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Antidiuretic hormone and the activation of glucose production during high intensity aerobic exercise

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ABSTRACT

Objective: This study aimed to investigate the role that antidiuretic hormone (ADH) may play in the activation of glucose production during high intensity aerobic exercise.
Materials/methods: This study was part of larger study based on a repeated measures cross-over study design and involved ten adult participants who exercised in the morning at 80 % VO_2peak for up to 40 min or until exhaustion. During and after exercise, the participants were subjected to a morning euglycaemic/euinsulinaemic clamp while [6,6-$^2H_2$]glucose was infused and blood sampled to measure the endogenous rate of glucose appearance (Ra) and ADH levels.
Results: The levels of plasma ADH were 1.8 ± 0.2 pmol/L (mean ± SEM) at rest and increased to 10.5 ± 2.1 pmol/L at the end of exercise (mean ± SEM), which lasted 8.5–40 min. In response to exercise, glucose Ra also rose significantly ($p < 0.05$), but there was no significant association between changes in ADH levels and glucose Ra ($r = 0.49$; $p = 0.150$).
Conclusions: Although the significant increase in glucose Ra and ADH levels during high intensity aerobic exercise suggest for the first time that these processes may be causally related, there was no significant association between these variables, maybe because of the small sample size and varying exercise durations. Hence, the importance of the causal role that ADH may play in the exercise-mediated activation of hepatic glucose production warrants further in depth investigations.

1. Introduction

It is well established that blood glucose levels (BGL) increase during high intensity aerobic exercise (>80 % VO_2peak) performed under basal insulinaemic conditions in people with or without T1D [1,2]. This exercise-mediated rise in BGL results from a disproportionate increase in the rate of glucose production (glucose Ra) relative to the rise in glucose disappearance rate [1,2]. Although there is evidence that catecholamines, and not glucagon or insulin, are important mediators of this increase in glucose Ra [1,2], some studies have reported that this increment in glucose Ra is not critically dependent on adrenergic receptor stimulation [3,4]. Indeed, under conditions where glucagon, insulin, and plasma glucose are maintained at stable levels, glucose Ra in responses to heavy exercise is unaffected by hepatic adrenergic receptor blockade [3,5]. In addition, during such intense exercise, attenuation of sympathetic nerve activity to the liver and adrenal medulla does not affect glucose R_a [4], and denervated liver transplant patients have a normal glucose Ra response [6], thus implying the participation of other hormones.

Antidiuretic hormone (ADH), also named arginine vasopressin, is a hormone that may be implicated in the activation of glucose Ra during intense exercise. Indeed, ADH is not only an important endocrine regulator of whole body fluid homeostasis [7], it can also activate glycogenolysis [8] and gluconeogenesis [9] via stimulation of ADH V1a

Abbreviations: ADH, Antidiuretic hormone; BGL, Blood glucose levels; Ra, Rate of glucose appearance; SE, Standard error; T1D, Type 1 diabetes; VO_2peak, Peak rate of oxygen consumption.

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receptors [10], and ADH infusion increases BGL [11]. In addition, high intensity exercise is associated with a rise in ADH levels [7,12]. Despite the evidence gathered mainly in the 1970s and 1980s, that implicates ADH in glucoregulation, this research area has been the object of little research effort since then, as reviewed recently [13], except in the context of hydration status [14,15]. In particular, the issue of whether ADH contributes to the activation of glucose Ra during high intensity aerobic exercise has never been investigated before. Hence, the aim of this study was to investigate for the first time the role that ADH may play in the activation of glucose production during high intensity aerobic exercise. As a first step toward meeting this aim, this study examined the association between changes in ADH levels and activation of glucose Ra during high intensity exercise in individuals with T1D subjected to a euglycaemic/euinsulinaemic clamp. Individuals with T1D exposed to such a clamp were the focus of our study to prevent the marked post-high intensity exercise rise in insulin levels that is typically found in non-diabetic individuals [1,2] from inhibiting glucose Ra post-exercise, and thus may be dampening the stimulatory effect of ADH.

2. Methods

2.1. Participants

Ten recreationally active young individuals aged 13–25 y with well-controlled, complication-free T1D were involved; with nine participants tested in a previous study from our laboratory using a repeated measures cross-over study design (16) and another one tested to increase the statistical power of this study. All participants had undetectable *C*-peptide (<0.05 nmol/L), and were not taking any prescribed medication other than insulin. Other inclusion criteria included duration of disease >1 year, glycated haemoglobin of <9.0 % (75 mmol/mol), and participants being either on MDI or insulin pump. The exclusion criteria included diabetes complications and other co-morbidities. The protocol was approved by the Child and Adolescent Health Service Human Research Ethics Committee (approval number 1846/EP), and informed consent obtained from the parents and participants.

2.2. Experimental procedure

All participants were subjected to a familiarisation session and tested as previously described [16]. After an overnight fast, the participants were subjected to a euglycaemic-euinsulinaemic clamp during which insulin was infused at a basal rate. A priming bolus dose of 3.3 mg kg^{-1} of [6,6-$^2H_2$]glucose was administered followed by the constant infusion of 2.4 mg kg^{-1} h^{-1} of [6,6-$^2H_2$]glucose for the remainder of the experiment. Once isotopic equilibrium and stable euglycaemia with no variable glucose infusion was achieved for at least 45 min, blood samples were collected before exercising each participant at 80 % VO_2peak for 40 min or until fatigue. During and after exercise, [6,6-$^2H_2$]glucose tracer infusion rate was changed as described previously [16] to avoid marked changes in isotopic enrichments [1,2]. The insulin infusion rate remained unchanged and glycaemia was maintained between 5 and 6 mmol/L by adjusting the glucose infusion rate of a 20 % (w/v) dextrose solution.

2.3. Assays and statistical analyses

The measurement of [6,6-$^2H_2$]glucose enrichment and calculations of glucose Ra were performed as described previously [16]. Heparinized plasma was treated with polyethylene glycol and centrifuged before being assayed for free insulin using a non-competitive immunoassay (Architect i2000SR; Abbott Laboratories, Abbott Park, IL USA). ADH levels were assayed by a double-antibody vasopressin radioimmunoassay kit (Buhlmann Laboratories AG, Switzerland). The lower limit of detection for this assay was 1.7 pmol/l. The intra-assay and inter-assay CVs were 7.6 % and 10 %, respectively. Of note, although copeptin, a surrogate marker of ADH, is a stable molecule and easy to measure, ADH and copeptin have different decay kinetics, with ADH having a shorter half-life [17]. For this reason, copeptin level may not be an adequate marker of ADH levels when ADH levels change rapidly, such as during and after intense exercise [18].

With respect to sample size calculation, there was no information available from the literature to help us calculate our sample size since this is the first study to examine the effect of high intensity exercise on the relationship between ADH levels and glucose production. However, previous work from our laboratory using this experimental approach [19], reported that a sample size of 8 generally provides enough statistical power ($1 - \beta = 0.8$) to identify clinically significant differences in the primary outcome measures. Hence a pragmatic target sample size of 10 was selected based, in part, on key logistical elements such as cost of sessions, access to eligible participants, and time and burden on the participants. Linear mixed models using restricted maximum likelihood were adopted to examine the change in each outcome over time from exercise, and included a factor for time point and a random effect for participant. Pairwise comparisons between each time point and baseline were conducted and p values calculated using Kenward Roger approximation of degrees of freedom due to the small sample size. Spearman rank order correlation was performed to explore the relationship between Glucose Ra and change in ADH (percent increase from baseline) at the end of exercise. Statistical significance was accepted at $p < 0.05$. Unless otherwise stated, all results are expressed as mean ± SEM.

3. Results

The combined descriptive characteristics of the participants are shown in Table 1. Of the ten participants, three participants completed the 40 min exercise. The others stopped exercising at 30, 24, 20, 12, 10, 10, and 8.5 min. During exercise, ADH levels differed as a function of time ($F(5, 38.3) = 11.2$, $p < 0.001$), and increased significantly, peaking at the end of exercise to 10.5 ± 2.1 pmol/L (Fig. 1A) before decreasing to baseline within 30 min post-exercise. During exercise, glucose Ra changed as a function of time ($F(5, 45) = 35.4$, $p < 0.001$), and increased significantly (Fig. 1B), peaking at the end of exercise and rapidly declining to baseline within 30 min post-exercise. Plasma insulin levels increased marginally during exercise and returned to baseline within 15 min post-exercise (Fig. 1C). The correlation between glucose Ra and change in ADH levels at the end of exercise was not statistically significant (rho = 0.49, p = 0.150, Fig. 1D).

4. Discussion

The aim of this study was to provide the first evidence that increases in ADH levels contribute to the stimulation of glucose production during intense aerobic exercise. The pattern of change in ADH levels, with peak ADH levels being achieved at the end of exercise and returning to baseline within 30 min post-exercise, was closely aligned with the rise and fall of glucose Ra. Although these similar temporal patterns of

Table 1
Descriptive characteristics of study participants.

Characteristic	n = 10
Age (years)	21.0 ± 4.0
Gender: male/female, n	4/6
Oral contraceptive users	3
Weight (kg)	74.3 ± 19.6
Height (m)	1.72 ± 0.09
Body mass index (kg $m^{2\ -1}$)	24.9 ± 5.5
VO_{2peak} (ml·kg body $weight^{-1}$·min^{-1})	37.3 ± 9.2
Diabetes duration (years)	10.6 ± 6.4
HbA1c (%)	7.9 ± 0.8
HbA1c (mmol mol^{-1})	60 ± 8.7

Data are expressed as mean ± standard deviation.

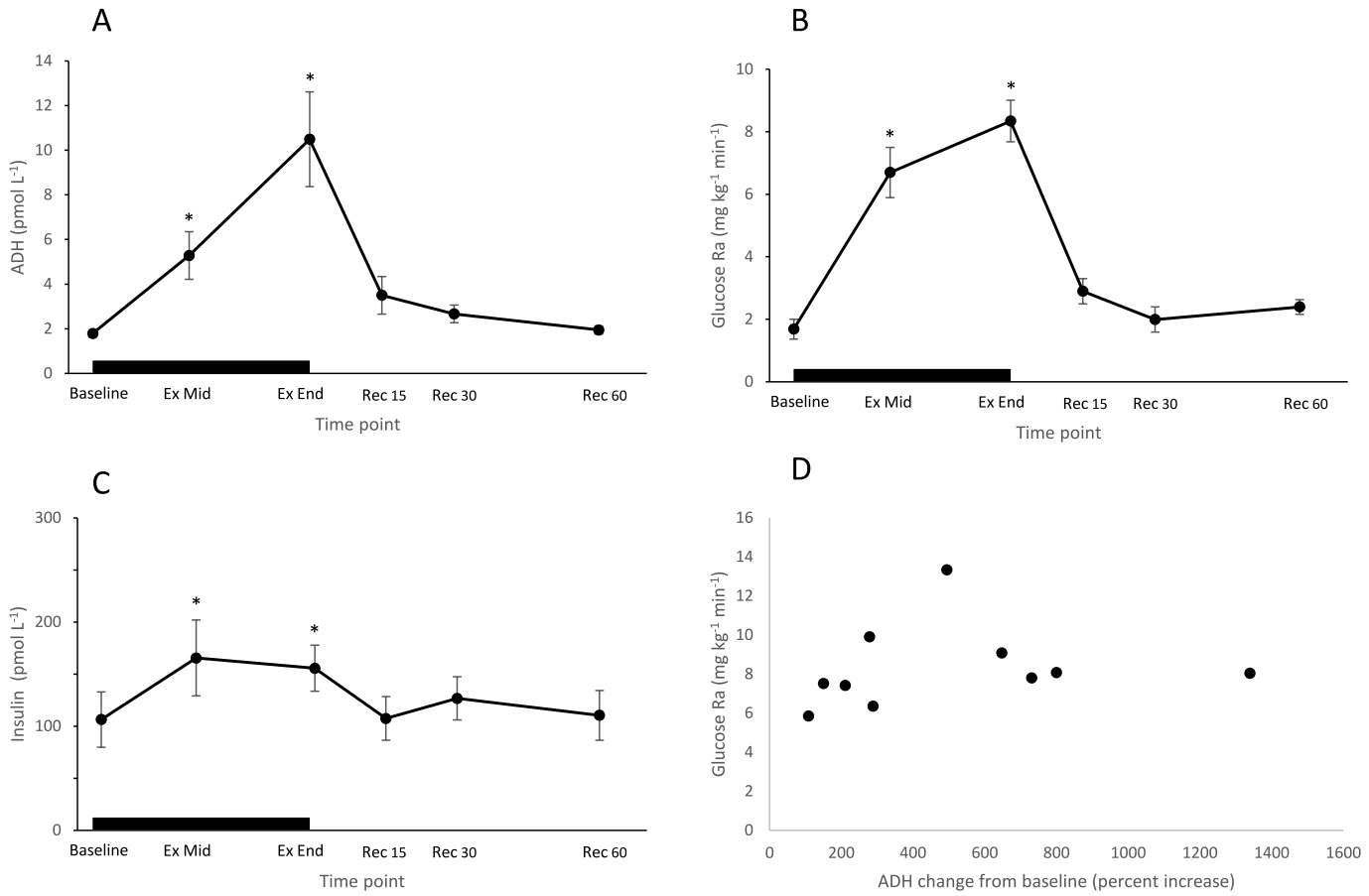

Fig. 1. Effect of high intensity exercise on plasma ADH (A), glucose Ra (B), plasma insulin levels (C) during exercise and 1 h after exercise, and correlation between glucose Ra and percent increase in ADH at the end of exercise (D). The time points used to measure ADH, glucose Ra and insulin levels were baseline, mid-exercise, end of exercise, and during recovery, 15, 30 and 60 min post-exercise. For participants who exercised less than 15 min, the mid-exercise time point was a sample collected minutes before the end of exercise when the participants indicated that they could not carry on much further. All data are expressed as mean ± SEM (n = 10). Horizontal bar indicates exercise at 80 % VO_{2peak}. * signifies $P < 0.05$, vs baseline.

change in ADH levels and glucose Ra suggest that these events may be causally related, there was no statistically significant association between the relative increase in plasma ADH concentrations and glucose Ra, maybe because of our small sample size and varying exercise durations (8–40 min).

The lack of a close association between ADH levels and glucose Ra cannot be explained on the grounds that the rise in ADH levels may have been inadequate to activate glucose production. This is because the peak ADH levels attained at the end of exercise were among the highest reported in the literature (10.5 ± 2.1 pmol/L) and comparable to those published by others for high intensity exercise [20,21], and higher than those attained in response to exercise of lower intensity [22–24] or longer duration [20,25].

The lack of a close association between ADH levels and glucose Ra does not imply that these variables are not causally related, as these negative findings may result from our small sample size and varying exercise durations (8.5–40 min). Based on our findings, we have calculated that a sample size of 30 individuals would be required for a significant association to be detected under our conditions of varying exercise durations, and probably less if exercise duration were to be well matched. However, exercising for 40 min at high intensity proved to be highly challenging and unachievable for most of our participants. Of note, even if a close association had been uncovered between changes in ADH levels and glucose Ra, this would not necessarily imply causality. Indeed, one would have to show, for instance, that the rise in glucose Ra is not mediated by other hormones, an important issue given that we and others have shown that the high intensity exercise-mediated increase in glucose Ra is associated with a rise in plasma catecholamines levels [1,2,16]. Nevertheless, since the roles played by glucagon [1,2] and catecholamines [3,4] in the activation of glucose Ra during intense exercise have been questioned, and considering that ADH can stimulate gluconeogenesis [9] and glycogenolysis in hepatocytes [8] as well as glucose Ra in humans directly or indirectly via other glucoregulatory hormones [11,13], the possibility raised by our findings that ADH may play a role in the activation of glucose production needs to be further investigated. Also, on practical grounds, this study raises the intriguing issue of whether the increased risk of hypoglycaemia associated with the consumption of alcohol, particularly when combined with exercise, may be mediated in part by an alcohol-mediated inhibition of ADH release in turn causing an inhibition of hepatic glucose production.

The strength of the study relates to its aim of providing the first evidence for a causal relationship between ADH levels and glucose production during intense aerobic exercise. The small sample size and varying exercise durations are the main limitations of this study. Preselecting a larger sample of participants who can perform high intense aerobic exercise for the same length of time should be attempted in future studies. Also, although examining the association between ADH levels and glucose production is necessary to establish a causal relationship between these variables, this approach is not sufficient to uncover such a relationship as an association between variables does not necessarily entail causality.

In conclusion, although the rise in both ADH levels and glucose Ra during high intensity exercise suggests that ADH may contribute to the activation of glucose production, there was no significant association

between these variables, maybe because of our small sample size and varying exercise durations. Our findings thus warrant further studies to evaluate the importance of the role played by ADH relative to other hormones in the activation of glucose Ra during high intensity exercise.

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CRediT authorship contribution statement

Vinutha B. Shetty: contributed to the conception and design of the study and the interpretation of data, contributed to the acquisition, Formal analysis, drafted the article and all authors revised it critically for important intellectual content, responsible for the integrity of this work. **Grant Smith:** contributed to the statistical analysis and interpretation of data. **Nirubasini Paramalingam:** : contributed to the acquisition. analysis and interpretation of data. **Heather C. Roby:** contributed to the acquisition, Formal analysis. **Elizabeth A. Davis:** contributed to the conception and design of the study and the interpretation of data. **Timothy W. Jones:** contributed to the conception and design of the study and the interpretation of data. **Paul A. Fournier:** contributed to the conception and design of the study and the interpretation of data, contributed to the acquisition, Formal analysis, All authors approved the final version of the manuscript.

Declaration of competing interest

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2021.100113.

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