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Neuroprotective properties of GLP-1 - a brief overview

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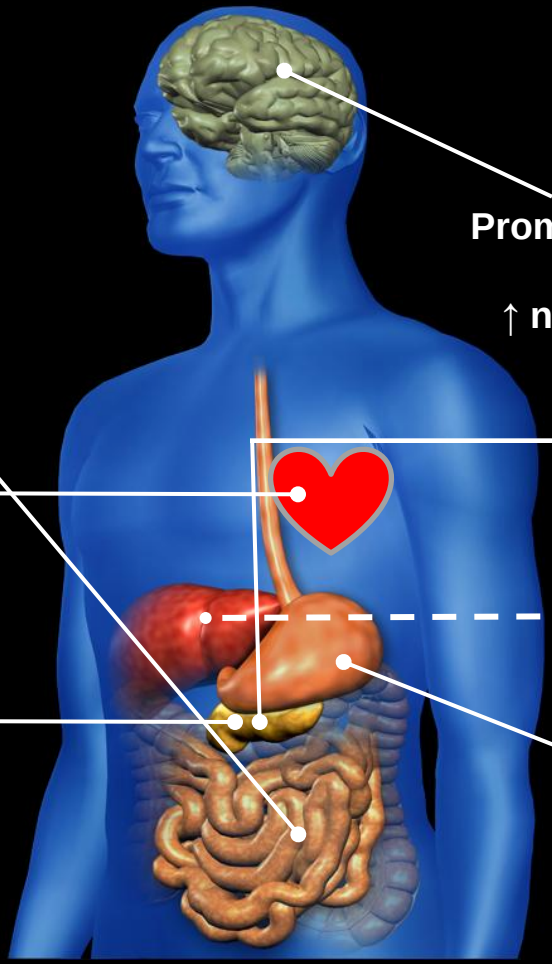
Agenda

- Glucagon-like peptide (GLP-1)
- GLP-1 and neuronal activity
- GLP-1 in disease-specific models
  - Alzheimer´s disease
  - Parkinson´s disease
  - Stroke
- Preliminary results from our group

GLP-1



GLP-1 secreted upon the ingestion of food

Promotes satiety and
↓ appetite
↑ neuroprotection

Heart:
↑ cardiac output
↑ cardioprotection

Alpha cells:
↓ Postprandial glucagon secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
↑ insulin biosynthesis
↑β cell proliferation
↓ β cell apoptosis
↑ glucose-dependent insulin secretion

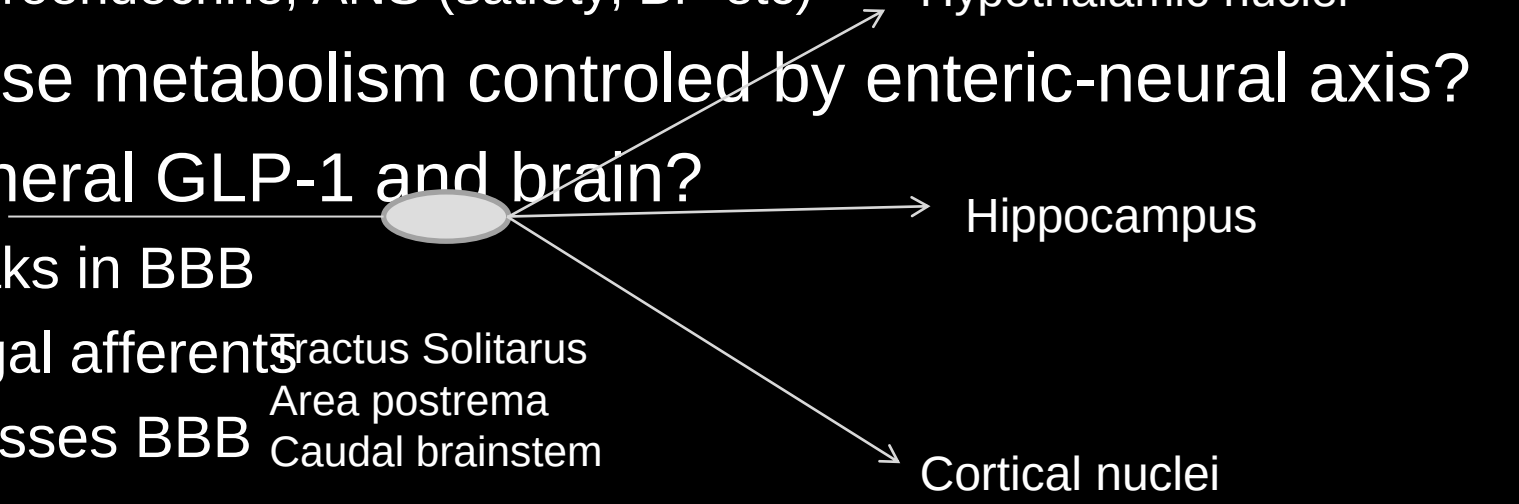
Stomach:
Slows gastric emptying

Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Drucker DJ. *Diabetes.* 1998;47:159-169;. Drucker DJ et al. Cell Metabolism. 2006;154.

GLP-1

Background:

- Multifunctional peptide – hormone/neuropeptide
  - Neuroendocrine, ANS (satiety, BP etc)
- Glucose metabolism controled by enteric-neural axis?
- Peripheral GLP-1 and brain?
  - Leaks in BBB
  - Vagal afferents
  - Crosses BBB



GLP-1

Background:

- GLP-1 7-36 amide $\longrightarrow$ GLP-1 9-36 amide
  - Heart and vascular system, not brain!
- T½= 2 min
- GLP-1R
  - G-protein-coupled
  - throughout the brain
- Mice, rats and humans
- In vitro/animal

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GLP-1

Background (cells/animals) :

- GLP-1R activation:
  - B-cell neogenesis (…)
  - Enhanced learning
  - Apoptosis protection
  - Reduced cell death secondary to stroke
- Knockout/antagonist impairs

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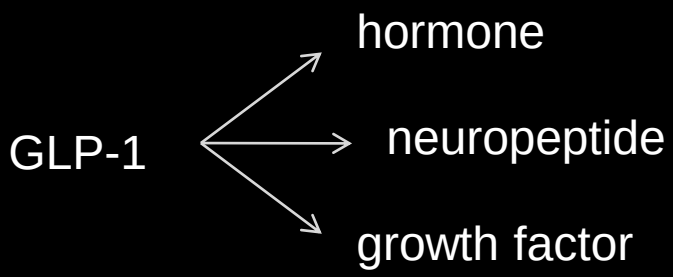
GLP-1

Background:

- 2 agonists
  - Exenatide, 54% seq. identity, cross BBB
  - Liraglutide, 97% seq. identity, cross BBB?
  - (native GLP-1, cross BBB?)
- Several nuclei activated by peripheral administration

GLP-1 and neuronal activity

- Growth factor – regulation of mitosis, cell growth, differentiation and pro-apoptotic (pancreatic cells)
- Neurogenesis in hypothalamic cells (murine), inhibited by antagonist
- Stimulate neuronal and glial cells in mammalian brain in vitro and in vivo
- Neurotrophic properties in all GLP-1R expressing cells



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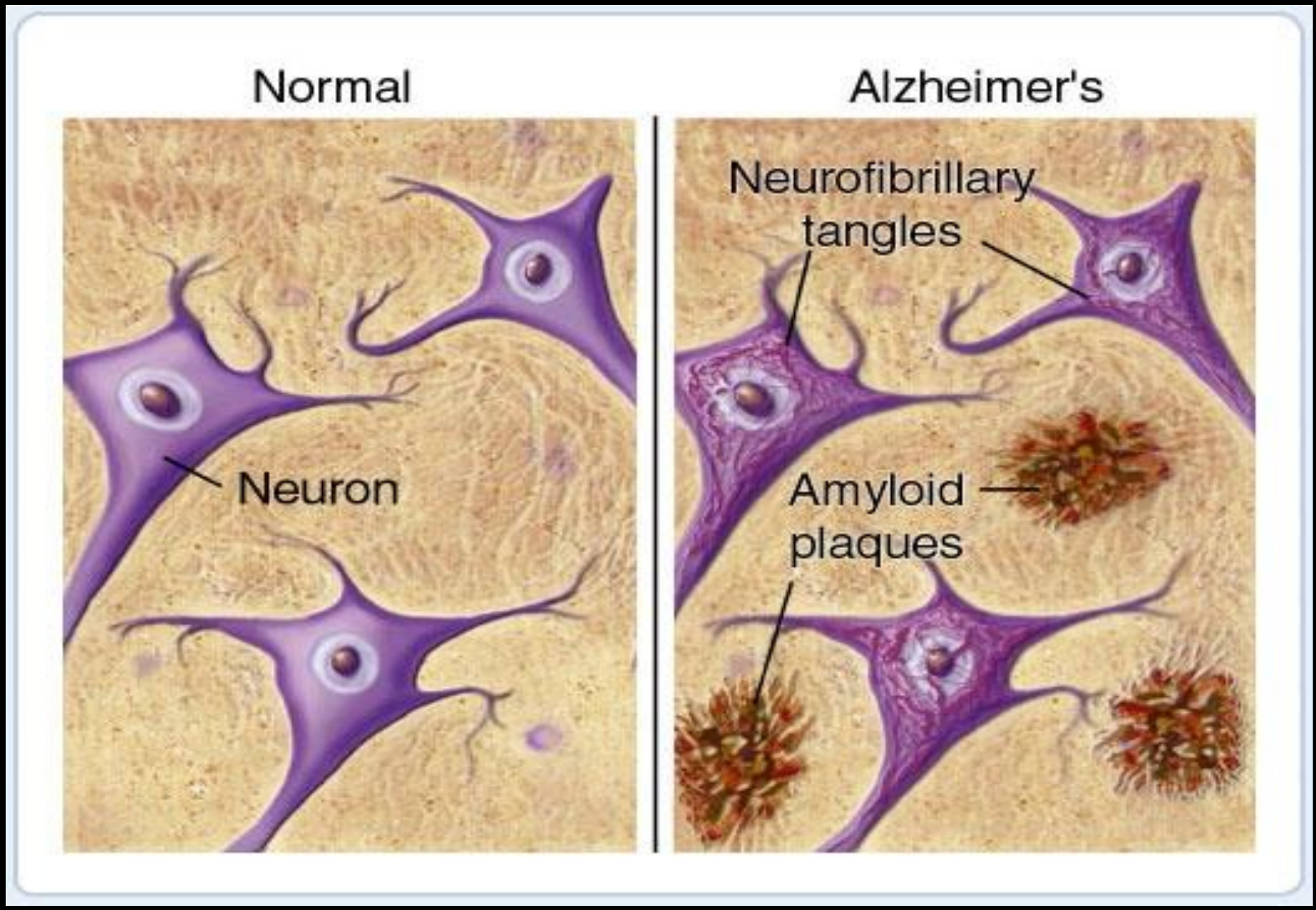
GLP-1 and Alzheimer's disease



GLP-1 and Alzheimer's disease

Insulin in AD:

- Defects in insulin signaling:
  - Increased sensitivity to insult
- Reduced brain insulin signa
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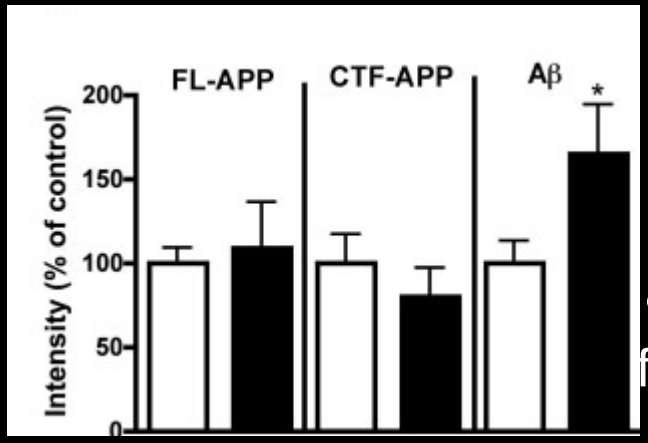

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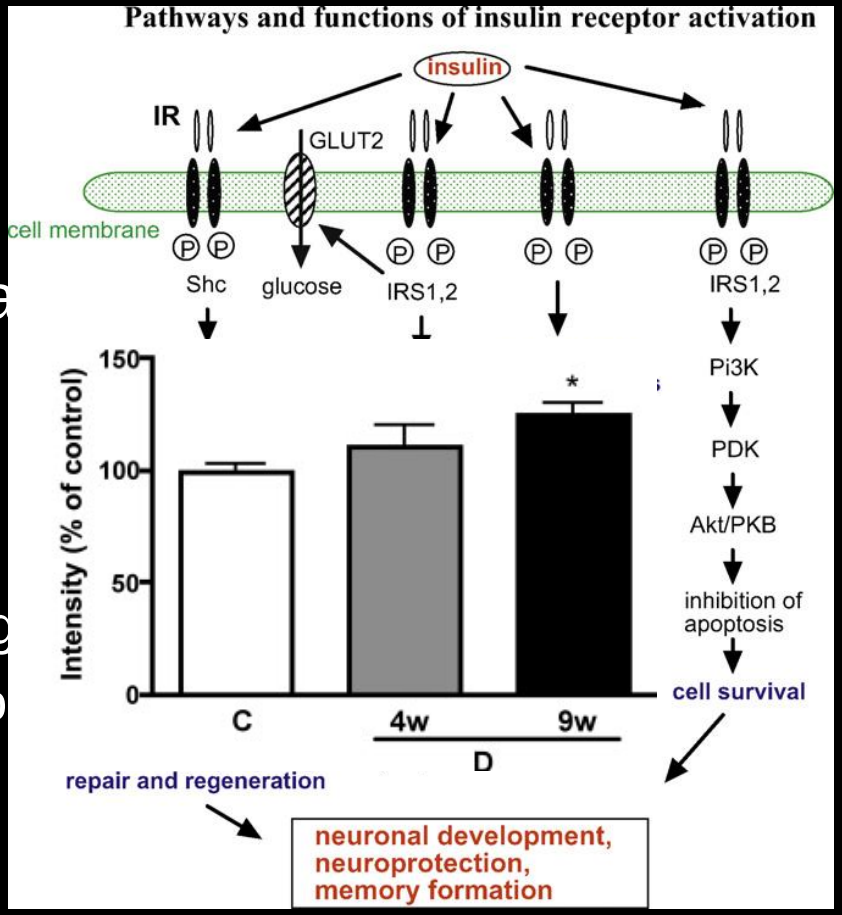

GLP-1 and Alzheimer's disease

GLP-1 in AD:

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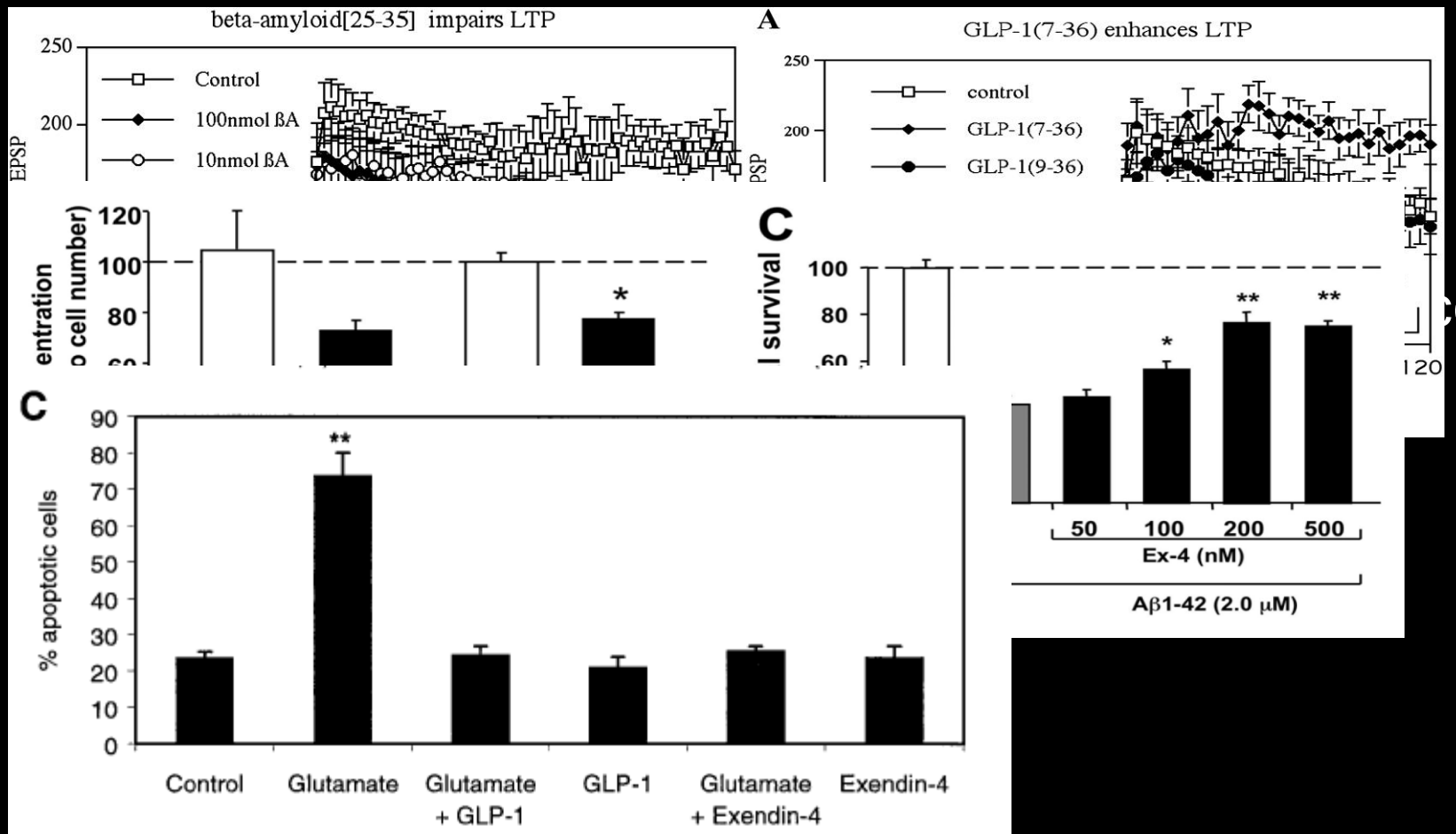

GLP-1 and Parkinson´s disease

Background:

- Progressive neurogenerative disorder
- Selektive loss of nigrostriale neuron – reduction in dopamine synthesis
- Cell loss by apoptosis, e oxidative processes
- 5 million worldwide – incr 2DM
- L-dopa/COMT inhibitors

GLP-1 and Parkinson´s disease

GLP-1 in PD:

- Decrease cell death in cerebocortical and ventral mesencephalic neurons
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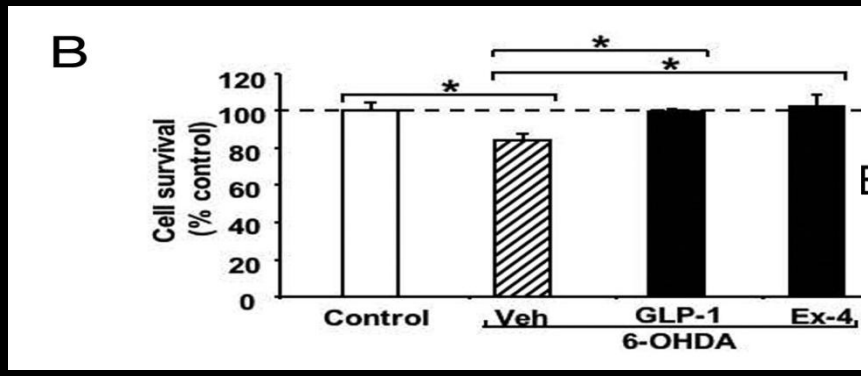
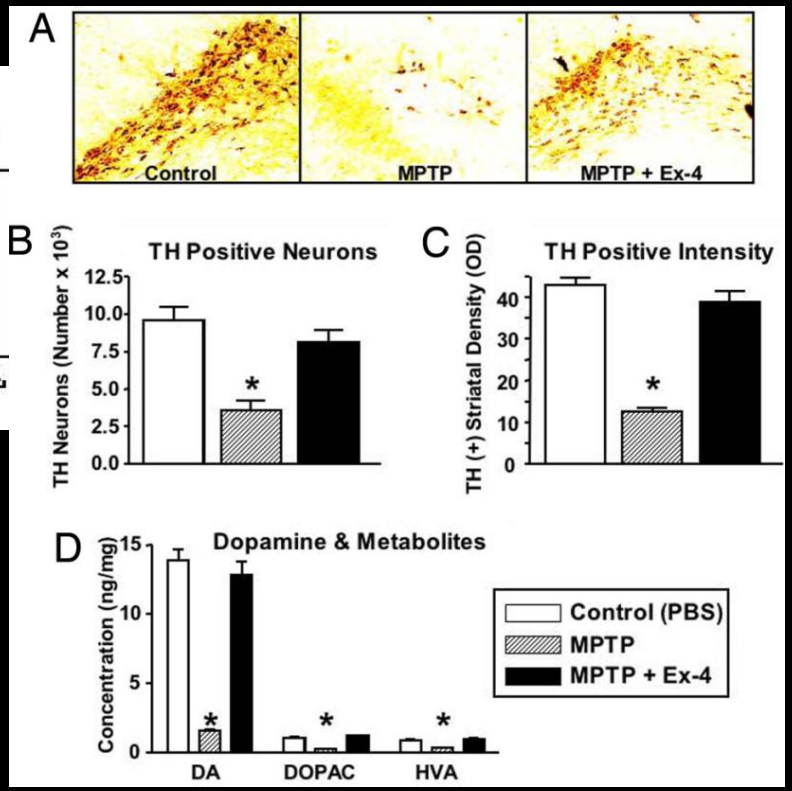
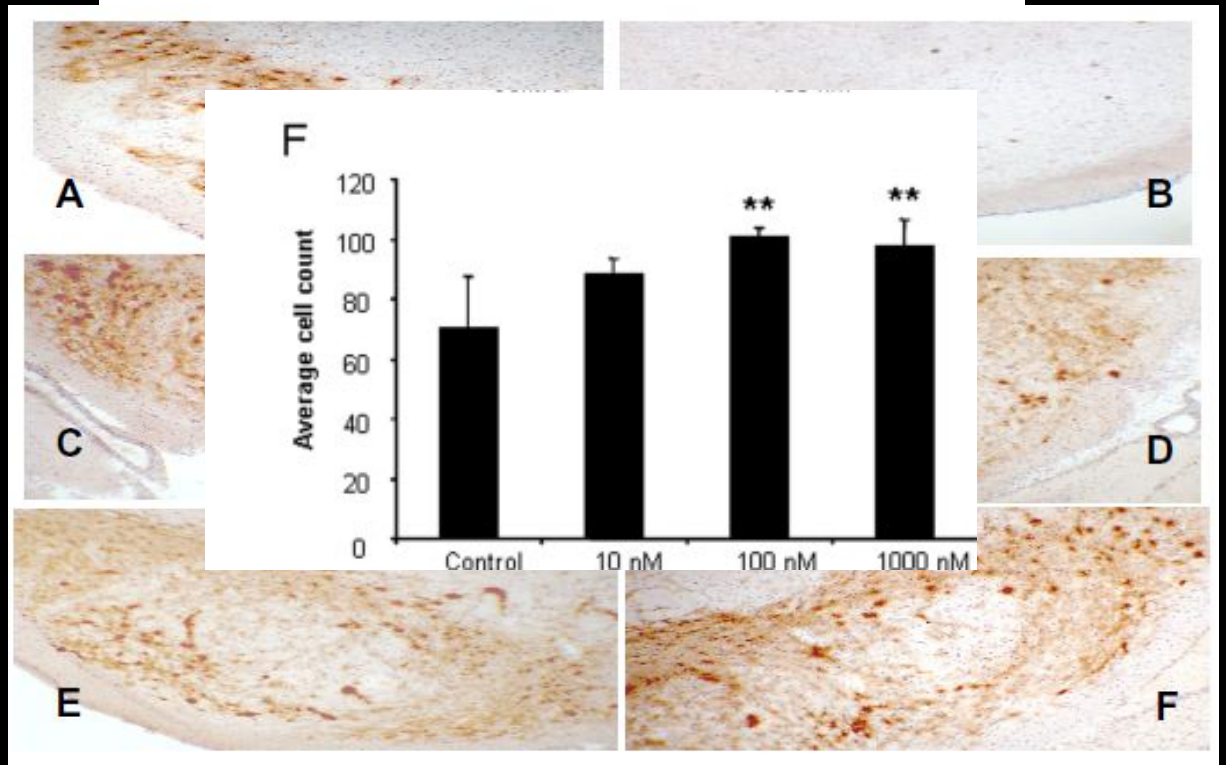




GLP-1 and Parkinson´s disease

GLP-1 in PD:

- Promote neurogenesis of neural stem cells (culture) and restore dopamine levels in rat models in SN



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GLP-1 and stroke

Background:

- 12000/year DK
- 2,9 times greater risk in T2DM

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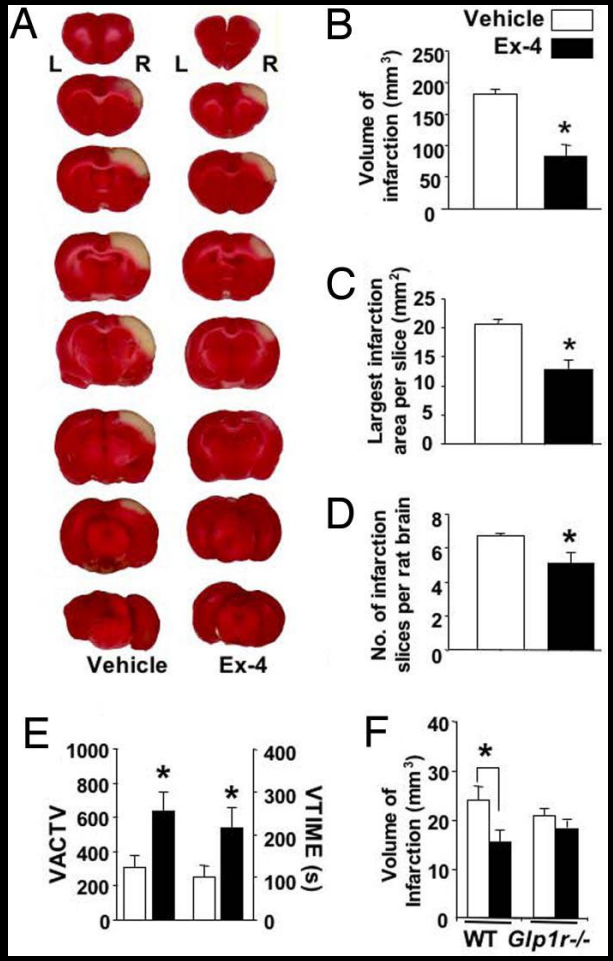
GLP-1 and Parkinson´s disease

GLP-1 in strokes:



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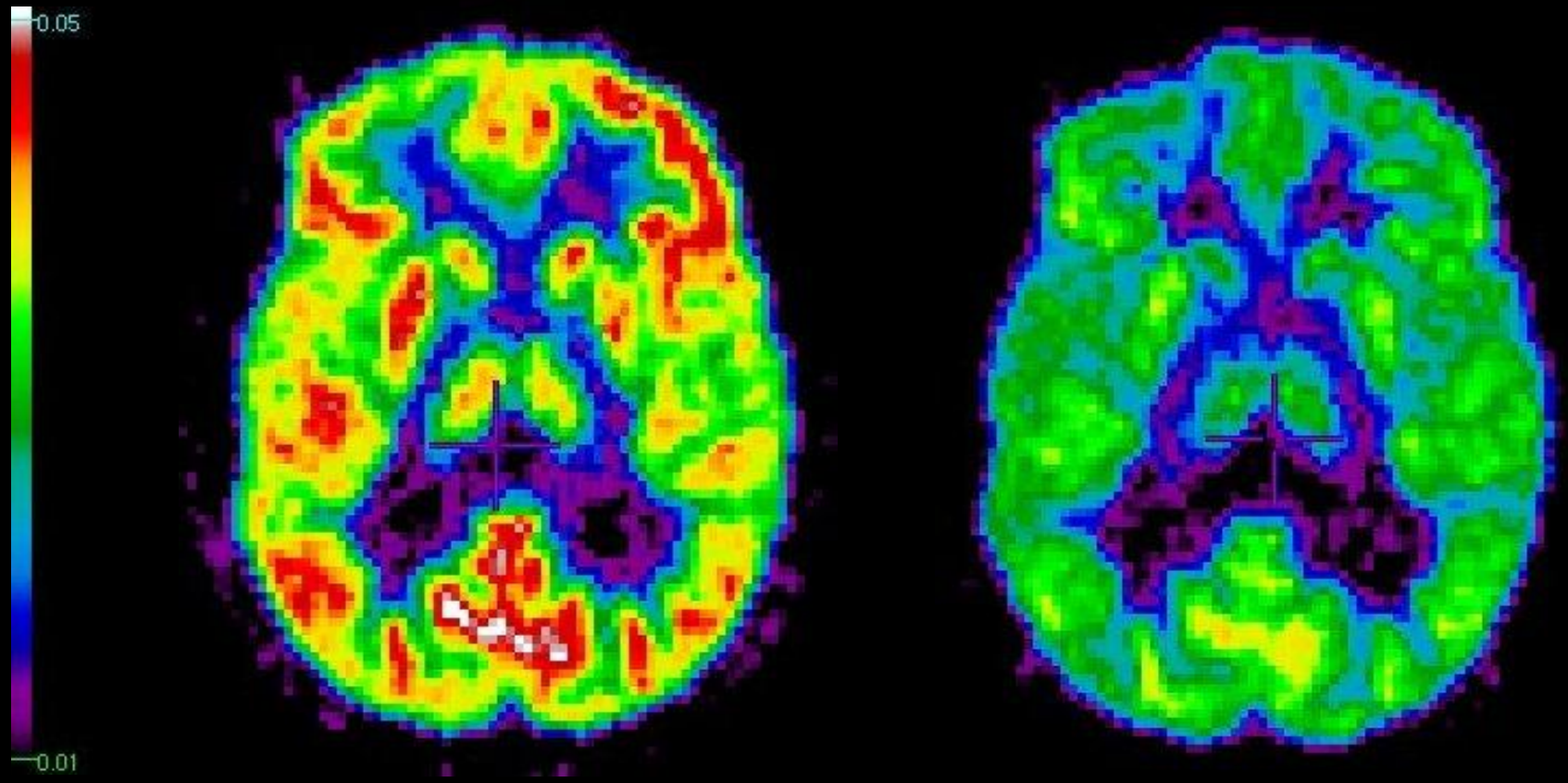
Placebo

GLP-1



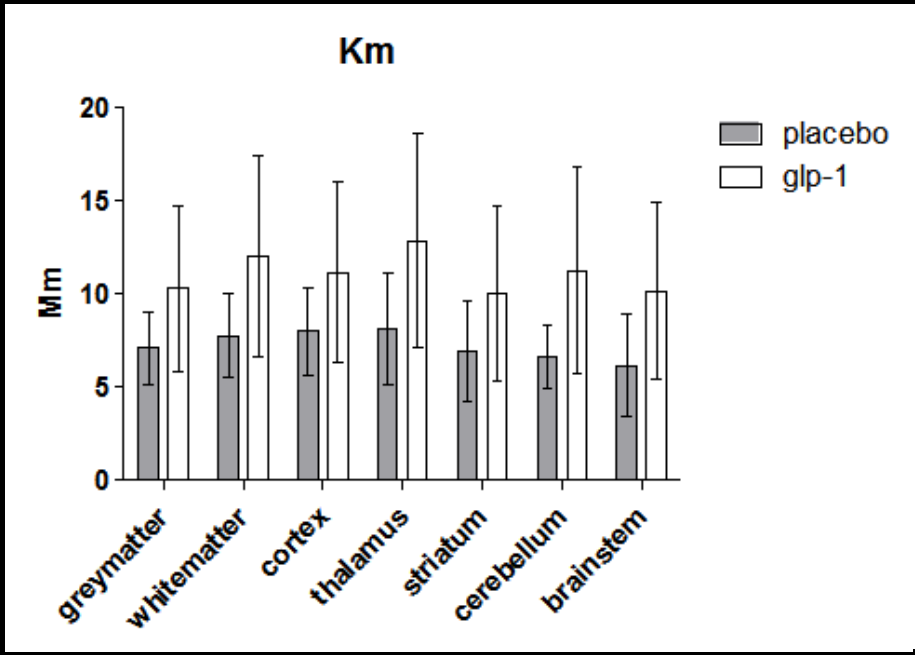
ml/cm^3/min

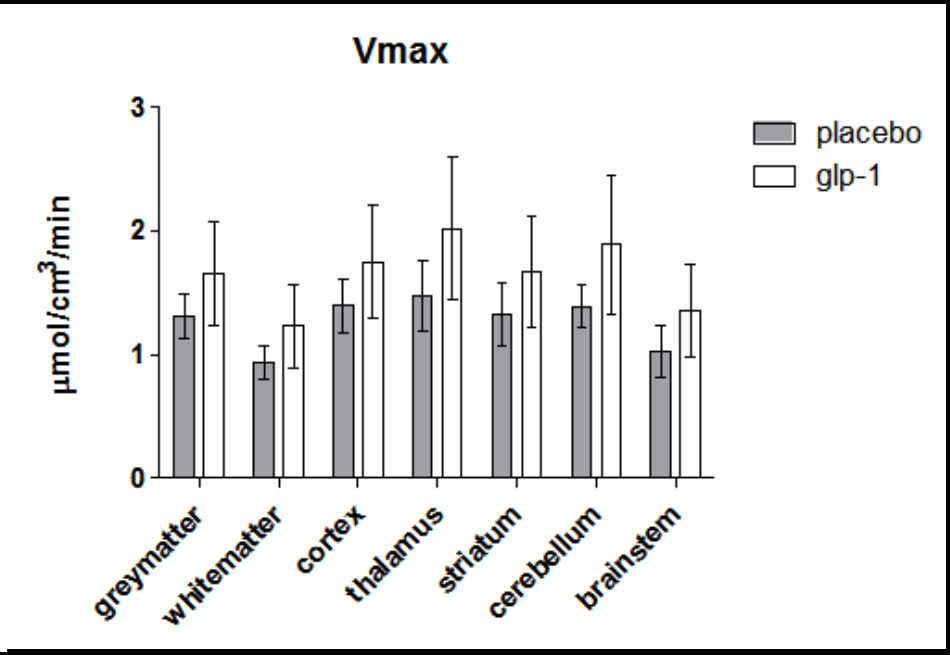
PET images of net clearance of FDG

(Example from a single subject
Normalised to dose and weight)

Preliminary data

- Grey and white matter: hexokinase affinity decreases
  - Km 0,01-0,08
- Gjedde and Crone, 1981: Tmax declined significantly and Kt tended to decline





Conclusion

- shared mechanisms and pathways of neuronal cell death in diabetes and several neurological disorders

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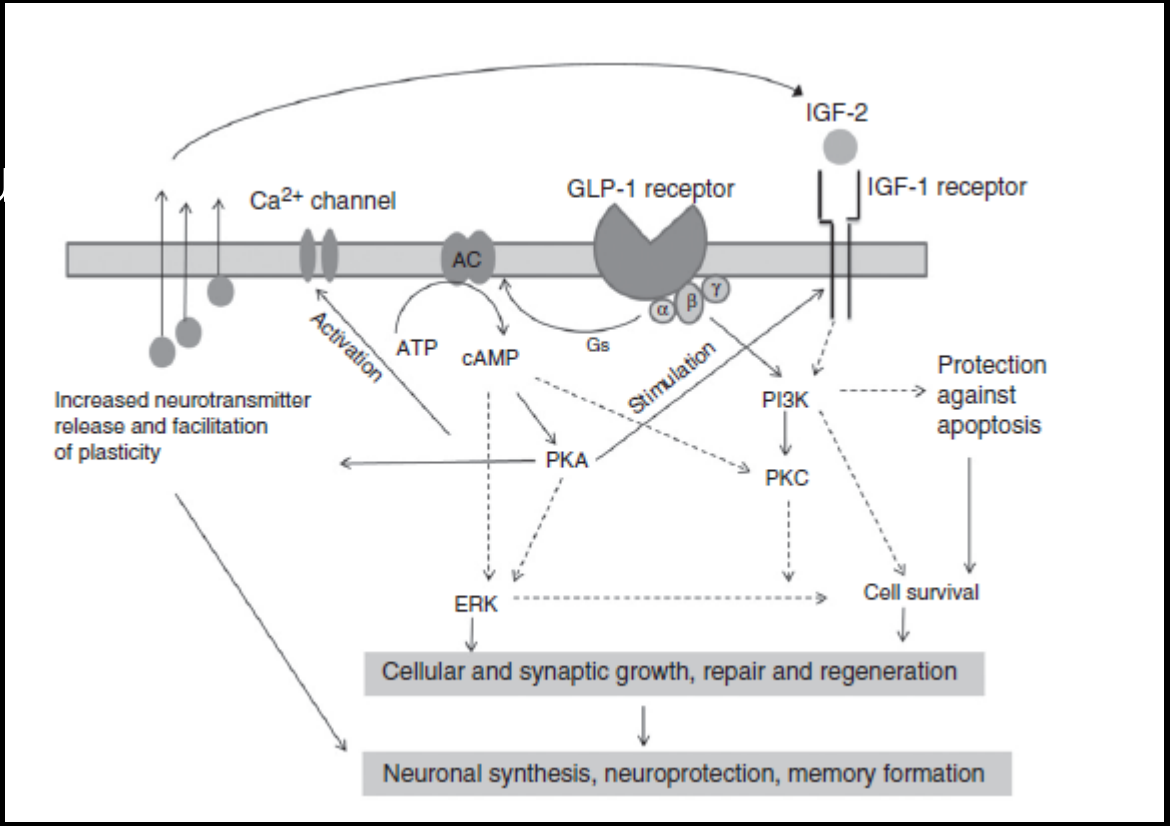
pathways
or in type
effects on



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Perspective

"Given the increasing interest in, and rapidly advancing commercial development of, GLP-1 receptor analogs as treatments for type 2 diabetes, such agents may find an additional role in the management of neurodegenerative disorders.

To date only preliminary in vitro and animal studies have investigated the potential neuroprotective functions of GLP-1-based therapies; **active development of additional preclinical and clinical studies** is necessary if we are to understand the therapeutic potential of these agents in treating neurological and neurodegenerative disorders."

Holst JJ, Curr Med Res Opin. 2011 Mar;27(3):547-58.