IHS Fellowship report

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The search for disease mechanisms and new drug targets in idiopathic intracranial hypertension (IIH)

Fellowship from October 2019 to September 2021
Danish Headache Center, Glostrup, Denmark
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Overview

The initial plan was to address the three aims of the fellowship: 1) Assess whether diet induced obesity modulated intracranial pressure (ICP); 2) Assess whether raised ICP can modulate headache-like behaviour; and 3) Assess whether pharmacological agents assumed to modulate ICP actually modulate ICP.

In aim 1, we aimed to assess the effects of diet induced obesity induced by a high fat diet and a 'cafeteria diet' as well as determine whether there were sex differences in the effect of obesity on intracranial pressure and assess potential molecular changes at tissues of interest. In aim 2, we were to use the rats generated in aim 1 and assess the effect of obesity in the context of raised pressure on cephalic cutaneous allodynia and assess molecular outcomes. In aim 3, we were to assess the effect of acetazolamide, topiramate and somatostatin analogues on ICP reduction at clinically relevant doses and then treat the phenotypes observed in aims 1 and 2.

Summary of research

My initial research activities focused on learning the techniques to allow me to complete the aims of the fellowship – telemeter implantation surgery for the ICP recording and von frey

testing for allodynia. I established the standard procedure for ICP analysis within my group. This initial period led to two publications, a method paper for our ICP measuring method in Fluids and barriers of the CNS (https://doi.org/10.1186/s12987-020-00199-z), and a review focused on the regulation of ICP pressure, also in Fluids and Barriers of the CNS (https://doi.org/10.1186/s12987-019-0155-4).

Assessing the first two aims of the fellowship, we assessed the effects of diet-induced obesity on intracranial pressure, cephalic sensitivity, and also ocular outcome. Here we demonstrated that obesity in female rats increases ICP and causes cephalic sensitivity and retinal swelling. Moreover, we demonstrated that trigeminal ganglia from obese rats had increased expression of CGRP and transient receptor potential cation channel subfamily V member 1 (TRPV1), corroborating our behavioural studies.

Finally, we assessed the effect of acetazolamide and topiramate on ICP in lean female rats. Here we focused on assessing both the chronic effects and the acute effects of these drugs. Additionally, we assessed the molecular consequences of these drugs on their proposed site of action, the choroid plexus. Here we demonstrate that these drugs lower ICP independently of weight loss. This was combined with alterations in gene expression at the choroid plexus with topiramate but not acetazolamide.

In the following 9 months, my experimental work focused on investigating the role obesity has on ICP, headache behaviour and ocular outcome. Over the course of three experimental rounds, each lasting 20 weeks, the obese female rats had raised ICP and cephalic cutaneous allodynia. Following completion of the rodent experiment I carried out molecular analysis on the trigeminal ganglion. During this period, we collaborated internally and a student within our institute assessed the ocular outcome in the rodents. This collaboration strengthened our research, allowing us to demonstrate that diet induced obesity recapitulates multiple facets of IIH. This work was published in *Scientific Reports* (https://doi.org/10.1038/s41598-022-13181-6). This work coincided with the start of the COVID-19 pandemic.

During the time of the pandemic, I conceived the idea for and wrote a review focusing on the link between obesity and headache. This was published in the *Journal of Headache and Pain*: https://doi.org/10.1186/s10194-021-01337-0.

The final year of the fellowship focused on investigating the effects of acetazolamide and topiramate on intracranial pressure. I spent my time doing ICP surgeries and assessing the

effects of these drugs. During this period, I supervised two masters students from The Pharma Institute, Copenhagen University. These students assessed the role of these drugs at the choroid plexus, the organ that secretes cerebrospinal fluid (CSF), thus allowing a determination of whether these drugs act at this organ. Also during this period I fostered a collaboration with a group at the University of Copenhagen where they carried out CSF secretion assays for us to complement our ICP data. This manuscript is ready to submit.

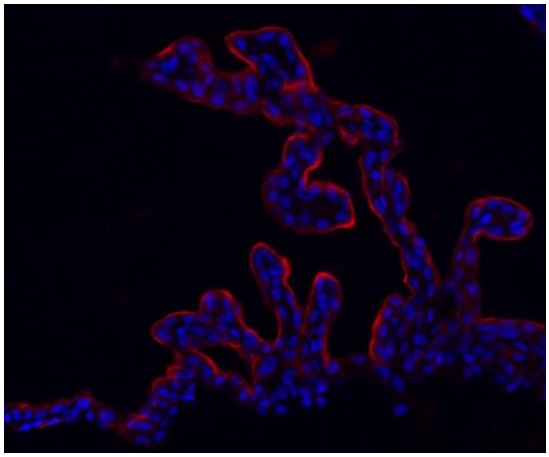
During the fellowship the work has been presented at various meetings: DHOS October 2021, Copenhagen: Invited talk 'Diet induced obesity causes cephalic cutaneous allodynia in the context of raised intracranial pressure'; IHC September 2021, online: IHS Fellowship lecture 'The search for disease mechanisms and drug targets in IIH; Brain water symposium August 2021, Copenhagen: Invited talk 'Towards an animal model of IIH'.

Conclusion

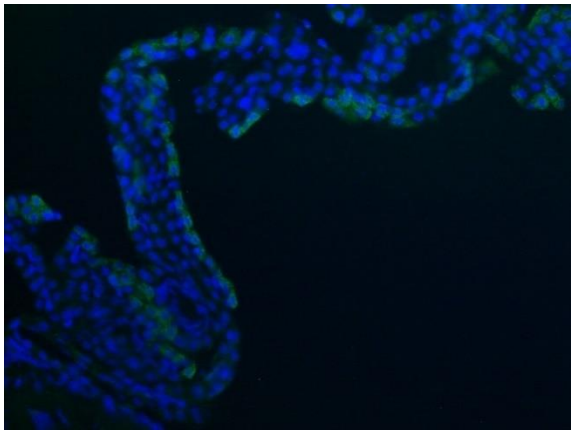
The COVID-19 pandemic necessitated re-evaluation of the aims so the primary aims could be achieved, whereas the more secondary aims were excluded. However, we have achieved a broad set of aims which are in keeping with the original aims. We demonstrated that obese female rats have increased ICP and this is accompanied by optic disk swelling and cephalic cutaneous allodynia, reaching our goals for aims 1 and 2. Additionally, for aim 3 we assessed the effect of the ICP modulating drugs in ICP in normal pressure female rats, showing a reduction in ICP. Despite the pandemic limiting our research, I am incredibly pleased with the work that I have produced.

The fellowship will affect my future career in a multitude of ways. From 1 October 2022 I am starting a post-doctoral fellowship at the Danish Headache Centre which was awarded by the Lundbeck Foundation, allowing me to investigate in detail the interplay between headache and ICP. This would not have been possible if not for the training and skills that I gained because of the fellowship. Moreover, the fellowship has allowed me to network within multiple fields, allowing the formation of productive collaborations. Finally, the fellowship, in combination with the pandemic, has allowed me to gain my first real experience of student supervision.

I would recommend taking the opportunity to take up mentoring/supervision positions while undertaking the fellowship. For me this was the highlight as it has helped facilitate my transition from a pure bench researcher to a position of responsibility. Don't be afraid to foster collaborations, these will add substantially to your work.



Delicate apical staining of aquaporin-1 (red) at choroid plexus performed by myself.



Staining of a G-protein coupled receptor of interest in green at choroid plexus, note that not every cell expresses the protein of interest, performed by myself.

Danish Headache Centre colleagues