SRP Diabetes Postdoctoral Fellowship Program 2025

Project Title: Brain Circuit Dysfunctions Linking Diabetes and Parkinson's Disease Comorbidity.

BACKGROUND

In this multidisciplinary project, the postdoctoral fellow will combine metabolism, anatomical and neurophysiological studies to uncover the brain circuit mechanisms by which type 2 diabetes (T2D) exacerbates, and glucagon-like peptide-1 receptor agonists (GLP-1RA) mitigate Parkinson's disease (PD)-related alterations in dopamine (DA) function.

Patients with T2D have an increased risk of developing PD and often experience worsened PD severity and progression[1]. Recently, GLP-1RA, commonly used for glycemic management in T2D[2], are being explored as potential PD therapeutics[3,4]. GLP-1RA are neuroprotective and exhibit anti-inflammatory properties that may counteract DAergic neurodegeneration[5], the hallmark pathological feature of PD. However, the effects of GLP-1 on DA neuron physiology— and whether these effects change in T2D, contributing to PD-related pathophysiology—remain unclear.

Brain-derived GLP-1 is secreted by neurons of the nucleus solitary tract (NTS), a heterogenous region involved in feeding behavior, regulation of energy expenditure and glucose metabolism[6]. Our preliminary results show that NTS neurons innervate non-DA neurons in the midbrain of mice (**Fig 1**), suggesting that GLP-1R signaling regulates DAergic function through glutamatergic or GABAergic interneurons.

To determine whether this newly identified NTS-midbrain circuit contributes to T2D-induced PD-related pathophysiology, we will investigate its potential impairment in mice exhibiting T2D features, including hyperglycemia and insulin resistance, following prolonged high-fat diet (HFD) consumption. We will then assess whether GLP-1RA can restore normal circuit function.

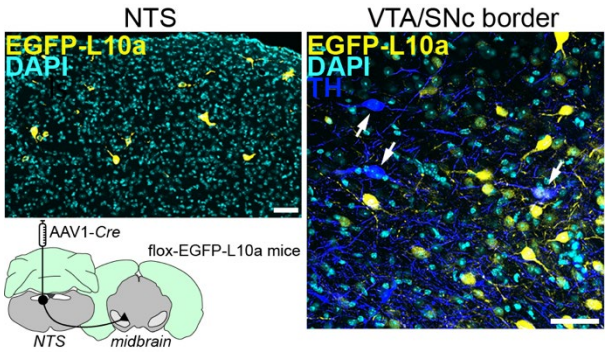

Fig 1. Preliminary results showing a monosynaptic circuit between NTS and midbrain neurons. AAV1-Cre spreads anterogradely and transsynaptically, depositing Cre in interconnected circuit components. Following injection of AAV1-Cre into the NTS of transgenic mice carrying a floxed EGFP-tagged ribosomal protein subunit L10a, we observed EGFP-positive starter cells in the NTS (left) and target cells in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc, right). Staining with antibodies against tyrosine hydroxylase (TH, arrows) revealed that NTS neurons target non-DAergic neurons. Scale: 100 µm.

OBJECTIVES

Aim 1: Resolve GLP1-R expression in the NTS-midbrain axis' anatomy using virus-assisted transsynaptic circuit mapping and RNAscope in situ hybridization. To which subregion of the midbrain GLP-1R+ NTS neurons project; which neurotransmitters do these neurons utilize; do NTS indirectly contact DA neurons?

Aim 2: Reveal DAergic pathophysiological changes in HFD-consuming T2D *versus* control mice and target them with GLP-1RA. Can GLP1-R agonist treatment reduce detrimental synaptic and intrinsic electrophysiological effects on DA neurons in T2D?

Aim 3: Establish a causal link between impaired NTS-midbrain activity and T2D-induced DAergic pathophysiology. Can T2D-related PD pathophysiology of DA neurons be mitigated by modulation of NTS-midbrain synaptic activity?

METHODOLOGY

Aim 1: With stereotactic surgery[7], the postdoc will inject AAV1-Cre into the NTS of floxed-reporter mice (available in Borgkvist lab) to fluorescently label neurons in the NTS-midbrain axis. Fixed slices with fluorescent cells will be co-stained with RNAscope riboprobes against glutamate and GABA-vesicular transporters across VTA and SNc subregions. Midbrain cells expressing GLP-1R will be identified by co-staining with GLP-1R riboprobes.

Aim 2: With *ex vivo* patch clamp electrophysiological recordings[7,8], the postdoc will determine the effect of T2D and GLP-1R activation by subcutaneous Semaglutide administration on intrinsic (*e.g.* spiking rate, membrane resistance, voltage gated cation current density) and synaptic (miniature excitatory and inhibitory currents) properties of DA and non-DAergic neurons. To acquire functional access to NTS-midbrain synapses, channelrhodopsin will be virally transduced in the NTS of mice expressing GFP in DA neurons, enabling circuit-selective analysis of NTS-midbrain synapses with photostimulation. T2D-related features will be confirmed via blood sampling and metabolic analysis.

Aim 3: We will inhibit NTS-midbrain neurons in HFD-consuming mice using designer receptor exclusively activated by designer drugs (DREADD)-technology. We will determine T2D-related features with metabolic analysis on blood samples after oral administration of the DREADD ligand clozapine-*n*-oxide and then record intrinsic and synaptic properties of DAergic neurons and striatal dopamine release with patch clamp and cyclic voltammetry.

WORK PLAN

We have carefully designed this project so that it can be completed within two years. Briefly, breeding of transgenic mouse lines is ongoing and we already have all the equipment necessary for launching these studies, including a stereotactic instrument, patch-clamp rigs fully equipped for fluorescence imaging and optogenetic studies, a vibratome for live and fixed-tissue preparation, and confocal microscope access from our department, free of charge. The postdoc will complete AIM1 during the first eight months. Meanwhile, animals will be placed on a high-fat diet (HFD) for seven months (alternatively, HFD mice can be obtained ready for experiments from Janvier). AIM2 will be completed by the beginning of year two. AIM3 is high-risk requiring CNO dose optimization and metabolic analyses with an additional six months for completion. By the 3rd quarter of year 2, we should be ready to start writing the paper.

The postdoc is hosted in the Borgkvist lab at Biomedicum in Solna under **Anders Borgkvist** (neurophysiologist) supervision. In addition, he/she will also be mentored by **Cesare Patrone** (KI SÖS) who has extensive experience with GLP-1RA-based strategies for the treatment of Parkinson's disease in T2D (see his CV). This co-supervision will create a unique training/educational opportunity on the interface between brain and diabetes research. The postdoc will participate in lab meetings in both Borgkvist's and Patrone's groups and bimonthly provide a report. If successful, these studies are expected to have such high impact that the postdoc can attract additional funding from neuroscience and diabetes-related funding sources to expand the studies.

SIGNIFICANCE

Epidemiological studies (both prospective and retrospective) have shown the prevalence of T2D in PD patients, the risk of developing PD in T2D patients and the negative effects of T2D on PD severity and progression[1]. The mechanisms through which this occurs are largely unknown, but since T2D people will reach 700 million by 2045[9], this creates a social/economic burden with a substantial and unmet medical need.

This project will show, for the first time, the role of the NTS-midbrain axis in regulating midbrain DA neuron physiology. We will identify impairment of this brain circuit as central to PD-related pathophysiology in T2D and provide novel evidence of the connection between T2D and PD. Finally, by showing that GLP-1R activation can counteract the impairment of the NTS-midbrain axis, the results will also be novel in the perspective of developing therapeutics for both preventing the risk of PD and counteracting PD-related pathophysiology in T2D.

REFERENCES

1. König, A., and Outeiro, T.F. (2024). Diabetes and Parkinson's Disease: Understanding Shared Molecular Mechanisms. J Parkinsons Dis *14*, 917-924. 10.3233/JPD-230104.
2. Drucker, D.J., and Holst, J.J. (2023). The expanding incretin universe: from basic biology to clinical translation. Diabetologia *66*, 1765-1779. 10.1007/s00125-023-05906-7.
3. Meissner, W.G., Remy, P., Giordana, C., Maltête, D., Derkinderen, P., Houéto, J.L., Anheim, M., Benatru, I., Boraud, T., Brefel-Courbon, C., et al. (2024). Trial of Lixisenatide in Early Parkinson's Disease. N Engl J Med *390*, 1176-1185. 10.1056/NEJMoa2312323.
4. Athauda, D., Maclagan, K., Skene, S.S., Bajwa-Joseph, M., Letchford, D., Chowdhury, K., Hibbert, S., Budnik, N., Zampedri, L., Dickson, J., et al. (2017). Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet *390*, 1664-1675. 10.1016/S0140-6736(17)31585-4.
5. Verma, A., and Goyal, A. (2024). Beyond insulin: The Intriguing role of GLP-1 in Parkinson's disease. Eur J Pharmacol *982*, 176936. 10.1016/j.ejphar.2024.176936.
6. Holt, M.K., Richards, J.E., Cook, D.R., Brierley, D.I., Williams, D.L., Reimann, F., Gribble, F.M., and Trapp, S. (2019). Preproglucagon Neurons in the Nucleus of the Solitary Tract Are the Main Source of Brain GLP-1, Mediate Stress-Induced Hypophagia, and Limit Unusually Large Intakes of Food. Diabetes *68*, 21-33. 10.2337/db18-0729.
7. Molinari, M., Lieberman, O.J., Sulzer, D., Santini, E., and Borgkvist, A. (2024). 5-HT1B receptors mediate dopaminergic inhibition of vesicular fusion and GABA release from striatonigral synapses. bioRxiv. 10.1101/2024.03.14.584991.
8. Borgkvist, A., Avegno, E.M., Wong, M.Y., Kheirbek, M.A., Sonders, M.S., Hen, R., and Sulzer, D. (2015). Loss of Striatonigral GABAergic Presynaptic Inhibition Enables Motor Sensitization in Parkinsonian Mice. Neuron *87*, 976-988. 10.1016/j.neuron.2015.08.022.
9. Cho, N.H., Shaw, J.E., Karuranga, S., Huang, Y., da Rocha Fernandes, J.D., Ohlrogge, A.W., and Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract *138*, 271-281. 10.1016/j.diabres.2018.02.023.

CONTACT DETAILS

Anders Borgkvist, PhD
Department of Neuroscience
Karolinska Institutet
Solnavägen 9
17169 Solna

E-mail: anders.borgkvist@ki.se
Phone: +46-8-52487165
Web: http://www.borgkvistlab.se

Cesare Patrone, PhD
Department of Clinical Science and Education
Södersjukhuset (Stockholm South General Hospital)
Internal Medicine
118 83 Stockholm

E-mail: cesare.patrone@ki.se
Phone: +46-8-6165084
Web: https://ki.se/en/kisos/the-neurocardiometabol-group