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TITLE: Restless Legs Syndrome and the Melanocortin System

PRINCIPAL INVESTIGATOR: Brian Koo, MD

CONTRACTING ORGANIZATION: Yale University, New Haven, CT

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14. ABSTRACT The objective of this proposal is to study the underlying biological mechanisms of restless legs syndrome (RLS) . We propose to study the hormonal melanocortin (MC) system in humans with RLS, based upon similarities between the MC hormones and features of RLS. Central to RLS are an urge to move associated with sensory discomfort and increased movement to alleviate symptoms. The MC hormones are well known to mediate increased locomotion and pain sensitivity in rats and cause motor restlessness when administered in humans. In this proposal, we will evaluate MC biology in humans by measuring MC hormone levels in blood and CSF of persons with RLS compared to persons without RLS. We hypothesize that MC hormone levels will be higher in persons with RLS and will correlate to the severity of RLS.					
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1. Introduction

The biological mechanisms underlying restless legs syndrome (RLS) are largely unknown. The melanocortin (MC) hormones are a family of hormones produced in the brain which modulate numerous essential life functions such as metabolism, sleep, eating, movement, and mood. Many properties of these hormones bear resemblance to core features of RLS, such that the hormones given to rodents produce excessive movement and a state of hyperalgesia, similar to the central sensorimotor hallmark of RLS. Furthermore, the hormones are released in a diurnal pattern and have negative effects on mood, similar to the nighttime character of RLS and that RLS is tightly tied with depression. Also, the main MC agonist, alpha-melanocyte stimulating hormone, administered intravenously in humans causes an intense feeling of motor restlessness. Based upon these lines of evidence, our central hypothesis is that the MC hormone levels are higher in the serum and cerebrospinal fluid of persons with RLS than non-RLS controls. The purpose of this research project is to measure levels of MC hormones in the blood and CSF of persons with RLS and controls without RLS and in the RLS cohort, to determine if MC hormone levels correlate to the severity of RLS.

2. Keywords

Restless legs syndrome, RLS; hormones, melanocortin, sleep, cerebrospinal fluid

3. Accomplishments

Our goal was to enroll 40 persons with RLS and 40 controls by the end of the study. Last year's report (12/1/2021), we had enrolled 26 persons with RLS and 24 controls. Currently we have met this goal and enrolled 45 controls and 42 RLS subjects. We have been approved to increase the number of total subjects to 120 as we were powered to detect a difference in hormone level based upon number of CSF samples. Of the 45 controls, we have 38 controls with CSF as in 7 we were not able to perform the LP successfully. Of the 42 RLS patients, we have CSF in 37 as in 5 persons we were not able to successfully perform the LP.

We have measured levels of alpha-MSH, beta-endorphin, ACTH, POMC in the blood and CSF of approximately two-thirds of these samples. We will complete measurement of hormones early in 2023. We will also work to recruit about 5 more RLS subjects and 5 more controls.

4. Impact

This research is critical as the biological mechanisms underlying RLS are not known. Our poor knowledge of RLS pathobiology is reflected in the problems which have arisen due the widespread use of dopamine medications to treat RLS. RLS is exquisitely responsive to dopamine medications initially, but over time, usually years, and as doses escalate, the dopamine medicines commonly cause a paradoxical worsening of RLS, termed augmentation. Given the initial exquisite response of RLS to dopamine agonist medication, it was thought early on that dopamine was deficient in RLS, but more recent evidence has shown that dopamine is actually in excess in those with RLS. The MC hormone system has not been studied to any degree in humans with RLS. If found to be involved in the pathophysiology of RLS, the MC system would represent a novel target for more precisely directed and hopefully effective treatments for RLS.

5. Changes/Problems

As noted above, we increased the number of subjects from a total of 80 to a total of 120. The purpose for this was to make up for persons in whom we were unable to successfully perform the lumbar puncture. We were powered to detect a difference in hormone levels in CSF.

On 10/31/2022, the Yale IRB made a determination of Serious Non-Compliance associated with the study based upon the results of an audit conducted by the Human Research Protection Program. The audit cited consent documentation issues, a lack of appropriate study documentation, and potential privacy violations that do not align with applicable regulatory requirements, Yale HRPP policies, Good Clinical Practice and Yale Institutional requirements and guidelines. A Corrective and Preventative Action (CAPA) Plan has been issued and we are currently working through to address these issues so that we can resume work on this study. We expect that the study will resume in January or February of 2023.

6. Products

Nothing to report

7. Participants & Other Collaborating Organizations

Brian Koo: PI

Dr. Koo is a co-investigator on the VA grant I01 HX002324-01A2 (PI Sico), Addressing Sleep Apnea Post-Stroke for 1.2 calendar months per year (10/1/2020 – 9/30/2025).

Dr. Koo is a collaborator on a Michael J Fox grant (PI Hafler), Tracing Origin of Parkinson's Disease through Neuro-Immune Interactome, for 1.2 calendar months per year (10/1/2020 – 9/30/2023).

8. Special Reporting Requirements

Nothing to report

9. Appendices

Nothing to report