SRP Diabetes Postdoctoral Fellowship Program 2025

Project title: Type 2 diabetes management by GLP-1R agonists: impact on neurological outcomes after stroke

Background

Type 2 diabetes (T2D) worsens stroke outcome and is a strong predictor of post-stroke disability (1-3). With the rising global T2D prevalence and the associated high risk of stroke, there is a significant unmet clinical need for effective post-stroke rehabilitative therapies (4, 5).

Despite showing a reduced stroke risk (6, 7), T2D people treated with glucagon-like peptide 1 receptor agonists (GLP-1RA) still experience high stroke incidence (8). Since GLP-1RA have been shown to improve stroke outcome in animal studies (9), it is important to find out if the same is true for T2D people who experience stroke while treated with GLP-1RA. If so, GLP-1RA should be recommended to all T2D people at high risk of stroke and stroke-related disability to improve their rehabilitation.

Potential mechanisms through which GLP-1RA improve stroke outcome, could be driven by the strong weight loss effects of these drugs (10). In fact, we showed that diet-induced weight loss before stroke increases the tolerance to stroke injury improving functional outcome in a T2D model (11) and suggesting that GLP-1RA will likely induce the same effect. Additionally, GLP-1RA also exert beneficial vascular and anti-inflammatory effects in the brain which could boost weight loss effects on stroke outcome. However, all this remains to be proven.

Objectives

In nationwide observational study we will determine whether GLP-1RA treatment associates with favorable neurological outcome after stroke.

Using experimental models of T2D and stroke, we will also: a) Determine whether improved stroke outcome by GLP-1RA treatment is secondary to weight loss or additional "non metabolic" mechanisms are involved, b) Identify important cellular pathways that drive neurological recovery after GLP-1RA treatment by using proteomics analysis.

Methodology and Work plan

Nationwide observational study

We will cross the National Diabetes Register (NDR), the Swedish Stroke Register (SSR), the National Cause of Death Register (NCDR), the National Prescribed Drug Register (NPDR) and the National Patient Register (NPR) to identify T2D subjects who received GLP-1RA treatment for at least 6 months before stroke. T2D subjects who did not receive GLP-1RA treatment and suffered stroke will be used as controls (Figure 1A). Stroke outcomes will be evaluated at admission and at 3-month follow-up by the gold-standard methods in stroke research: the National Institute of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (MRS) (Fig. 1A).

Feasibility: Between 2014-2023 about 450 000 people were living with diabetes in Sweden (www.ndr.nu) with around 160 000 receiving GLP-1RA treatment during this period (www.socialstyrelsen/statistik-och-data/klassifikationer-och-koder/icd-10). Additional, about 200 000 people suffered a stroke. Based on an estimated 20% prevalence of diabetes among stroke patients we calculate that approximately 42 000 T2D subjects experienced a stroke, of whom an estimated 3 500 were treated with GLP-1RAs. This sample size is expected to provide sufficient statistical power to address the study's research question.

Experimental trial

C57Bl/6 mice are fed with high fat diet (HFD) for 6 months to induce T2D features (≈ 50% weight gain, insulin resistance and hyperglycemia) (12). To induce weight loss, the GLP-1RA Semaglutide (3nM/Kg s.c.) is given for 4 weeks. Then, stroke is induced by *transient middle cerebral artery occlusion (tMCAO)* (13). To determine if the positive effects of GLP-1RA are driven by weight loss or other non-metabolic pathways are involved, we will include additional control group weight-matched to Semaglutide-treated group by caloric restriction (Fig. 1 B).

Stroke outcome is assessed by quantifying *functional recovery,* weekly, for 8 weeks by using the clinically-relevant *Grip Strength Test* (14, 15). We also assess *stroke severity* by immunohistochemistry (IHC) and stereological methods based on NeuN (neuronal marker). We will also analyze brain tissue using proteomics (available at KI core facilities) to identify important pathways involved in determination of neurological stroke outcome.

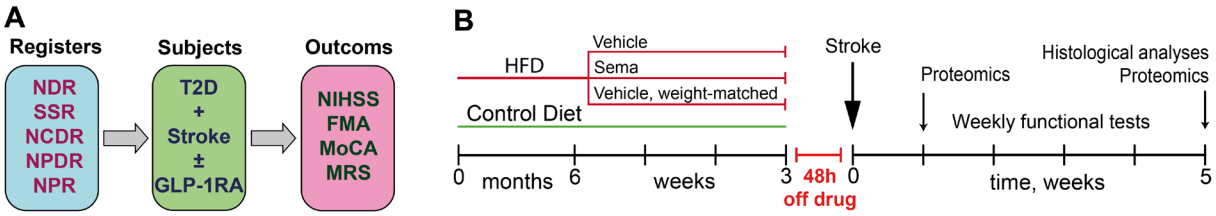

Figure 1. Project protocols. A) National registers, subject selection and outcomes for nationwide observational study. B) Study outline for experimental trial.

The role of the postdoc fellow: The project will achieve its objectives in 2 years. The ethical permit to perform the studies has been obtained (Dnr. 19666-2022 and Dnr. 2024-08569-01). An ideal candidate would be a clinician with good knowledge of medical statistics but also experience in animal research. I will supervise the postdoc work in the observational studies where the candidate will perform statistical analyses. The Candidate will also perform the majority of experimental stroke studies under the supervision of co-PI Dr. Vladimer Darsalia who is an expert in preclinical stroke & diabetes. Specifically for this project we are collaborating with Dr. Michael Mazya, the head of the Stroke Service at the Karolinska University Hospital who is an experienced clinical stroke researcher and will provide additional guidance to the candidate.

Relevance of project for diabetes

Stroke and stroke-related disability are severely overrepresented in diabetes. Since the number of T2D people will reach 700 million by 2045 (16), the medical need for effective treatments to prevent stroke-related disabilities is thus very urgent. Although GLP-1RA treatments have shown strong efficacy to reduce stroke risk, it is unknown whether the same applies to stroke-related disabilities and this project will address this question. This work is original since no previous study has addressed the potential of GLP-1RA before stroke to improve stroke outcome in people with T2D and to pinpoint the metabolic and non-metabolic mechanisms involved. Importantly, positive results of this project will be novel to extend the recommendations for the use of GLP-1RA in all T2D people at high stroke risk but also possibly to other groups of people at high risk of stroke with metabolic impairment i.e. people with pre-diabetes/obesity (17).

References

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