The Effects of Estrogen in the Glucoregulatory Response to Exercise in Type 1 Diabetes

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INTRODUCTION

Regular exercise has shown to benefit the health of individuals with type 1 diabetes mellitus (T1DM). However, a barrier to regular exercise for this population is the fear of low blood glucose (BG) levels, also known as hypoglycemia[1]. Hypoglycemia can result in short and long-term side-effects, such as recurring loss of consciousness or in severe cases death.

In non-diabetics, sex-related differences in fuel selection during exercise are well established. Women shift towards using fats as fuel whereas men rely mostly on sugars (i.e., carbohydrates) for energy production[2]. Exercise during the luteal phase of the female menstrual cycle, where estrogen levels are elevated, has shown to promote fat utilization[3].

For women with T1DM, exercise during elevated estrogen levels may potentially provide a protective mechanism against hypoglycemia as energy sources such as glycogen (i.e., stored sugar) may be preserved. This may reduce the need for the body to replete energy from the blood post-exercise, thereby keeping BG levels balanced.

PURPOSE

The purpose of this study was to investigate the effects of exercise during elevated estrogen levels on the expression of prominent gluconeogenic enzymes, Phosphoenolpyruvate Carboxykinase (PEPCK) and Glucose 6-phosphatase (G6Pase), in T1DM female livers.

METHODS

Animals:

- 4 groups of rats were used in this study. 5 control (non-T1DM) exercise males (CXM), 5 control exercise females (CXF), 5 T1DM exercise males (DXM), and 5 T1DM exercise females (DXF)

Diabetes induction:

- Daily STZ injections of 20 mg/kg were administered over one week until blood glucose ≥18 mmol/L
- A subcutaneous insulin pellet was implanted to maintain BG at an intended range of 4-8 mmol/L (2 units/day)

Exercise training protocol:

- Exercise training consisted of 1 hour of running on a motorized treadmill (18-25m/min on a 6% gradient, ~75 $V0_{2max}$) for 4 consecutive days, where day 1 = diestrus (low estrogen) and day 4 = proestrus (high estrogen)

Experimental measures:

- BG measurements were taken at 0-, 30-, and 60-mins (exercise), and at 90 and 120-mins (recovery). Following the final training bout, rats were euthanized, and liver tissues were removed. Western blot analysis was conducted for PEPCK and G6Pase protein content.

RESULTS

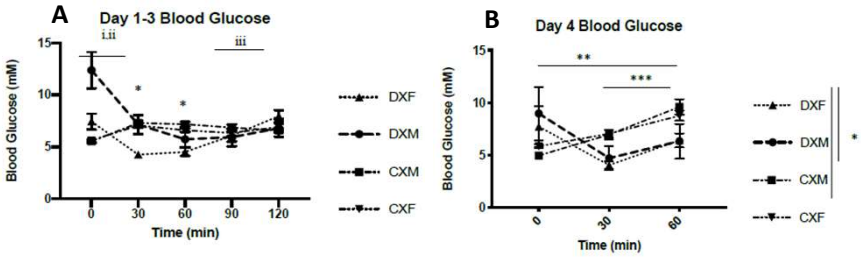

Figure 1: *(A) Mean blood glucose data (mmol/L) from days 1-3 are presented together. All data are presented as mean ± SEM. * denotes significance. (P < 0.0001) between diabetic and control females (DXF and CXF, respectively). i denotes significance within control males (CXM) (P < 0.0001) and ii denotes significance within CXF (P < 0.01). iii denotes significance within DXF (P < 0.05). DXM (diabetic males) had no significant changes or differences.*

Figure 1: *(B) Mean blood glucose (mM) from day 4 exercise. All data are presented as mean ± SEM. * denoted significance at t = 30 minutes (P < 0.05), ** denotes significance (P < 0.05) between starting and ending blood glucose in control females and males (CXF and CXM, respectively) *** denotes significance (P < 0.05) between 30 to 60 minutes in diabetic females (DXF). There were no differences in blood glucose between CXM and diabetic males (DXM).*

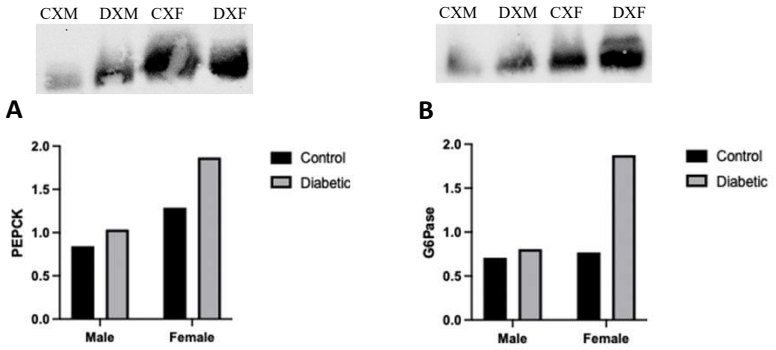

Figure 2: *(A) Liver PEPCK and (B) G6Pase protein content in arbitrary units following 4 days of aerobic exercise*

SUMMARY

- The normal glucose counterregulatory response to exercise is impaired in both male and female T1DM rodents, resulting in a reduction of BG levels at the onset of exercise
- Female T1DM BG levels during the final bout of exercise (day 4) did not remain optimal compared to male T1DM BG despite elevated estrogen levels
- However, female T1DM rodents had a greater post-exercise BG recovery compared to male T1DM rodents
- PEPCK (?) and G6Pase appear to be elevated in female compared to male T1DM rodents, as well as compared to control rodents (pre-analysis/normalization)
- These findings suggest that while there was a decrease in BG during exercise in T1DM females, they were able to counteract this effect more successfully than T1DM males. This enhanced BG recovery may be due to an increased protein content of important gluconeogenic enzymes in female T1DM livers which may help elevate BG at a faster rate compared to T1DM males
- Whether these differences in protein content are due to estrogen signaling is still unknown

REFERENCES

1. Yardley, J. E., & Sigal, R. J. (2015). Exercise strategies for hypoglycemia prevention in individuals with type 1 diabetes. Diabetes spectrum : a publication of the American Diabetes Association, 28(1), 32–38.
2. Tarnopolsky M. A. (2008). Sex differences in exercise metabolism and the role of 17-beta estradiol. Medicine and science in sports and exercise, 40(4), 648–654.
3. Campbell, S. E., Angus, D. J., & Febbraio, M. A. (2001). Glucose kinetics and exercise performance during phases of the menstrual cycle: effect of glucose ingestion. American journal of physiology. Endocrinology and metabolism, 281(4), E817–E825.

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