

Reasoning of dissertation topic and competency of potential supervisor for admission onto joint LSU and TU doctoral studies in 2022

Area of research (title and code)	Biology
Field of research (title and code)	Exercise physiology
Topic of research	Effects of physiological stress on kynurenine pathway activity
Institution	Karolinska Institutet, Dept of Physiology & Pharmacology, Stockholm, Sweden; Lithuanian Sports University, Institute of Sports Science & Innovations, Kaunas, Lithuania

Potential supervisor

Pedagogical and scientific degree	Name, surname	Academic position
Professor, PhD	Sophie Erhardt	Professor

Short reasoning of proposed dissertation topic

Title
Physiological stress-induced kynurenine pathway regulation: Implications for neuropsychiatric and degenerative illnesses
<p>Short research description (including aims and objectives) (maximum 1500 characters).</p> <p>The kynurenine pathway (KP), which is triggered in response to stress and infection, has been linked to neurodegenerative and mental illnesses. Specifically, inflammation-related depression is hypothesized to be characterized by a decrease in kynurenic acid (KYNA) relative to quinolinic acid (QUIN), an imbalance that may have ramifications for brain structure and function. Moreover, stress-induced activation of tryptophan 2, 3-dioxygenase (TDO), a rate limiting KP enzyme is suggested as a pathophysiological mechanism underlying cognitive dysfunctions. As a complement to pharmacological treatment with antidepressants, physical exercise is increasingly used. Moreover, physiological stress, both as a single session of whole-body hyperthermia (WBH) as well as as repeated thermal therapy, have been suggested to be useful as an alternative treatments. We hypothesize that WBH influences the activity of the KP and our first aim is to investigate whether a single session and/or repeated sessions of WBH influences the concentration of KYNA and QUIN. The second aim will be to investigate the molecular mechanisms underlying these changes. Thus, expression of KP enzymes in blood derived cells will be analyzed. Finally, we aim to investigate if physiological stress induces cognitive dysfunctions and if so responsible molecular mechanisms. In this regard, three variants of the <i>tdo</i> gene have been identified and we aim to identify which one is affected by physiological stress.</p>
<p>Relevance of the problem, its novelty at national and international level (maximum 1500 characters).</p> <p>When the KP is activated, neuroactive metabolites are produced, some of those having the ability to interfere with normal cellular function, resulting in disrupted neuronal transmission and the onset of symptoms of various brain illnesses. We have previously identified the KP as a putative pathogenic link between the immune system, aberrant brain neurotransmission and psychiatric symptoms, including cognitive dysfunctions (see Sellgren et al. Mol Psych. 2016;21(10):1342-50 and Sellgren et al. Mol Psych. 2021;26(11):6820-6832). As a complement to pharmacological treatment of psychiatric disorders, physical exercise is increasingly used and WBH has been suggested to have antidepressant effects. We have suggested that induction of KAT enzymes in the periphery, facilitating the conversion of kynurenine to KYNA in the muscles hereby limiting the delivery of the precursor kynurenine to the brain, as a plausible mechanism. However, no studies hitherto have investigated how physiological stress impacts the kynurenine pathway and how it relates to cognitive functions. It is of highest importance to understand how these factors interact</p>

with each other. To further understand the molecular underpinnings of physiological stress and how it may alleviate depression is of uttermost importance.

Research methods and possibilities for conducting these studies (maximum 1500 characters).

Gas analyser (Cortex or Omnicol) for metabolic activity; Isokinetic dynamometer for muscle torque measurement (Biodex); Thermometer for skin, rectal and muscle measurement (Ellab); Heart rate monitor (Polar); Electrical stimulator (Digitimer); Sleep and activity monitor MotionWatch 8; Equipment (-80 or -20 fridge (Thermofisher); Centrifuge) needed for blood and saliva sampling and storing; Plate reader for blood and saliva analysis (Tecan); Body composition (Tanita); Cognition testing (ANAM4 battery); Electroencephalography (Brain Products, Gilching, Germany). At KI we have all methods needed for the project up and running, i.e. LC/MS for the analysis of KP metabolites, qPCR and WB for investigating the expression of KP enzymes as well as methods for performing enzyme activity tests. All needed equipment and facilities for a successful PhD project is available at LSU and KI institutions.

Please indicate the links between the proposed topic for the doctoral thesis and biomechanics / physical therapy / sports study programs. This work is aiming to deal with different physical and/or thermal interventions and its effects on kynurenine pathway activity. A perspective of the current project is to treat and/prevent people who is suffering from depression or relevant disorders. Thus, taken together, the most relevant link is physical therapy.

Is the proposed topic for the doctoral thesis related to currently funded research projects? Please indicate the links between the proposed topic for the doctoral thesis and funded research projects

Current funding in the lab at KI is used for investigating the kynurenine pathway in patients with psychiatric disorders. It is also used for a drug discovery and development program, aiming at blocking one of the enzymes in the pathway. Understanding how environmental factors (i.e. thermal intervention and different physical interventions including for example high intensity training and sleep deprivation etc.) affect kynurenine metabolism in healthy subjects, and what sort of intervention shows the highest efficacy in inducing, or reducing, kynurenine pathway activity is of ultimate importance. It also desirable to increase our knowledge regarding environmental factors that should be avoided in sensitive individuals. These grants will be used for funding the analysis of KP metabolites and enzyme expression or activity analysis performed in the KI lab by the PhD candidate.

Main grants to be used:

A translational study aiming at finding psychosis patients suitable for treatment targeting the immune system; Stockholm City Council; 2.400.000 SEK; 2020-2022 (renewal submitted 2022).

Integrated understanding of the pathophysiology in severe psychiatric disorders – a translational approach with focus on immune activation. Swedish Research Council; 3.600.000 SEK; 2022-2024

Generation of enzyme inhibitors for the treatment of schizophrenia and related disorders; Swedish Brainfoundation; 5.400.000 SEK; Project Grant; 2013-2022 (Renewal submitted March 2022).

Is the proposed topic for the doctoral thesis related to joint research with a foreign institution? Please indicate the links between the proposed topic for the doctoral thesis and research with a foreign institution. The proposed doctoral project will bring together at least two major institutions Lithuanian Sports University (LSU) and Karolinska Institute (KI). At LSU, physiologically stressful interventions will be performed, and samples will be collected for kynurenine marker analysis which will be analysed at KI. We will closely cooperate with Lilly Schwieler (senior researcher; PhD) at Dept of Physiology & Pharmacology which has a long-lasting word leading experience on investigating kynurenine pathway in response to different physiological and psychological output/interventions.

Currently I am supervisor of 3 doctoral students.

Supervisor


(signature)

Sophie Erhardt

(Name, surname)

Date

May 2, 2022