Effect of eccentric exercise on muscle/brain crosstalk

Clémence Leger*[1], Marina Cefis[2,3], Julien Wirtz[4], Alexandre MÉloux[4], Stéphanie Lemaire[5], Philippe Garnier[3,4], and Anne Prigent-Tessier[4]

[1]Cognition, Action, et Plasticité Sensorimotrice [Dijon - U1093] – Université de Bourgogne, Institut National de la Santé et de la Recherche Médicale, UFR Sciences de Santé, Dijon – France

[2]Cognition, Action, et Plasticité Sensorimotrice [Dijon - U1093] – Université de Bourgogne, Institut National de la Santé et de la Recherche Médicale : U1093, Institut National de la Santé et de la Recherche Médicale – France

[3]Département Génie biologique (IUT de Dijon/Auxerre - Université Bourgogne Europe) – Institut Universitaire de Technologie - Dijon/Auxerre – France

[4]Cognition, Action, et Plasticité Sensorimotrice [Dijon - U1093] – Université de Bourgogne, Institut National de la Santé et de la Recherche Médicale : U1093, Institut National de la Santé et de la Recherche Médicale – France

[5]CHU Service de Biohimie Spécialisée, Dijon – Centre Hospitalier Universitaire de Dijon - Hôpital François Mitterrand – France

Résumé

Physical exercise (EX) is a widely recognized approach for enhancing both physical and mental well-being. Its positive impact on brain is largely attributed to increased levels of brain-derived neurotrophic factor (BDNF), a crucial neurotrophin that supports neuronal plasticity and cognitive function (Vaynman et al., 2003; Cefis et al., 2023). While the link between EX and elevated BDNF levels is well established, the molecular mechanisms driving this increase remain incompletely understood. One proposed pathway involves myokines, molecules released by skeletal muscles during contraction. Notably, irisin, a myokine derived from the cleavage of fibronectin type 3 domain containing 5 (FNDC5), has been shown to promote cerebral BDNF expression (Boström et al., 2012; Wrann et al., 2013). Our recent finding indicate that FNDC5/irisin is predominantly expressed in type II muscle fibers and is upregulated in response to horizontal treadmill running, showing a threshold-dependent increase relative to exercise intensity (Leger et al., 2024). However, the influence of the different muscle contraction types on irisin expression remains unexplored. Eccentric exercise (ECC), characterized by muscle lengthening under load, is often recommended for individuals with chronic illnesses due to its lower cardiovascular demand and neuromuscular benefits (Roig et al., 2008). While ECC has been linked to improvements in cognitive function (Lepley et al., 2018; Clos et al., 2021), the contribution of myokines to these neurocognitive effects remains poorly understood. Accordingly, the present study aimed to investigate the influence of ECC on FNDC5/Irisin expression in specific muscle groups, namely the quadriceps, gastrocnemius, and soleus, and to explore its potential role on hippocampal BDNF expression. Experiments were conducted on adult male Wistar rats subjected to a treadmill protocol (30 min/day, 7 days, 70% of MAS) involving either horizontal or -28∘ incline (eccentric) running. Muscular expression of FNDC5 and phosphorylated focal adhesion kinase at Tyr397

*Intervenant

(p-FAKTyr397) as well as hippocampal BDNF expressions, were assessed by Western blotting. Additionally, muscular FNDC5/Irisin localization and serum/hippocampal irisin levels were studied by immunofluorescence and ELISA, respectively.

The findings revealed that downhill treadmill running, unlike horizontal running, induced damage in type II muscle fibers and led to a reduction in irisin secretion in the blood. This was accompanied by decreased FNDC5/Irisin and p-FAKTyr397 expressions in the hippocampus. Moreover, the attenuated increase in hippocampal BDNF under these conditions underscores the importance of the irisin-dependent signaling in promoting BDNF upregulation in the hippocampus.

References

Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., Rasbach, K. A., Boström, E. A., Choi, J. H., Long, J. Z., Kajimura, S., Zingaretti, M. C., Vind, B. F., Tu, H., Cinti, S., Højlund, K., Gygi, S. P., & Spiegelman, B. M. (2012). A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, *481*(7382), 463–468.

Cefis, M., Chaney, R., Wirtz, J., Méloux, A., Quirié, A., Leger, C., Prigent-Tessier, A., & Garnier, P. (2023). Molecular mechanisms underlying physical exercise-induced brain BDNF overproduction. *Frontiers in Molecular Neuroscience*, *16*, 1275924.

Clos, P., Lepers, R., & Garnier, Y. M. (2021). Locomotor activities as a way of inducing neuroplasticity: Insights from conventional approaches and perspectives on eccentric exercises. *European Journal of Applied Physiology*, *121*(3), 697–706.

Leger, C., Quirié, A., Méloux, A., Fontanier, E., Chaney, R., Basset, C., Lemaire, S., Garnier, P., & Prigent-Tessier, A. (2024). Impact of Exercise Intensity on Cerebral BDNF Levels: Role of FNDC5/Irisin. *International Journal of Molecular Sciences*, *25*(2), 1213.

Lepley, L. K., Grooms, D. R., Burland, J. P., Davi, S. M., Mosher, J. L., Cormier, M. L., & Lepley, A. S. (2018). Eccentric cross-exercise after anterior cruciate ligament reconstruction: Novel case series to enhance neuroplasticity. *Physical Therapy in Sport*, *34*, 55–65.

Roig, M., Shadgan, B., & Reid, W. D. (2008). Eccentric Exercise in Patients with Chronic Health Conditions: A Systematic Review. *Physiotherapy Canada*, *60*(2), 146–160.

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2003). Interplay between brain-derived neurotrophic factor and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. *Neuroscience*, *122*(3), 647–657.

Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M. E., & Spiegelman, B. M. (2013). Exercise Induces Hippocampal BDNF through a PGC-1α/FNDC5 Pathway. *Cell Metabolism*, *18*(5), 649–659.