NO-cGMP PATHWAY ENHANCES THE HEART RATE RESPONSE TO PERIPHERAL VAGAL NERVE STIMULATION IN EXERCISE-TRAINED MICE

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RESULTS

Aerobic exercise training increases cardiac vagal tone and decreases resting heart rate. The mechanisms by which these effects are brought about are not fully understood. The nitric oxide – cyclic guanosine monophosphate (NO-cGMP) pathway is implicated in cholinergic regulation of heart rate and is a potential modifier of cardiac sensitivity to vagal stimulation.

AIMS of the study

(1) To investigate whether male mice that had been selectively bred for increased wheel-running had increased heart rate responses to peripheral vagal nerve stimulation or bath-applied carbamylcholine following a period of 20 weeks voluntary wheel-running.

(2) To assess the role of upstream and downstream NO-cGMP pathways in cholinergic modulation of HR following training.

METHODS

Animals & Training
Mice were selectively bred for wheel-running over 10 generations. Male mice, 8-12 weeks old were provided with wheels (+EX, n=8) and running distances were logged daily. Controls (–EX, n=8) were singly-housed in cages without wheels.

Physiology and Pharmacology
A double atrial/right vagal preparation was dissected free, placed into an organ bath containing mouse physiological saline saturated with carbogen (95% O2, 5% CO2) and connected to an isometric force transducer. Heart rate was triggered from the change in heart rate with vagal stimulation for 30s or bath-applied CCh (3x10^-7 - 3x10^-5 mol/L) was measured. Drugs were added to the organ bath after control protocols were completed.

Running Performance

Daily distance run on wheel

Ventricle/Body Weight Ratio

Pre-synaptic role

Table: There was no difference between the HR response to carbamylcholine (CCh) in –EX (n=8) and +EX (n=8)

HR Response (bpm) vs. conc. of CCh (mol/L)

<table>
<thead>
<tr>
<th>Conc. (mol/L)</th>
<th>–EX (n=8)</th>
<th>+EX (n=8)</th>
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<tbody>
<tr>
<td>3 x10^-8</td>
<td>24 ± 6</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>1 x10^-7</td>
<td>25 ± 8</td>
<td>73 ± 11</td>
</tr>
<tr>
<td>3 x10^-7</td>
<td>139 ± 27</td>
<td>145 ± 31</td>
</tr>
</tbody>
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Western Blot Analysis

Figure 4A:

Figure 4B:

Western blot analysis showed significantly increased expression of eNOS protein in atria taken from +EX animals. * p<0.01, unpaired t-test.

CONCLUSION

Evidence presented here suggests that exercise-trained mice have an increased peripheral vagal bradycardia, and that this may be due to upregulation of neuronal NOS resulting in NO facilitating ACh release.

References


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