IHS Fellowship Report

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Investigating the role of the AMY1 receptor activation and sex hormones in CGRP release and expression in the trigeminovascular system

Fellowship from December 2023 to November 2024
King's College London, UK
Mentor: Jan Hoffmann / Philip Holland

Overview

We planned to investigate the effect of amylin (AMY) receptor activation on calcitonin gene-related peptide (CGRP) release and regulation in the trigeminovascular system, and investigate if sex hormones alter the expression of the CGRP and its receptors to facilitate this difference in nociception observed across the different phases of the oestrous cycle.

To achieve this, we would conduct ex vivo investigations of the trigeminovascular system, using techniques such as explant culture, ELISA, qRT-PCR, and immunohistochemistry. These techniques would be used to examine CGRP release from trigeminovascular system components (dura mater, trigeminal ganglia, and trigeminal nucleus caudalis) in response to acute AMY receptor activation and measure changes in the expression of the CGRP system (calcitonin receptor, calcitonin receptor-like receptor, receptor activity-modifying proteins, CGRP, and amylin) and sex hormone receptors during the oestrous cycle.

Summary of research

This study investigated CGRP release from trigeminal ganglia (TG) and the spinal trigeminal nucleus (STN) of Sprague Dawley rats using ELISA and immunohistochemistry. CGRP release was significantly higher in female TG after KCl stimulation, especially during oestrus and early dioestrus when oestrogen and progesterone levels are declining. Although CGRP release were modestly higher in male STN samples, the difference was not statistically significant. When TG were preincubated with salmon calcitonin (sCT), a calcitonin and amylin receptor agonist, before KCl stimulation, CGRP release increased significantly in both sexes. This effect was reduced when co-treated with sCT(8-32), an antagonist, suggesting possible receptormediated action. Female TG treated with sCT released significantly more CGRP (pg/ml) than male TG, although this difference was not significant after normalisation to basal levels. CGRP release was also significantly higher in sCT-treated TG from females in oestrus/early dioestrous compared to other stages. Gene expression analysis using qPCR showed significantly higher levels of Calcb in female TG, with a non-significant trend toward higher expression in female STN. Other components of the calcitonin receptor family showed no significant

sex or cyclestage differences. Overall, these findings highlight a sex-specific and cycle-dependent regulation of CGRP release and expression.

Conclusion

This fellowship has been instrumental in advancing my career trajectory. It enabled me to generate robust pilot datasets that have laid the groundwork for several intermediate fellowship applications, including the Wellcome Early-Career Award and the King's Prize Fellowship, for which I was shortlisted and interviewed. Being part of the Headache Group at King's College London significantly expanded my professional network, fostering ongoing collaborations with both clinicians and basic scientists across the UK and the US. Additionally, through engagement with KCL and the Migraine Trust, I had the valuable opportunity to interact directly with migraine patients during patient engagement events. Being based in the UK also allowed me to attend multiple international conferences and training academies (EHF-SAS, iHEAD, EHF 2023 & 2024, MTIS), which deepened my understanding of migraine and inspired future research directions.

Several significant challenges arose during the fellowship period. Obtaining the Home Office Licence required to work with animals took over three months, which considerably shortened the time available to carry out the planned research. Additionally, as the fellowship was administered through King's College London, my position was funded at 0.8 FTE, requiring me to supplement my income through teaching. While this teaching experience was both enjoyable and beneficial to my professional development, it inevitably reduced the time I could dedicate to laboratory work. Lastly, my original sponsor and host, Dr. Jan Hoffmann, transitioned to a role in industry in early 2024, leading to some administrative changes and temporary disruptions in access to certain equipment and resources.

I strongly recommend undertaking research in a different country and environment. Immersing yourself in a new setting provides invaluable exposure to diverse techniques and equipment that may not have been accessible previously, broadening your perspective on experimental approaches and inspiring more innovative, cuttingedge research. Working within new teams and with individuals from varied backgrounds and thought processes significantly enhances your ability to collaborate effectively and adapt within the research community. Being physically present in a different research environment and attending events and conferences that would otherwise be out of reach creates endless opportunities for meaningful collaborations and the development of high-impact, translational research.