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The effect of acute exercise intensity on plasma interleukin-6 and activation of the hypothalamic-pituitary-adrenal axis

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Purpose

This project explores how acute cycling exercise intensity affects the release of Interleukin-6 (IL-6) from active muscle into the blood stream and the potential for circulating IL-6 to activate the hypothalamic-pituitary-adrenal (HPA) axis to release ACTH and cortisol. Understanding how active skeletal muscle communicates to peripheral organs is critical to determining how physical activity protects against debilitating inactivity-related diseases and neurological disorders.

Introduction

The search for 'the exercise factor' that mediates the health benefits of exercise has revealed interleukin-6 (IL-6) as a strong candidate. The IL-6 gene in muscle is silent at rest but rapidly transcribed during exercise, releasing IL-6 into the circulation in concentrations up to 100-fold. Muscle-derived IL-6 plays a role in regulating the availability of carbohydrates and fats for use as energy by the contracting muscle[1].

Recent studies have provided evidence to suggest that IL-6 is capable of activating the hypothalamic-pituitary-adrenal axis (HPA axis), which may function in the regulation of the metabolic state of the brain under stress (i.e. exercise) by releasing adrenocorticotropin (ACTH) and cortisol.

There is a remarkable gap in knowledge regarding the acute effects of exercise intensity on IL-6 concentration and the activation of the HPA axis by this circulating IL-6 in *healthy* human subjects.

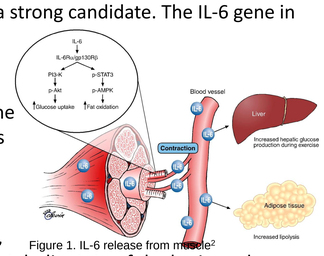
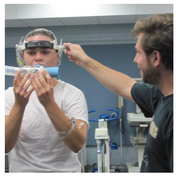
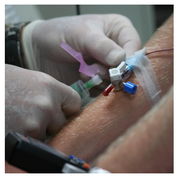
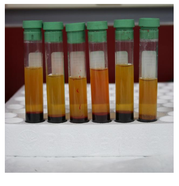


Figure 1. IL-6 release from muscle[2]

Method







• College-aged male and female subjects (Table 1) underwent three cycling tests:

Table 1.Subject Demographics*

	Age (years)	Height (in)	Weight (lbs)	VO_2 Max (ml/kg/min)
Females (n=5)	20.6+1.14	65.9+2.66	154.8+16.45	41.1+6.98
Males (n=5)	20.8+0.84	71.8+3.46	165.6+32.99	53.1+6.90
Total (n=10)	20.89+0.78	69.44+4.05	161.11+26.58	48.28+8.81

* All data are presented as Mean ± SD

1.VO_2 Max Test: to familiarize subject with equipment and measure maximal oxygen consumption as a quantitative level of fitness

2. High Intensity (HI) Test: four 30 s Wingate cycling tests[3], each separated by 4 min of recovery while cycling at 20 W for a total test duration of 14 min

3. Low Intensity (LI) Test: The total work performed during the HI test equally distributed over a continuous 14 min

•Blood collected from indwelling catheter in HI and LI tests:
- pre-exercise
- during exercise: 1.5, 6, and 10.5 min
- post-exercise: +1, +15, +30, +60 min, +48hr

•Hematocrit and hemoglobin were determined by routine microcapillary and cyanmethoglobin techniques, respectively, to estimate plasma volume (PV) shifts from pre-exercise. IL-6, ACTH and cortisol were measured by chemiluminescent immunoassay and concentrations were corrected for shifts in PV.

Results

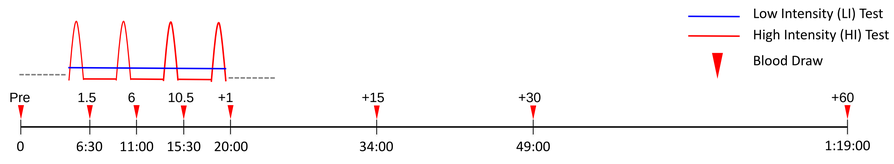


Figure 2. Method Summary. Points above axis represent pre, during and post exercise time points (in min). Points below axis represent blood draws on a continuous time scale (in hr:min:sec).

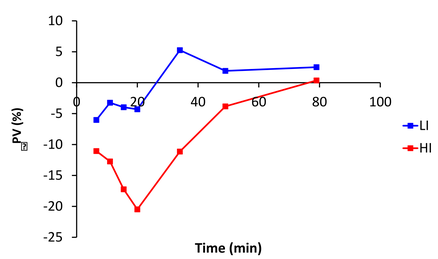


Figure 3. Blood plasma volume (PV) changes followed the same trend in both LI and HI tests (p=.212), but PV loss was greater during the HI test than the LI test (p=0.001) and greater during exercise than post-exercise (p=0.032). All plasma changes are from the pre-exercise plasma value.

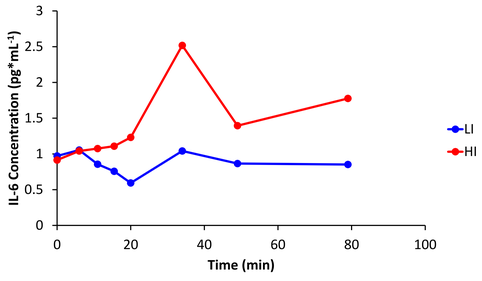


Figure 4. IL-6 response was greater during the HI test than the LI. The mean responses show nearly a three-fold increase from pre at the +15min HI point. IL-6 levels recovered by +48h after both HI and LI tests.

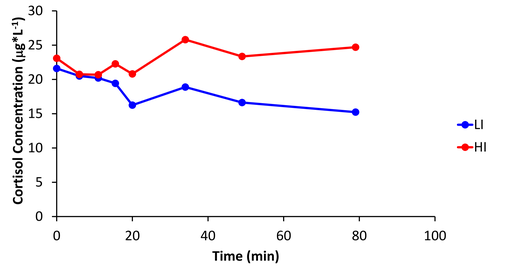


Figure 5. Mean cortisol concentration was higher during the HI test than LI and greatest at +15 min after the HI.

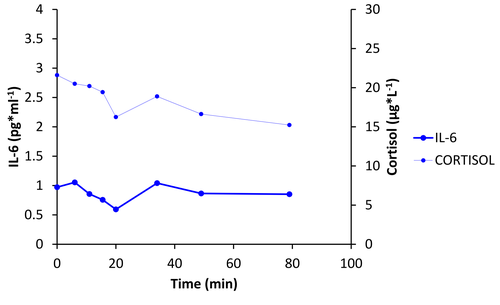


Figure 6. LI Mean IL-6 and cortisol responses follow the same pattern during and post-exercise with peaks at +15 min.

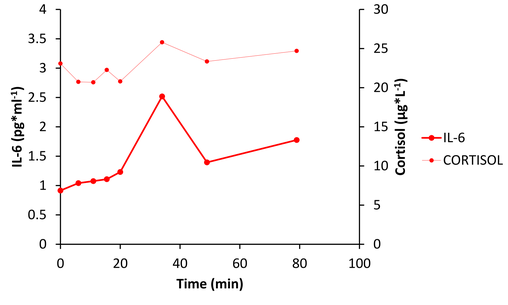


Figure 7. HI mean IL-6 and cortisol responses demonstrate a similar pattern with peaks at +15 min.

Conclusions

•Differences in PV shifts between LI and HI tests were significant (p=0.001) and may have accounted for the strength of the changes in IL-6 and cortisol concentration between the two tests

•After correcting for PV shifts, IL-6 response may be greater during high intensity exercise (p= 0.103)

• During the HI test, IL-6 values were nearly three-fold at the +15min time point, which may be due to one subject who appears to be an abnormally high responder

• Cortisol responses are similar during both low and high intensity exercise

• IL-6 and cortisol responses follow a similar pattern in both HI and LI tests

These results raise several questions regarding the IL-6 response:

• What is the stimuli for IL-6 transcription and/or release from skeletal muscle during exercise? How is it affected by the intensity or duration of exercise?

•How do other factors, such as metabolic state of active muscle, immune system activation, etc. affect the IL-6 response?

•How long does it take to transcribe the IL-6 gene, synthesize IL-6, and release it into circulation?

•Are IL-6 and cortisol each released from diverse tissues in response to the same exercise stimuli?

•How does the ACTH response fit in with the Il-6 and cortisol responses?

Future Directions

We are in the process of running the last few IL-6 and cortisol assays to complete our data set of n=10, and then we will run the ACTH assay for all subjects and time points to better understand how activation of the HPA axis is involved in the IL-6 response.

This Fall, we hope to gain a better understanding of the inter-individual genetic variation of the IL-6 response by identifying the presence of the -174G→C single nucleotide polymorphism, a region in the promoter of the IL-6 gene that is thought to functionally affect IL-6 transcription and release.

Next summer, the McCall lab will be looking at the IL-6 response during and after longer duration cycling bouts at varying intensities (ex. 1 hour at 80% max).

It is evident that there are still many questions to be answered regarding the IL-6 response during and after exercise in order to better understand how skeletal muscle communicates with endocrine, nervous, and immune systems to maintain homeostasis. The search for answers to these questions is important to furthering knowledge about the health beneficial effects of exercise and the protection against diseases associated with inflammation, insulin resistance, type 2 diabetes, and cancer.

Acknowledgments

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References

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