Role of the nitric oxide pathway in the heart rate response to sympathetic nerve stimulation following exercise training

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British Heart Foundation

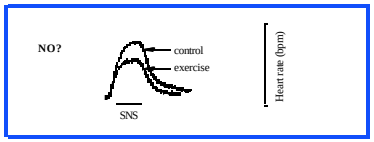
Supported by the British Heart Foundation

INTRODUCTION

Sustained aerobic exercise training reduces the sympathetic control of heart rate at sub-maximal work rates [1]. Similarly, nitric oxide (NO) donors attenuate the increase in heart rate with sub-maximal cardiac sympathetic nerve stimulation *in vitro* [2]. Exercise training has been reported to enhance NO-synthase (NOS) expression and endothelial NO production [3-4].

We have therefore investigated the hypothesis that an enhanced NO level associated with exercise training contributes to the attenuated heart rate response to sympathetic nerve stimulation (SNS) following training (see Fig. 1).

Figure 1. Schematic diagram showing that exercise training atenuates the increase in heart rate with sympathetic nerve stimulation (SNS) and indicating that NO could contribute to this effect.



METHODS

- Guinea-pigs were assigned to a sedentary (SED; n=20) or exercise (EX; n=20) group. EX animals swam 5 days/week for 6 weeks (60 min/day weeks 1-2, 75 min/day weeks 3-4, 90 min/day weeks 5-6).
- Atrial/right stellate ganglion preparations were dissected free [2] and the increase in heart rate with SNS (1-10Hz) was measured.
- The effects of NOS inhibition (N$_\omega$nitro-L-arginine; L-NA; 100µM), and its reversal with excess L-arginine (L-arg; 1mM), was investigated on the heart rate response to SNS (3 & 5Hz).
- Neuronal NOS protein expression in stellate ganglia from EX and SED animals was determined by Western blot analysis.

RESULTS

- **Efficacy of training**
  EX animals had significantly higher ventricular weight / body weight ratios and citrate synthase activity in the latissimus dorsi than SED animals [see FEPS poster 107 for details].
- **Effect of training on the sympathetic control of heart rate**
  The heart rate response to sympathetic nerve stimulation (1, 3, 5 & 7Hz) was significantly attenuated in EX animals (Fig. 2).
- **Role of NO in the heart rate response to SNS**
  NOS inhibition significantly caused a small but significant increase in the magnitude of the heart rate response to SNS in EX atria. This effect was reversed with L-arg. (Figs. 3 & 4).

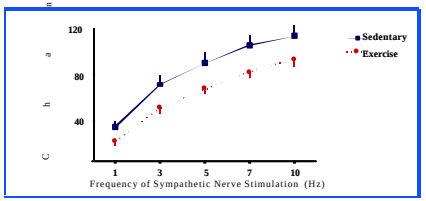


Figure 2. The increase in heart rate with sympathetic stimulation (1-10Hz, 10V, 30s) in atria from SED (n=16) and EX (n=16) animals. The positive chronotropic response to sympathetic stimulation was significantly attenuated in EX animals at 1,3,5 and 7Hz (* unpaired t test; P< 0.05).

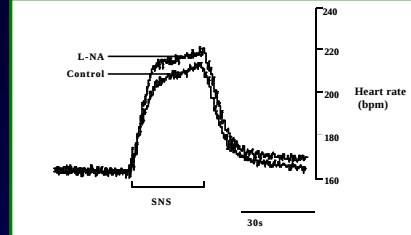


Figure 3. Superimposed raw data traces from an EX atria showing that NOS inhibition (L-NA; 100µM) enhanced the heart rate response to sympathetic nerve stimulation (SNS; 5Hz, 10V, 30s)

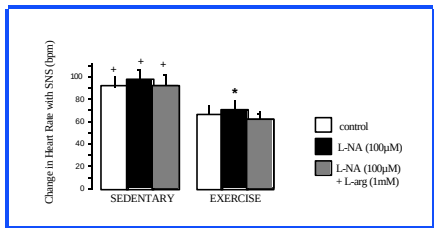


Fig 4. The effect L-NA and its reversal with L-arg on the increase in heart rate with sympathetic nerve stimulation (SNS; 5Hz, 10V, 30s) in sedentary (n=15) and exercised (n=13) atria.
P < 0.05: *ANOVA ; + SED vs. EX

·Neuronal NOS protein was present in stellate ganglia

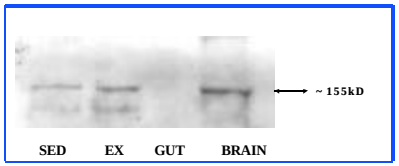


Fig. 5. Western blotting of neuronal NOS (nNOS) protein. Weak bands for neuronal NOS protein are seen at ~160 kD for stellate ganglia from SED (n=4, combined) and EX (n=4, combined) animals. No immunoreactivity for nNOS was found for gut samples (-ve control) and strong nNOS immunoreactivity is seen for brain tissue (+ve control).

SUMMARY

- Inhibition of NO synthesis enhanced the heart rate response to SNS in EX (but not SED) animals. This effect was reversed with L-arginine.
- Exercise training attenuated the positive chronotropic response to sympathetic nerve stimulation *in vitro*, even in the presence of NOS inhibition (L-NA) and reversal with excess L-arginine.

CONCLUSION

- NO seems unlikely to be the primary regulator of the attenuated heart rate response to SNS in EX animals because the heart rate response to sympathetic nerve stimulation was still significantly decreased in EX atria during NOS inhibition.

References

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