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Effects of PGC1a-induced exercise adaptations in muscle on plasticity and recovery mechanisms in the CNS

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 13:e juni 2019, klockan 13:00.

av Lars Karlsson

Fakultetsopponent:
Heikki Kainulainen, Professor of Exercise Physiology
University of Jyväskylä, Finland

Avhandlingen baseras på följande delarbeten

I. Karlsson L., González-Alvarado M.N., Larrosa-Flor M., Osman A., Börjesson M., Blomgren K., Kuhn H.G. "Constitutive PGC-1α overexpression in skeletal muscle does not improve morphological outcome in mouse models of brain irradiation or cortical stroke". Neuroscience. 2018 Aug 1;384:314-328.

II. Karlsson L, González-Alvarado M.N., Motalleb R., Blomgren K., Börjesson M., Kuhn H.G. "Constitutive PGC-1α overexpression in skeletal muscle does not protect from age-dependent decline in neurogenesis". *Submitted.*

III. Karlsson L., González-Alvarado M.N., Motalleb R., Blomgren K., Börjesson M., Kuhn H.G. "Constitutive PGC-1α overexpression in skeletal muscle does not contribute in exercise-induced neurogenesis". *Manuscript.*

IV. Karlsson L., Savvidi P., Onyeanwu C., Kumar Malipatlolla D., Vidal A., Motalleb R., Kuhn H.G. "Effects of exercise and muscle-specific PGC-1α overexpression on neural stem cell responses in vitro". *Manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Effects of PGC1a-induced exercise adaptations in muscle on plasticity and recovery mechanisms in the CNS

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Abstract

In this thesis, we sought to determine if muscle-derived exercise-induced signaling via PGC-1α muscle activation influences neuroplasticity under physiological or pathophysiological conditions. For this purpose, transgenic mice with muscle-specific overexpression of PGC-1α that display an endurance exercise muscle phenotype were evaluated in models of cranial irradiation and photothrombotic stroke, as well as in aging and in a voluntary running paradigm. We also measured the response on proliferation and differentiation of NSPCs from treatment with either serum from exercised and transgenic mice, or conditioned media from PGC-1α-transfected myocytes.

In **paper I**, muscular PGC-1α overexpression in mice did not ameliorate irradiation-induced reduction of neurogenesis and resulted in larger infarcts without any differences in inflammatory responses. In **paper II** and **paper III**, animals of both sexes displayed robust age-related reductions, and exercise-induced increases, in hippocampal neurogenesis. No differences were detected in these measurements between the genotypes. Further, transgenic animals had increased levels of myokines and reduced levels of pro-inflammatory cytokines. In **paper IV**, mouse sera from exercised or transgenic animals had no effect on proliferation of NSPCs, while conditioned medium from PGC-1α-overexpressing myocytes slightly increased proliferation.

We conclude that artificial chronic muscle activation through the PGC-1α pathway, despite potent systemic changes, does not translate into exercise-induced effects on hippocampal neurogenesis, and is not sufficient to mimic exercise-induced effects on recovery after cranial irradiation or stroke, or prevent age-related reduction in neurogenesis. Likewise, circulating factors in serum from exercised animals, or from animals with muscle-specific PGC-1α overexpression, are not sufficient to directly induce changes in proliferation or differentiation of NSPCs *in vitro*.

Despite evidence indicating that exercise-induced factors from muscle and other tissues are capable of influencing brain function, our results highlight the difficulty in mimicking sustained effects of exercise on the brain. The study of PGC-1α and related molecular pathways, in muscle and other tissue, contributes to our understanding of mechanisms behind exercise-related benefits on the brain.

Keywords: muscle, brain, exercise, transgenic, PGC-1α, FNDC5, irisin

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