Abstrakt

Metabolisme beskriver summen af biokemiske reaktioner, der finder sted i en levende organisme, som giver energi til vitale processer; dette kan studeres på hel krops-, organspecifikt- eller cellulært niveau. Energitilgængelighed, som bestemmes af forskellen mellem energiindtag og energiforbrug under fysisk aktivitet, påvirkes af forskellige eksterne faktorer som f.eks. ophold i højden, fysisk aktivitet og kost. Systemiske energiunderskud har konsekvenser for reguleringen af organspecifik substratudnyttelse og funktion. ***Formålet med denne afhandling var at integrere hjerne-, skeletmuskulatur- og systemisk substratoxidation og relativ substratudnyttelse i sammenhæng med udvalgte miljømæssige og energi stressorer (ophold i højde, motion, kalorieunderskud).*** *Studie 1* behandlede et grundlæggende spørgsmål for integrativ cerebrovaskulær fysiologi: Hvordan påvirkes de cerebrale metaboliske hastigheder for ilt- og glukoseudnyttelse (henholdsvis $CMRO_2$ og CMR_{Glu}) af ændringer i arteriel PCO_2 ($PaCO_2$)? Resultaterne af denne undersøgelse viste, at cerebral oxidativ metabolisme ($CMRO_2$) ændres med ca. 1 % pr. mmHg ændring i $PaCO_2$. Disse ændringer kan tildels forklares af et øget kompenserende bidrag fra anaerobe metaboliske veje. *Studie 2* undersøgte forskningsspørgsmålet: Hvordan påvirker systemisk brændstofudnyttelse ved ophold i højden, hjernens inflammatoriske reaktion på fysisk aktivitet? Resultaterne af denne undersøgelse giver nye beviser for, at 6-8 dages akklimatisering ved 3.800 m ikke fremkalder immunundertrykkelse eller forværrer systemiske proinflammatoriske reaktioner i hvile eller med maksimal fysisk aktivitet. Endvidere påvirkede højdeinducerede ændringer i systemiske inflammatoriske reaktioner ikke direkte frigivelsen af proinflammatoriske cytokiner i hjernen efter maksimal fysisk aktivitet. *Studie 3A* viste, at 14-dages lav energitilgængelighed (LEA) - der effektivt involverer 50% daglig kaloriebegrænsning - hos udholdenhedstrænede kvinder, fremkalder immunologisk stress, systemisk inflammation og forringer træningspræstationen. *Studie 3B* afslørede endvidere, at 14-dages LEA hos de samme kvinder fremkalder en øget afhængighed af fedtoxidation til det samlede energiforbrug under submaksimal fysisk aktivitet, der var uafhængig af ændringer i hvilestofskifte, insulinfølsomhed og mitokondriel respirationskapacitet i skeletmuskulaturen. Denne afhandling fremmer vores forståelse af integrativ hjerne, skeletmuskulatur og systemisk substratoxidation og relativ substratudnyttelse i forbindelse med miljømæssig og energi stressorer.

Lay Summary

Metabolism describes the sum of biochemical reactions that take place within a living organism which provide energy for vital processes; this can be studied at the whole-body, organ specific, or cellular level. Energy availability, which is determined by the difference between energy intake and exercise energy expenditure, is affected by selected environmental and energetic stresses (e.g., high-altitude, exercise, diet/nutrition). Systemic energy deficits have implications for the regulation of organ-specific metabolism. ***This thesis provides novel insights for integrative brain, skeletal muscle, and systemic substrate oxidation and relative fuel utilization in the context of environmental and energetic stress (e.g., high-altitude, exercise, nutritional caloric deficits).*** Experiments included: metabolism in the brain in response to CO_2; the brain's inflammatory response to maximal exercise following 6-8 days of acclimatization at 3,800 m; and a diet intervention in females involving 14-days of effectively 50% caloric restriction while maintaining 8 hours of endurance training per week.

Preface

The University of British Columbia Clinical Research Ethics Board approved all experimental chapters in this thesis (CREB IDs: H16-01028, H18-01755, H15-00166, H21-00773, H22-01091).

Chapter 1.

Written by Hannah Caldwell with insightful and extensive feedback by Professor Philip Ainslie.

Chapter 2.

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Author contributions: HGC, JMJRC, and PNA drafted, edited, and revised the initial version of this review. JSM and ERS provided intellectual and expert feedback. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Author contributions: HGC, LG, and PNA drafted, edited, and revised the initial version of this review. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Chapter 3.

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Chapter 4.

Author contributions: Study design: HGC, TDG, JPL, MS, PNA. Data collection: HGC, TDG, CAH, JST, EJ, LMB, ARS, JAM, KF, DBM, PNA. Data analysis: HGC, TDG. Data interpretation: HGC, TDG, JPL, PNA. Drafted manuscript: HGC. Critically approved manuscript: HGC, TDG, CAH, JST, EJ, LMB, ARS, JAM, JPL, MS, KF, DBM, PNA. Approved final version: HGC, TDG, CAH, JST, EJ, LMB, ARS, JAM, JPL, MS, KF, DBM, PNA.

Chapter 5.

Author contributions: Study design: HGC, JSJ, JPL, PNA, YH, LG. Data collection: HGC, JSJ, LOL, JPA. Data analysis: HGC, JSJ. Data interpretation: HGC, JSJ, JPL, PNA, YH, LG. Drafted manuscript: HGC, JSJ. Critically approved manuscript: HGC, JSJ, LOL, JPA, JPL, PNA, YH, LG. Approved final version: HGC, JSJ, LOL, JPA, JPL, PNA, YH, LG.

Chapter 6.

Author contributions: Study design: HGC, JSJ, JPL, PNA, YH, LG. Data collection: HGC, JSJ, LOL, JPA. Data analysis: HGC, JSJ. Data interpretation: HGC, JSJ, JPL, PNA, YH, LG. Drafted manuscript: HGC, JSJ. Critically approved manuscript: HGC, JSJ, LOL, JPA, JPL, PNA, YH, LG. Approved final version: HGC, JSJ, LOL, JPA, JPL, PNA, YH, LG.

Chapter 7.

Written by Hannah Caldwell, and edited by Professor Philip Ainslie.

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