Muscle-to-Brain communication in the context of obesity: impact of physical exercise?

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Mens sana in corpore sano"
Exercise training (Endurance) affects obesity through various mechanisms:

1. **Effect of different ET modalities?**

   - Irisin activates PGC1α, which increases P-CREB, NFATc, and MEF2.
   - AMPK increases CaMKIV, which enhances Calcineurine.
   - ATP/AMP decrease, and Ca^{2+}_{ic} increase.

2. **Effect of obesity?**

   - Glucose metabolism increases due to increased lipolysis.
   - Neuronal survival, differentiation, and plasticity improve.
   - Neuronal functions like BDNF are activated.

3. **Obesity?:**

   - Effect of obesity on different ET modalities is unclear.
In vivo model

<table>
<thead>
<tr>
<th>Diet</th>
<th>Week 0</th>
<th>Week 13</th>
<th>Week 20</th>
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<tbody>
<tr>
<td>Standard Diet</td>
<td>LFNV</td>
<td>LFTNV</td>
<td>HFTNV</td>
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<tr>
<td>Low-Fat Diet</td>
<td>LFV</td>
<td>LFV</td>
<td>LFV</td>
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<tr>
<td>High-Fat Diet</td>
<td>HFNV</td>
<td>HFV</td>
<td>HFV</td>
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</tbody>
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Training schedule:
- Week 0: Not-Voluntary (NV)
- Week 13: Voluntary (V)
- Week 20: Not-Voluntary (NV)

<table>
<thead>
<tr>
<th>Speed (cm/s)</th>
<th>Week</th>
<th>Speed (cm/s)</th>
<th>Week</th>
<th>Speed (cm/s)</th>
<th>Week</th>
<th>Speed (cm/s)</th>
<th>Week</th>
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<td>5</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>70% MRV</td>
<td>3</td>
<td>70% MRV</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>70% MRV</td>
<td>7</td>
<td>70% MRV</td>
<td>8</td>
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</table>

Time (min) | Week | Time (min) | Week | Time (min) | Week | Time (min) | Week |
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<td>5</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
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<td>MRV test</td>
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Voluntary (V) and Not-Voluntary (NV) setup images.
Exercise training stabilizes body weight and restores fasting glycaemia in High-Fat diet mice

Two Way ANOVA on RM
# p<0.001 HFV Vs HFTV ;
* p<0.001 T vs UT in HF groups

One Way ANOVA, *** : p < 0.001 ; ** : p = 0.002 ; * : p < 0.05
In muscle, the increase of FNDC5 protein level associated to voluntary exercise is inhibited by obesity.

Two Way ANOVA, * : $p < 0.05$
Exercise training increases Irisin plasmatic level

Three Way Anova, * p = 0.008 T Vs UT
In brain, FNDC5 protein level is not modified by exercise or HF diet
In Not-Voluntary trained mice, BDNF protein level is increased by exercise and HF diet in brain cortex but not in the hippocampus.

Three Way ANOVA, B. * : p < 0.05 and p < 0.05 T Vs UT in NV
Evaluation of spatial learning and memory

Morris Water Maze
The enrichment applied in Voluntary trained mice improves spatial learning and memorization.

Learning

- Escape Latency (s)

Day 1

Day 2

Day 3

One Way ANOVA on Repeated Measures, * p < 0.05

Memory

- Time in SE Quad. (s)

Three Way ANOVA, * p < 0.05
Conclusion and take home message

ET in mice increases Irisin plasmatic level.

**FNDC5** protein level in skeletal muscle depends on training modalities and is influenced by diet:
- only voluntary ET induces FNDC5 protein expression.
- this effect is impaired in obese mice.

**FNDC5** protein level in the brain cortex and hippocampus are not modified by ET or diet.

Enrichment, *per se*, improves spatial learning and memory.
This effect is not associated to BDNF expression changes in the hippocampus.
BDNF protein level in the cortex is influenced by ET and diet in Not-Voluntary groups.

→ Differential regulation of FNDC5 expression and cleavage into Irisin according to ET modalities and diet.
Acknowledgements

Collaborators

Dr A. Villers, Neurosciences lab., UMONS

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Prof. KZ Boudjeltaia, Experimental medicine lab., ULB