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Pre-Exercise Carbohydrate Status and Immune Responses to Prolonged Cycling: II. Effect on Plasma Cytokine Concentration

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Ingesting carbohydrate (CHO) beverages during heavy exercise is associated with smaller changes in the plasma concentrations of several cytokines. The influence of dietary CHO availability on these responses has not been determined. Therefore, the present study investigated the influence of pre-exercise CHO status on plasma interleukin (IL)-6, IL-10, and IL-1 receptor antagonist (IL-1ra) responses to prolonged cycling. Seven trained male cyclists performed a glycogen-lowering bout of cycling and were randomly assigned to follow a diet ensuring either greater than 70% (HIGH) or less than 10% (LOW) of daily energy intake from CHO for the next 3 days. On day 4 subjects performed an exercise test that comprised cycling for 1 hour at 60% W_{max} immediately followed by a time-trial (TT) ensuring an energy expenditure equivalent to cycling for 30 min at 80% W_{max}. Subjects repeated the protocol after 7 days, this time following the second diet. The order of the trials was counterbalanced. At 1 and 2 hours post-TT, plasma concentrations of IL-6 and IL-10 were 2-fold greater on the LOW trial than on the HIGH trial, and peak plasma concentrations of IL-1ra were 9-fold greater on the LOW trial than on the HIGH trial. These findings suggest that pre-exercise CHO status can influence the plasma cytokine response to prolonged cycling.

Key Words: exercise, immune, nutrition

Introduction

Prolonged, strenuous exercise induces the release of a number of cytokines including interleukin (IL-6), IL-1 receptor antagonist (IL-1ra), tumor necrosis factor-α (TNF-α) and IL-10 (5, 17). Interleukins are polypeptide messenger substances that are secreted mainly from macrophages and lymphocytes, but also from other cells

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such as fibroblasts, endothelial cells, and myocytes. Their actions influence cells of the immune system as well as other tissues and organs, including the liver and brain (9).

The local tissue response to infection or injury involves the production of cytokines that are released at the site of inflammation (17). It has been suggested that the increase in plasma cytokine concentration observed following heavy physical exertion is due to the initiation of an inflammatory response in response to muscle damage (5). Certainly increases in the plasma concentration of IL-6 of more than 120-fold have been reported following a marathon (17). However, the release of these cytokines may not be specific to muscle damage, since a recent study in rats found that mRNA for IL-6 was elevated similarly in response to both eccentric and concentric electrically stimulated contractions (12). Furthermore, it has recently been shown that circulating monocytes do not contribute to the increase in plasma IL-6 concentration during prolonged exercise (22).

The findings that infusing recombinant human IL-6 (rhIL-6) increases fasting blood glucose levels in a dose-dependent manner (24) and that increases in plasma IL-6 concentration appear to be closely related to exercise duration (23) have led to the suggestion that IL-6 may have a hormone-like glucoregulatory role (23). This is supported by studies that have shown that regular ingestion of carbohydrate (CHO) beverages throughout prolonged, heavy exercise is associated with smaller increases in the plasma concentrations of IL-6 and IL-1ra (14, 15). Therefore, liver and/or muscle glycogen availability could be factors that influence the plasma cytokine response to exercise. However, the effect of dietary CHO on the plasma cytokine response to exercise has not yet been investigated. Therefore, the aim of this study was to manipulate glycogen stores by a combination of prior exercise and low or high CHO diets and examine the effect of this on the IL-6, IL-1ra, and IL-10 responses to prolonged, strenuous cycling.

Methods

Seven healthy trained male cyclists (mean ± *SEM*: age 27 ± 2 years; body mass 72.3 ± 3.3 kg; $\dot{V}O_{2max}$ 63.4 ± 3.4 ml · kg^{-1} · min^{-1}) volunteered to participate in the study. These were a subset of 12 subjects who completed the previous study investigating the influence of CHO status on neutrophil degranulation (3). All subjects provided written informed consent prior to the study, which was approved by the Ethics Committee of the University of Birmingham. Subjects did not report any symptoms of infection and had not taken any medication in the 6 weeks prior to the study, nor were they currently on medication.

Each subject's maximal oxygen uptake ($\dot{V}O_{2max}$) and maximal workload (W_{max}) was determined by an incremental cycling test to volitional fatigue as described in the previous study (3). The British Association of Sport and Exercise Sciences criteria for attainment of $\dot{V}O_{2max}$ were adopted (2).

Subjects were instructed to refrain from participating in any strenuous physical activity for 24-hours preceding each exercise test. The protocol for the study was the same as in the previous study (3), but a brief description will be given for the sake of clarity and completeness. All subjects completed two trials, each of which comprised two visits to the Human Performance Laboratory at the University of Birmingham. On the first visit of each trial subjects arrived at the laboratory at 08:30 following an overnight fast and performed a glycogen-lowering bout of exercise,

comprising cycling on a stationary ergometer (Lode Excalibur Sport, Groningen, the Netherlands) for 30 min at 80% W_{max}, immediately followed by a further 30 min at 70% W_{max}. For the rest of that day and for the following 2 days, subjects were randomly assigned to follow either a high or low CHO diet. To achieve this, subjects chose foods from a comprehensive list specific to each trial (10) that ensured a daily energy intake of either greater than 70% (HIGH) or less than 10% (LOW) from CHO. Each subject kept a diary of their dietary intake over this period, and energy intake and dietary composition were subsequently analyzed using the Salford Microdiet dietary analysis computer program (v. 9.01; University of Salford, 1995).

On the morning of day 4, subjects returned to the laboratory, following an overnight fast, and completed an exercise test. This comprised cycling on the stationary ergometers for 1 hour at 60% W_{max}, immediately followed by a time trial that ensured an energy expenditure equivalent to cycling for 30 min at 80% W_{max}, as described by Jeukendrup and Li (11). Oxygen uptake and non-protein respiratory exchange ratio (RER) were determined after 20 min of fixed duration exercise using open-circuit breath-by-breath spirometry (Oxycon-alpha, Jaeger, Mannheim, Germany) to allow estimation of rates of CHO oxidation (8). Throughout the fixed duration bout of exercise and the TT heart rates were recorded continuously using short-range radio telemetry (Sportstester®, Polar, Kempele, Finland) and water was available ad libitum.

Blood samples were obtained from an antecubital vein by venepuncture at the first glycogen-lowering visit (pre-diet sample) and then at the following times during the exercise test: pre-exercise, immediately after the 1 hour cycling at 60% W_{max}, immediately at TT completion, and at 1 hour and 2 hours post-exercise. All samples were taken with the subject seated. Food was not allowed until after the final blood sample had been taken, but water intake was not restricted.

After a period of at least 7 days, subjects returned to the laboratory and performed a second bout of glycogen-lowering exercise. After this, each subject followed the second diet for the rest of that day and for the following 2 days. On day 4, subjects reported to the laboratory following an overnight fast and completed the exercise tests as described above.

For all tests, the laboratory temperature and relative humidity were 21.5 ± 0.6 °C and 56 ± 1%, respectively.

Analytical Methods

Blood samples were collected into three separate vacutainer tubes (Becton Dickinson, Oxford, UK), two containing K_3EDTA and the other containing lithium heparin. Blood taken into one of the K_3EDTA vacutainers (4 ml) was used for hematological analysis, including hematocrit and hemoglobin using a Technicon H-2 laser system (Bayer Diagnostics, Basingstoke, UK). Plasma volume changes were estimated according to Dill and Costill (7).

Blood taken into the lithium heparin vacutainer (7 ml) and remaining K_3EDTA vacutainer was spun at 1500 g for 10 min in a refrigerated centrifuge (4 °C) to obtain plasma, which was immediately stored at –70 °C. After thawing, aliquots of heparinized plasma were analyzed to determine the concentration of glucose and cortisol using hexokinase (No. 16-50 Kit, Sigma, Poole, UK) and ^{125}I radioimmunoassay (ICN Pharmaceuticals, Costa Mesa, CA) methods, respectively. The intra-assay coefficient of variation for glucose was 2.4% and for cortisol was 1.8%.

Plasma concentrations of IL-6, IL-1ra, and IL-10 were determined in aliquots of K_3EDTA plasma with the use of quantitative sandwich-type enzyme-linked immunosorbant assay (ELISA) kits (IL-6 and IL-1ra, R&D Systems, Abingdon, UK; IL-10: Diaclone, Besançon, France). A high-sensitivity kit was used for analysis of IL-6. All assays use monoclonal antibodies specific to the interleukin to be determined as capture antibodies. The detection limit was as follows: IL-6: < 0.1 pg · ml^{-1}, IL1-ra: < 14 pg · ml^{-1} and IL-10: < 5 pg · ml^{-1}. The intra-assay coefficient of variation was 6.9%, 4.9%, and 2.6% for IL-6, IL-1ra, and IL-10, respectively.

Statistical Analysis

Data in the text, tables, and figures are presented as mean values and the standard errors of the mean (±*SEM*). The data were examined using a two-factor (trial × time of measurement) ANOVA with repeated measures design. Any significant *F* ratios shown were assessed using post hoc Tukey tests and paired *t* tests where appropriate. If a data set was not normally distributed, statistical analysis was performed on the logarithmic transformation of the data. Assumptions of homogeneity and sphericity in the data were checked and, where appropriate, adjustments in the degrees of freedom for the ANOVA were made. Performance times were analyzed using the Wilcoxon signed ranks test for non-parametric data. Correlation analysis was performed using Pearson's product-moment formula. Statistical significance was accepted at $p < .05$.

Results

Table 1 summarizes the dietary and performance data for the 7 subjects. Changes in plasma volume were similar between the trials (after 1 hour at 60% W_{max}: –6.7 ±

Table 1 Dietary and Performance Measures on the LOW and HIGH Trials

Variable	LOW	HIGH
CHO (% daily energy intake)	8.5 (1.1)*	77.8 (0.8)
CHO (g · kg^{-1} · body $mass^{-1}$)	1.1 (0.2)*	8.8 (1.3)
Protein (% daily energy intake)	23.9 (1.1)*	12.9 (4.6)
Fat (% daily energy intake)	66.8 (1.4)*	9.2 (1.2)
Energy intake (MJ · day^{-1})	13.6 (1.9)	12.5 (1.6)
Time to complete TT (min)	37.92 (1.53)*	28.48 (1.43)
HR during 1 hour at 60% W_{max} [a] (beats · min^{-1})	154 (3)	151 (4)
HR during TT[b] (beats · min^{-1})	162 (5)	177 (11)
% $\dot{V}O_{2max}$ after 20 min at 60% W_{max}	69.4 (2.0)	67.7 (2.2)
RER after 20 min at 60% W_{max}	0.85 (0.01)*	0.94 (0.01)
Rate of CHO oxidation (g · min^{-1})	2.0 (0.1)*	3.2 (0.3)

Note. Data are presented as mean values and the standard errors of the mean (±*SEM*). CHO: carbohydrate; TT: time trial; $\dot{V}O_{2max}$: maximal oxygen uptake; RER: respiratory exchange ratio.

[a,b]Mean of all recordings. *Significantly different from HIGH, $p < .01$.

Table 2 Plasma Glucose and Cortisol Concentrations During the LOW and HIGH Trials

Variables	Pre-diet	Pre-exercise	1 hour at 60% W_{max}	Time post-TT		
				0 hour	1 hour	2 hours
Glucose (mmol · L^{-1})						
LOW	5.2 (0.2)	5.1 (0.2)	4.6 (0.3)*†	3.2 (0.2)*†	4.1 (0.1)*†	4.2 (0.2)*†
HIGH		5.4 (0.1)	6.1 (0.1)	7.4 (0.4)*	5.1 (0.1)	5.2 (0.2)
Cortisol (nmol · L^{-1})						
LOW	389 (50)	387 (49)	490 (47)	812 (60)*†	824 (88)*†	688 (113)*†
HIGH		378 (35)	383 (28)	594 (27)*	530 (36)*	365 (32)

Note. Data are presented as mean values and the standard errors of the mean (±*SEM*). TT: time trial.
*Significantly different from pre-exercise within trial, $p < .01$. †Significantly different from HIGH, $p < .01$.

1.0% and –7.1 ± 0.9%; at TT completion: –7.8 ± 0.2% and –9.7 ± 1.1% on the LOW and HIGH trials, respectively). Body mass, when corrected for fluid intake, fell similarly on both trials (LOW: –1.8 ± 0.2 kg, HIGH: –1.9 ± 0.1 kg). At TT completion, plasma glucose concentration was significantly lower on the LOW trial than on the HIGH trial ($p < .01$; Table 2). At this time, plasma cortisol concentration was 37% higher on the LOW diet compared with the HIGH diet ($p < .01$; Table 2).

Resting plasma levels of all of the cytokines measured were similar before and after dietary control. Plasma IL-6 levels increased similarly during the exercise on both trials and peaked at TT completion (all $p < .01$). Values remained significantly elevated above pre-exercise at 1 hour and 2 hours post-exercise on both trials (all $p < .01$). However, at 1 hour post-exercise, plasma IL-6 concentration was significantly greater on the LOW trial than on the HIGH trial ($p < .05$; Figure 1). Plasma IL-1ra concentration remained close to pre-exercise values on both trials during the exercise and at TT completion. However, on the LOW trial plasma IL-1ra concentration was markedly elevated above both pre-exercise values and values on the HIGH trial at 1 hour ($p < .02$) and 2 hours ($p < .01$) post-exercise (Figure 2). A significant correlation was found between the plasma concentrations of IL-6 at 1 hour post-exercise and IL-1ra at 2 hours post-exercise on the LOW ($r = 0.90$, $p < .01$) and HIGH ($r = 0.81$, $p < .05$) trials. Plasma IL-10 concentration was similar on both trials during the exercise and at TT completion. However, during recovery, values tended to be higher on the LOW trial; at 1 hour post-exercise, plasma levels of IL-10 on the LOW trial were more than 2-fold higher than concentrations on the HIGH trial at this time ($p = .07$; Figure 3).

Discussion

Results from the present study suggest that consuming a high versus low CHO diet for 3 days prior to prolonged strenuous exercise is associated with attenuated elevations in plasma concentrations of IL-6, IL-1ra, and IL-10. Marked increases in

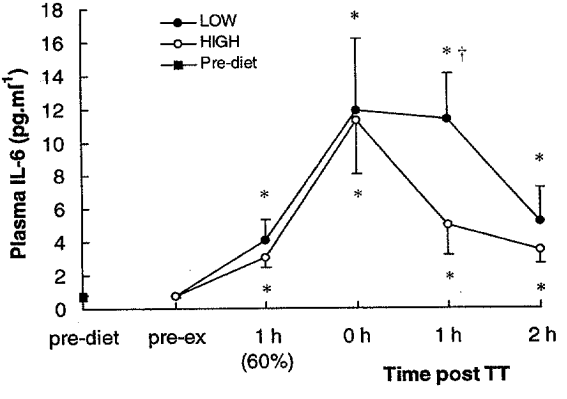

Figure 1 — Plasma interleukin (IL)-6 concentration before dietary manipulation (pre-diet) and during the LOW and HIGH trials. Data are presented as mean values and the standard errors of the mean (±*SEM*). Pre-ex: pre-exercise; (60%): 60% W_{max}; TT: time trial. *Significantly different from pre-exercise within trial, $p < .01$. †Significantly higher than HIGH, $p < .01$.

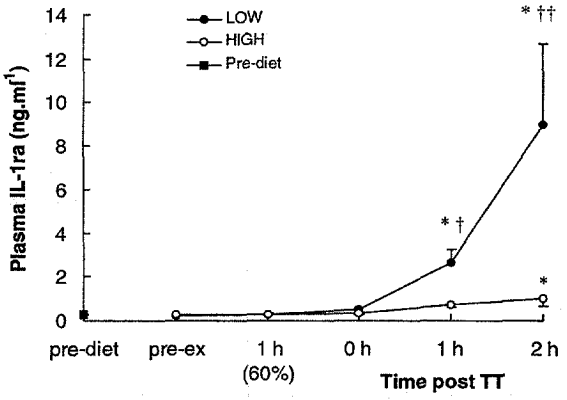

Figure 2 — Plasma interleukin-1 receptor antagonist (IL-1ra) concentration before dietary manipulation (pre-diet) and during the LOW and HIGH trials. Data are presented as mean values and the standard errors of the mean (±*SEM*). Pre-ex: pre-exercise; (60%): 60% W_{max}; TT: time trial. *Significantly different from pre-exercise within trial, $p < .01$. Significantly higher than HIGH: †$p < .02$, ††$p < .01$.

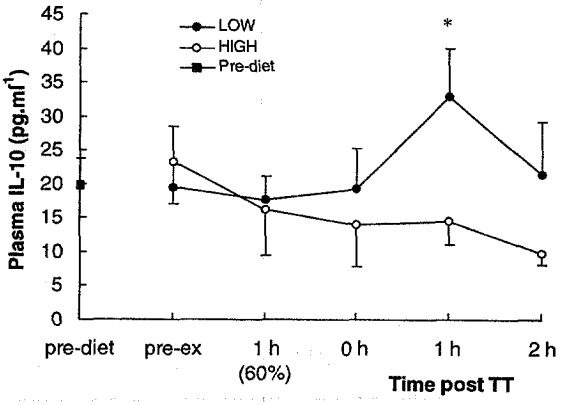

Figure 3 — Plasma interleukin (IL)-10 concentration before dietary manipulation (pre-diet) and during the LOW and HIGH trials. Data are presented as mean values and the standard errors of the mean (±*SEM*). Pre-ex: pre-exercise; (60%): 60% W_{max}; TT: time trial. *Compared with HIGH, $p = .07$.

plasma levels of these cytokines have been reported in runners following a marathon (17); the findings of the present study, although smaller in magnitude probably due to the shorter duration of the protocol, are in accordance with this. IL-6 plays an important role in inflammation, since it stimulates the release of acute phase proteins from the liver and is involved in the down-regulation of the response to allow a return to homeostasis (21). Its release is countered by an up-regulation of the production of anti-inflammatory cytokines, such as IL-10, and the naturally occurring cytokine inhibitor IL-1ra (1). Since exercise-induced changes in mRNA for IL-1ra have been recently detected in blood mononuclear cells (19), it seems likely that

IL-6 acts directly to increase monocyte IL-1ra production. This is supported by the finding that the peak plasma concentrations of both IL-10 and IL-1ra occurred 1 hour and 2 hours, respectively, after the peak in plasma IL-6 concentration on both trials in the present study.

In the present study, plasma concentrations of IL-6 and IL-1ra were lower following the exercise on the HIGH trial than on the LOW trial. This agrees with previous studies in which CHO was ingested during strenuous exercise (14, 15). Since the release of IL-1ra (and IL-10) typically follows that of IL-6, it appears that the reduced IL-1ra and IL-10 responses observed on the HIGH trial are a consequence of the smaller IL-6 response. During prolonged, heavy exercise, there is a net release of IL-6 from active (but not inactive) muscle (23). This net release appears to be closely related to exercise duration and occurs after 1 hour of exercise, leading to the suggestion that IL-6 may act in a hormone-like glucoregulatory manner (23).

This is supported by a number of studies. Blumberg et al. (4) reported that IL-6 stimulated gluconeogenesis in isolated rat hepatocytes in a dose-dependent manner. Ritchie (20) demonstrated that the addition of rhIL-6 to [^{14}C]-glycogen labeled rat hepatocytes stimulated [^{14}C]-glucose release. Moreover, a study in isolated rat hepatocytes demonstrated that IL-6 inhibited [^{14}C]-glucose incorporation into glycogen even after just 2 hours of incubation (13). In the presence of insulin, IL-6 completely inhibited the insulin-stimulated increase in glycogen deposition after a 4-hour incubation period, and the effects were sustained for 24 hours. It was shown that IL-6 inhibited glycogen synthase activity, yet enhanced glycogen phosphorylase activity. Interestingly, half-maximum responses were observed at an IL-6 concentration of 30 pg · ml^{-1}; this is substantially less than that reported in plasma following strenuous exercise lasting 2 hours or more (~100 pg · ml^{-1}) (14, 17). Importantly, one recent study in humans found that injecting rhIL-6 increased fasting blood glucose in a dose-dependent manner (24). It is, therefore, an intriguing possibility that IL-6 acts as a signal from the muscle to the liver, indicating that muscle glycogen levels are reaching critically low levels.

In the present study, it can be assumed that pre-exercise glycogen levels were lower on the LOW trial than on the HIGH trial as a consequence of the initial glycogen lowering bout of exercise and the subsequent restricted CHO intake over the 3 days before the exercise test. When muscle glycogen is low, muscle uptake of blood glucose is increased; hence, some additional stimuli to the liver to increase its glucose output to prevent a drastic fall in the blood glucose concentration is required. The finding that IL-6 levels on the LOW trial at 1 hour post-TT were substantially elevated above those on the HIGH trial at this time lends support to the suggestion that IL-6 acts as this stimuli. Furthermore, given the inhibitory effect of IL-6 on glycogen synthase activity in rat hepatocytes, it may be speculated (assuming IL-6 similarly affects muscle glycogen synthase activity) that these findings are related to the delay in muscle glycogen resynthesis associated with muscle tissue injury (6, 16).

In the present study, the plasma cortisol response to the exercise was substantially greater following the TT on the LOW trial compared with the HIGH trial. This may be attributed to the lower plasma glucose levels on the LOW trial stimulating the hypothalamus-pituitary-adrenal (HPA) axis to secrete adrenocorticotrophic hormone from the anterior pituitary. This in turn stimulates secretion of cortisol from the adrenal cortex. IL-6 is also known to stimulate the HPA axis. It is thought that

this is a counter-regulatory mechanism, since cortisol has anti-inflammatory actions and plays an important part in the negative feedback system involved in the down-regulation of the inflammatory response (1). However, given the potential role of IL-6 in glucose homeostasis, it may be that IL-6 stimulates the release of this stress hormone for its glucoregulatory role. Furthermore, post-exercise IL-6 production has also been shown to be closely related to plasma catecholamine levels (18), and in humans both plasma IL-6 and IL-1ra levels increase, with a delay, in response to adrenaline infusion suggesting *de novo* synthesis of IL-6 (21). However, although CHO ingestion during exercise results in smaller plasma cytokine responses, plasma catecholamine levels are not reported to be altered by CHO availability (14, 15).

Dietary fat intake has been found to modulate cytokine production, and diets high in fat content are associated with higher plasma concentrations of cytokines following strenuous exercise (25, 26). In the present study, the dietary fat content on the HIGH and LOW trials was ~10% and ~70% of the daily energy intake, respectively; hence, it may be that the fat content of the diet was an important factor in determining the cytokine responses observed. However, studies that have investigated the effects of fat intake on cytokine and other immune responses have controlled the diet for periods of at least 4 weeks, yet the period of dietary control in the present study was just 3 days. Therefore, it could be argued that for this study, the CHO content of the diet, rather than its fat content, was the more important determinant of the responses observed.

In conclusion, increasing pre-exercise CHO availability was associated with a smaller plasma cytokine response to prolonged, strenuous cycling exercise. This agrees with findings from studies in which CHO was ingested during prolonged exercise and may lend support for a role of IL-6 in glucose homeostasis.

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