

Sex differences in behavior and metabolism

Ivana Maric

Department of Metabolic Physiology, Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg, Sweden

ABSTRACT

Men and women exhibit distinct illness patterns and disparate responses to pharmacotherapies. However, there is a scarcity of preclinical studies that systematically compare the sexes. The overarching aim of this thesis was to identify sex differences, and their underlying mechanisms, in metabolic and behavioral control within rodent models of obesity and anxiety. Specifically, we explored novel brain targets and mechanisms for the control of appetite, energy expenditure, and emotionality. In **Paper I**, we found that mice and rats subjected to diet-induced obesity responded with sexually divergent eating behavior and adaptations in energy expenditure. In **Paper II**, we showed that obesity reduced the expression of interleukin-6 (IL-6) in the brain of males only, and that the role of IL-6 in the parabrachial nucleus (PBN) is sexually dimorphic, such that it is only necessary for normal brown adipose tissue thermogenesis in males. In **Paper III**, we discovered that the locus coeruleus (LC) is a novel site for the behavioral effects of the hunger hormone ghrelin. We demonstrated that males have higher ghrelin receptor levels in the LC, and that there is a sex difference in response to ghrelin receptor activation and blockade, in regards to food motivation and anxiety-like behavior. Finally, in **Paper IV**, we investigated whether brain-produced estrogen plays a role in body weight regulation. We found a sexually dimorphic role of aromatase in the amygdala, such that it is only necessary for normal energy homeostasis and food motivation in females. Collectively, the work presented in this thesis underscores the significance of considering biological sex in the context of energy balance regulation and associated behaviors. These findings contribute to a broader conversation on addressing sex differences in human disease, with the ultimate goal of enhancing the success of drug development.

Keywords: sex differences, eating, brown adipose tissue, motivation, anxiety-like behavior

ISBN 978-91-8069-509-1 (PRINT)

ISBN 978-91-8069-510-7 (PDF)

Sex differences in behavior and metabolism

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs Universitet kommer att offentligt försvaras i **Hörsal M106 Karl Isaksson**, Medicinaregatan 16a, **torsdag den 7 december 2023, kl. 13:00**

av **Ivana Maric**

Opponent:

Dr. Morgane Thomsen, Associate Professor
Department of Neuroscience, University of Copenhagen, Denmark

Avhandlingen baseras på följande delarbeten

- I. **Sex and species differences in the development of diet-induced obesity and metabolic disturbances in rodents.**
Maric I, Krieger JP, van der Velden P, Borchers S, Asker M, Vujicic M, Wernstedt Asterholm I, Skibicka KP.
Frontiers in Nutrition, 2022; 9: 828522.
- II. **Parabrachial interleukin-6 reduces body weight and food intake and increases thermogenesis to regulate energy metabolism.**
Mishra D, Richard JE, Maric I, Porteiro B, Häring M, Kooijman S, Musovic S, Eerola K, López-Ferreras L, Peris E, Grycel K, Shevchouk OT, Micallef P, Olofsson CS, Wernstedt Asterholm I, Grill HJ, Nogueiras R, Skibicka KP.
Cell reports, 2019; 26(11): 3011-3026.e5.
- III. **From the stomach to locus coeruleus: new neural substrate for ghrelin's effects on ingestive, motivated and anxiety-like behaviors.**
Maric I, López-Ferreras L, Bhat Y, Asker M, Borchers S, Bellfy L, Byun S, Kwapis J, Skibicka KP.
Frontiers in Pharmacology, 2023; 14: 1286805.
- IV. **Sex-specific effects of amygdala aromatase in the control of energy balance and food reward.**
Maric I, Richard JE, Taing L, López-Ferreras L, Byun S, Bhat Y, Skibicka KP.
Manuscript