Novel drug developed to treat type 2 diabetes are neuroprotective Alzheimer’s disease

Prof. Christian Hölscher, PhD
Biomed and Life Sciences
Faculty of Health and Medicine
Lancaster University, UK
Alzheimer’s disease

- About 4.5 million people in Europe have AD
- 28 million people worldwide
- Will double by 2040 due to ageing population
Diabetes- a risk factor in AD

- Insulin not only acts as a hormone to regulate blood glucose
- Insulin acts as a growth factor in all tissues
- Protects neurons of oxidative stress effects
- Inhibits apoptosis, promotes cell repair
- Enhances neuronal proliferation and dendritic sprouting in neurons
- **Insulin signaling in the AD brain de-sensitises**
Diabetes – a risk factor for Alzheimer’s disease

Type 2 Diabetes sufferers have a 80-150% increased risk of developing AD
Insulin signaling is desensitised in AD patients

- Insulin signaling is reduced in non-diabetic AD patients’ brains
- Brain analysis shows a reduction of Insulin Receptor signaling
- The biochemical profile in the brain is similar to those in diabetic people in the periphery
Novel strategies for treatments

- Testing diabetes drugs that prevent the desensitisation of insulin signaling
- Accessing parallel signaling pathways - the incretin hormones (GLP-1, GIP)
- Making use of the findings from diabetes research
- Prevention of neurodegeneration at an early stage
Currently on the market to treat type 2 diabetes:

- **Twice daily:** Exendin-4 (Byetta®; Exenatide®)
- **Once daily:** Liraglutide (Victoza®), Lixisenatide (Lyxumia®)
- **Once-weekly:** Albiglutide (Tanzeum®; Eperzan®), Dulaglutide (Trulicity®)
- **Once-weekly version of Byetta:** (Bydureon®)
- **Others are under development**
Transgenic mouse strain expressing human mutated APP and PSN1 genes that cause Alzheimer’s

Develops plaques in the brain, memory loss, synapse loss, chronic inflammation
Memory is rescued by the drugs

Object recognition task

A = saline
B = 1nm Lixisenatide
C = 10nm Lixisenatide
D = 2.5nm Liraglutide
E = 25nm Liraglutide

McClean et al., 2014
Synapse numbers increased

Density of synapses

- APP/PS1 Saline
- APP/PS1 Lixisenatide (1nmol/kg)
- APP/PS1 Liraglutide (2.5nmol/kg)
- APP/PS1 Lixisenatide (10nmol/kg)
- APP/PS1 Liraglutide (25nmol/kg)
- Wild-type Saline

OD

- Stratum radiatum
- Stratum pyramidal
- Molecular layer
- Stratum oriens

APP/PS1 Liraglutide (2.5nmol/kg)
APP/PS1 Lixisenatide (1nmol/kg)
APP/PS1 Liraglutide (25nmol/kg)
APP/PS1 Lixisenatide (10nmol/kg)
Wild-type Saline

Histology

*McClean et al., 2014*
Amyloid plaques are reduced

Beta-amyloid plaque load in the cortex

-49%  -46%  -43%  -45%

APP/PS1 Saline
APP/PS1 Lixisenatide (1nmol/kg)
APP/PS1 Liraglutide (2.5nmol/kg)
APP/PS1 Lixisenatide (10nmol/kg)
APP/PS1 Liraglutide (25nmol/kg)

McClean et al., 2014
Chronic inflammation is reduced

Level of activated microglia in the brain is reduced

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**McClean et al., 2014**
Testing liraglutide in AD patients in a pilot clinical trial

Study design:
38 patients, placebo controlled study, 6 months duration, PET imaging of $^{18}$FDG, amyloid.

Results:
- Liraglutide prevented the decline of brain activity as shown in $^{18}$FDG-PET brain imaging
FDG-PET imaging: Neuronal metabolism is compromised in AD

In $^{18}$FDG-PET imaging:

- Progressive decline of glucose uptake over time
- Correlates well with cognition and disease progression

Femminella and Edison, 2014
Liraglutide prevents reduction in metabolism

Abstract ADA 2015
Gejil et al., 1309-P
Our clinical trial, testing liraglutide in AD patients

- Liraglutide- phase II clinical trial (UK)

200 MCI/AD patients, placebo controlled double blind study, 12 months duration, PET imaging of FDG uptake and also of inflammation markers, CSF and blood analysis of tau / amyloid biomarkers, ADAS-cog cognitive test battery, daily living score

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