from α-synuclein aggregates, in oligodendrocytes. Despite some similarities to Parkinson's disease, there are no effective symptomatic therapies for the motor features of MSA, and there is no avenue for slowing disease progression. The suggestion that exendin-4 could offer a therapeutic approach for MSA is therefore potentially of enormous importance and deserves close scrutiny.

Exendin-4 is a glucagon-like peptide-1 (GLP-1) agonist that belongs to a group of drugs called incretin mimetics, which are approved for the treatment of type 2 diabetes mellitus (T2DM). In its earliest stages T2DM develops from insulin resistance, which is generally defined as the inability of tissue to respond sufficiently to physiological insulin levels or the requirement for a higher concentration of insulin to induce a normal response. In terms of its impact on the brain, numerous studies have identified T2DM as a risk factor for stroke, Alzheimer's disease, vascular dementia, and Parkinson's disease, among other disorders. Patients with T2DM have an approximately 40% increased risk of developing Parkinson's disease (Xu *et al.*, 2011), while the relative aggregate risk of Alzheimer's disease for people with diabetes is 1.5 (Cheng *et al.*, 2012). Further, T2DM may accelerate progression of these neurodegenerative diseases. In turn, through an increasing number of preclinical and human clinical trial studies, it appears that targeting aberrant insulin signalling with GLP-1 agonists may provide a disease-modifying therapy for Parkinson's disease, Alzheimer's disease and, now, MSA.

Arising from these studies is a suggestion that these age-related neurological diseases share dysregulation of insulin and insulin-like growth factor 1 (IGF-1) signalling as a common contributing cause. We have previously suggested that brain insulin resistance follows from the neuroinflammation that is a hallmark of neurological diseases (Clark *et al.*, 2012). Consequently, it is possible that peripheral T2DM may not be a requirement for insulin resistance to occur in the brain. In fact, the term 'type 3 diabetes' has been coined to draw attention to the suggestion that Alzheimer's disease, at least, may follow from insulin resistance in the brain. Given the essential role of glucose metabolism, energy regulation, insulin and IGF-1 signalling in the CNS, it is feasible that T2DM and CNS insulin resistance could each, alone or in combination, contribute to pathology in a range of neurological diseases. It is therefore of great interest that Bassil and colleagues now report insulin resistance in the CNS of patients with MSA.

Peripheral insulin and IGF-1 levels are increased in serum of MSA patients (Pellecchia *et al.*, 2010) and this is correlated with clinical disease progression (Numao *et al.*, 2014), suggesting a link between MSA and impaired insulin/IGF-1 signalling. Bassil *et al.* have now taken this a major step further by assessing insulin resistance in the brains of seven MSA patients. Specifically, they assessed expression of phosphorylated insulin receptor substrate-1 at serine residues 312 (IRS-1pS312) or 616 (IRS-1pS616), accepted markers of insulin resistance.

While almost all neurons in the putamen of both MSA and healthy controls expressed IRS-1pS312 and IRS-1pS616, the numbers of neurons expressing these markers was decreased in MSA patients, reflecting severe neuronal loss in the putamen that occurs in MSA. Importantly, however, the authors demonstrated that the fluorescence intensity of IRS-1pS312 was higher in MSA patients. Furthermore, the longer a person survived with MSA after diagnosis the greater was the staining intensity in the neurons at death, which could indicate that, as in Alzheimer's disease (Talbot *et al.*, 2012), the extent of insulin resistance in neurons correlates with disease stage.

While clinical symptoms of MSA appear to represent grey matter dysfunction, the pathological hallmark of the disease is the presence of glial cytoplasmic inclusions in myelin-producing oligodendroctyes. In contrast to their findings in neurons, the authors demonstrated an increase in staining intensity of IRS-1pS312 in oligodendrocytes of MSA patients that negatively correlated with time from diagnosis to death. It is not possible to determine if this means that disease progression is slower when there is less insulin resistance in oligodendrocytes, or that insulin resistance decreases over time in oligodendrocytes.

The authors' results meanwhile provide evidence to support the hypothesis that insulin resistance and abnormal protein aggregation are linked. They noted that IRS-1pS312 staining intensity was higher in glial cytoplasmic inclusion-containing oligodendrocytes compared to oligodendrocytes lacking glial cytoplasmic inclusions in all MSA patients. This is interesting in view of previous *in vitro* studies showing that reversal of insulin resistance through the activation of the IGF-1 pathway suppresses α-synuclein aggregation and toxicity in neurons (Kao, 2009). It is therefore possible that a similar effect would occur in MSA, where α-synuclein aggregation is a key pathological hallmark. More work is needed to test this hypothesis.

Development of insulin resistance in humans is closely correlated with immune cell infiltration and inflammation. While they did not investigate immune cell infiltration in the brain, Bassil *et al.* investigated insulin resistance in microglia and astrocytes, often regarded as the brain's immune cells. While the expected increases in astrocyte and microglial populations were observed in MSA patients, staining intensity of IRS-1pS312 and IRS-1pS616 in glia, though present, was not altered compared to controls. It is accepted that pro-inflammatory cytokines such as tumour necrosis factor (TNF), which has been shown to be elevated in serum of MSA patients (Kaufman *et al.*, 2013), can cause insulin resistance through the interruption of insulin-stimulated tyrosine phosphorylation. Given that the glial reaction to a variety of neurological insults is to release inflammatory cytokines, possibly in turn contributing to insulin resistance (Clark *et al.*, 2012), it seems feasible that glia contribute to the development of insulin resistance without becoming vulnerable to it themselves. Assessment of the co-localization of insulin resistance with immunohistochemical or morphological markers of 'activated' glia would be an interesting next step to address this question.

In a final and important next step, the authors investigated the impact of treating insulin resistance with exendin-4 in a widely used preclinical model of MSA, the PLP-SYN mouse model. Importantly, they first validated that, similar to human tissue, expression of IRS-1pS307 (corresponding to human IRS-1pS312) was elevated in the striatum of transgenic animals compared to controls, while IRS-1pS612 (corresponding to human IRS-1pS616) was not. Mice were next separated into three groups receiving either placebo, 3.5 pmol/kg/min (lower dose) or 8.75 pmol/kg/min (higher dose) of exendin-4 for 12 weeks. Remarkably, exendin-4 treatment had an overall effect on the expression of insulin resistance markers in the brains of PLP-SYN mice and the higher dose significantly reduced both IRS-1pS307 and IRS-1pS612 levels.

Exendin-4 treatment did not, however, ameliorate the progressive motor impairment seen in the mice as they age. This is in contrast to the potent effects on motor behaviour found with treatment of exenatide (a synthetic form of exendin-4) in mouse models of Parkinson's disease as well as an average 7-point advantage on the MDS-UPDRS III motor scale seen in an open-label clinical trial in Parkinson's disease patients, which persisted after a 12-month washout period (Aviles-Olmos *et al.*, 2013, 2014).

The inability of exendin-4 to improve motor function does not rule out the possibility that it slows disease progression. Similar to MSA patients, PLP-SYN mice exhibit loss of dopaminergic neurons, in addition to glial cytoplasmic inclusions. Remarkably, Bassil and colleagues demonstrated that the higher dose of exendin-4 resulted in a significant increase in the survival of dopaminergic neurons. Meanwhile, while exendin-4 did not decrease oligomeric α-synuclein in the striatum of PLP-SYN mice, the higher dose significantly decreased monomeric α-synuclein. The authors therefore conclude that exendin-4's effects on α-synuclein are modest and insufficient to limit the aggregation of the insoluble α-synuclein species, which are the most toxic and relevant to the disease process. Nevertheless, the present study provides the first exciting *in vivo* evidence that GLP-1 analogues may greatly decrease dopamine neuron degeneration and, to some extent, the accumulation of monomeric α-synuclein in MSA.

Finally, the authors set out to determine if peripheral neural-derived markers of insulin resistance could act as a biomarker for MSA. They measured plasma exosomal levels of IRS-1pS307 and Alix (a cytosolic protein that is associated with pro-apoptotic signalling) in MSA mice treated with the higher dose of exendin-4. PLP-SYN mice with highest plasma exosomal IRS-1pS307 concentrations had greater inferred dopamine neuron loss and a higher oligomeric α-synuclein load in the striatum. This finding suggests that indeed, exosomal levels of IRS-1pS307 may be a marker of disease, though much more work will be required to assess if this is relevant in humans.

In summary, this study provides evidence of insulin resistance in neurons and oligodendroctyes in the putamen of MSA patients and demonstrates that dysfunction of insulin/IGF-1 signalling and dopamine neuron loss in a mouse model of MSA is reversed by exendin-4. Recent studies provide suggestion that GLP-1 mimetics offer promise as a disease-modifying therapy for Parkinson's disease (Aviles-Olmos *et al.*, 2013) and studies are underway to investigate its potential in Alzheimer's disease. The well-known

Glossary

Exosomal: Relating to exosomes, extracellular vesicles that are released from cells

Glial cytoplasmic inclusions: Inclusions within the cytoplasm of oligodendrocytes. In regards to MSA these inclusions are formed from α-synuclein aggregates

GLP-1: Glucagon-like peptide-1

MDS-UPDRS III: Movement Disorder Society – Unified Parkinson's Disease Rating Scale Part 3.

PLP-SYN mouse model: A mouse model of MSA represented by overexpression of human α-synuclein in oligodendrocytes driven by the proteolipid protein promoter

safety profile of GLP-1 mimetics, combined with the exciting results described in the study of Bassil *et al.*, now provide a foundation for further studies in humans to assess whether repurposing exendin-4 and related GLP-1 mimetics offers the first disease-modifying treatment of MSA, a devastating and untreatable neurological disease. The possibility raised by this study is both tantalizing and exciting.

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Knowing your enemy: from post-mortem scene reconstruction to real-time monitoring of the spread of tau and amyloid

This scientific commentary refers to 'Association between tau deposition and antecedent amyloid-β accumulation rates in normal and early symptomatic individuals', by Tosun *et al.* (doi:10.1093/brain/awx046).

Alzheimer's disease encompasses a patient's trajectory of many years from mild clinical symptoms to a terminal stage of severe dementia. The clinically manifest phase is preceded by clinically silent changes of the brain, referred to as the preclinical phase. Current models of how Alzheimer's disease pathology evolves over time heavily rely on post-mortem reconstruction. Through methodical microscopic scrutiny of sections from hundreds of post-mortem brains and inferential reasoning required to construct a timeline