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Are Alzheimer's disease and other neurodegenerative disorders caused by impaired signalling of insulin and other hormones?

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Alzheimer's and Parkinson's disease are the most common neurodegenerative disorders, and case numbers are increasing due to the fact that life expectancies in the developed nations are increasing. Both diseases entail intense suffering to patients, family members and caregivers, and impose heavy tolls on public health systems. Unfortunately, we do not have a clear understanding of how these diseases develop. In Alzheimer's disease, recent attempts to develop novel treatment to stop or prevent disease progression have failed. This questions our understanding of the fundamental processes the underlie these progressive neuropathological disorders. This situation of uncertainty has kindled the interest for new ideas of how these diseases develop. For example, chronic inflammation has moved into the spotlight as a key pathological process that drives the ongoing neurodegeneration. Other ideas are now taking centre stage in particular as first positive clinical data have become available.

This special issue of *Neuropharmacology* is trying to open up new avenues of how to understand these diseases, and shine the light onto underlying mechanisms that previously have not received their due attention. The observation that type II diabetes is a risk factor for the development of both Parkinson's and Alzheimer's disease has inspired research into the underlying causes which lead to the observation that insulin signalling in the brains of patients with these diseases is impaired. In fact, further research has found that many other hormones and growth factors have lost their efficacy in the brain, most likely due to the chronic inflammation response and to the release of pro-inflammatory cytokines that block growth factor signalling.

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The special issue features a selection of reviews that describe the roles of a range of growth factors that appear to play key roles in the ontogenesis of neurodegenerative diseases. Apart from insulin, IGF-1, leptin, amylin, GLP-1 and GIP are among those signalling peptides that were found to be affected, and importantly, show neuroprotective effects when signalling functionality was reinstated. Excitingly, first clinical trials are ongoing to test insulin or long-acting GLP-1 analogues, and first positive outcomes have been reported. These encouraging results demonstrate that this new research area has hit on an important underlying mechanism that plays a key role rather than a less important side effect. Overall, these findings invigorate new areas of research in Parkinson's and Alzheimer's disease and shows great promise of actually developing treatments that can stop or delay disease progression.

The first section of the special issue summarises the role of insulin signalling impairment in AD, how type II diabetes and chronic inflammation contributes, and the potential therapeutic effects of nasal insulin treatment. First encouraging data from clinical trials are presented and discussed. The second section describes the neuroprotective effects of other energy-signalling hormones, the incretins. Drugs that activate the GLP-1 incretin receptor are on the market as a treatment for diabetes. Encouraging results showing neuroprotective effects of two of these drugs in clinical trials are presented in detail. A phase II trial in Parkinson's patients showed most impressive protective effects. The third section describes the neuroprotective effects of incretins in stroke and epilepsy. In the fourth section, other energy-signalling hormones such as ghrelin, amylin and leptin are discussed and their neuroprotective properties are presented in detail. In the final section, evidence for the roles of insulin and GLP-1 signalling in mood disorders and reward is presented.

We hope that this special issue will make an important contribution by informing the scientific community of these novel and promising developments in these research areas, and hope that the next generation of scientists will be stimulated and pursue these novel paths of discovery with enthusiasm.