Immunoendocrine Responses to Daily Repeated Exercise and the Influence of Carbohydrate Supplementation

單日重複性運動暨碳水化合物補充對免疫內分泌之影響

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Abstract

It is still not clear how time of day and daily repeated bouts of prolonged exercise influence the immune system. In this review the immunoendocrine responses to repeated exercise bouts on the same day and the influence of carbohydrate (CHO) supplementation are addressed. Summaries were concluded in this review according to the current knowledge: (1) A single bout of prolonged exercise performed in the afternoon induced a larger perturbation in leukocyte trafficking into the circulation than an identical bout of morning exercise, which may be due to higher hypothalamic-pituitary-adrenal (HPA) activation and circadian rhythms. However, there was no effect on mucosal immune responses (salivary IgA). (2) The second compared with the first of two bouts of prolonged exercise induced a greater HPA activation, a larger leukocyte trafficking into the circulation, and a greater fall in neutrophil function, but did not further increase plasma IL-6, or change sIgA secretion rate. (3) CHO ingestion during any period of two bouts of prolonged exercise showed limited beneficial effect to blunt these higher responses in the second exercise bout compared with the first. When two bouts of exercise were performed in a day, the greatest benefit in terms of limiting immunoendocrine responses was obtained by feeding CHO at the earliest opportunity. (4) A 3-h interval was insufficient, whereas an 18-h interval was sufficient, for recovery of leukocyte mobilization and neutrophil function from the impact of previous exercise whether subjects consumed placebo or CHO during exercise or recovery.

Key words: repeated exercise, leukocyte redistribution, neutrophil function, stress hormone, carbohydrate ingestion

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Introduction

The human immune system can be functionally divided into innate immunity and adaptive immunity and the various cellular and humoral factors in the complex network are modified by stress. The steady state of the internal milieu can be challenged by either internal or external stress, which subsequently activates both the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the elevation of circulating catecholamines and glucocorticoids in concert to maintain homeostasis (Elenkov, Wilder, Chrousos, & Vizi, 2000). Exercise has been recognized and adopted as a reliable tool to manipulate reproducible and quantifiable stress responses via tuning exercise type, intensity, frequency and duration (Smith & Pyne, 1997). Recently exercise has been applied to investigate the effects of exercise-induced stress on endocrine and immune systems (Ostrowski, Rohde, Zacho, Asp, & Pedersen, 1998; Suzuki et al., 1999). Although the relationship between exercise and immunity is not entirely understood, it can be stated that exercise induces transiently reversible alteration in immunoendocrine parameters and excessive exercise can further elicit immuno-depression (Gleeson & Bishop, 1999). This may open a window to pathogens and place athletes at a higher risk of infection after heavy exertion (Pedersen, 1999).

Routine training programs of elite athletes commonly consist of several bouts of intensive exercise in a day. This is especially so for endurance athletes, such as marathoners, triathletes, road race cyclists, and cross-country skiers whose daily training schedule usually includes repeated bouts of prolonged exercise. It seems likely that the higher incidence of infection in elite athletes is due, at least in part, to the repeated bouts of intensive exercise without sufficient recovery. Failure to fully recovery between training sessions has been suggested to evoke chronic fatigue, under-performance, and more immunodepression (Gleeson, Lancaster, & Bishop, 2001b). Recently, several studies have focused on investigating how repeated bouts of exercise affect immunoendocrine responses (Li & Gleeson, 2004b, 2004c; Ronsen, Haug, Pedersen, & Bahr, 2001a; Ronsen, Kjeldsen-Kragh, Haug, Bahr, & Pedersen, 2002a; Ronsen, Lea, Bahr, & Pedersen, 2002b; Ronsen, Pedersen, Oritsland, Bahr, & Kjeldsen-Kragh, 2001b) and have shown that a second exercise bout on the same day evoked more pronounced changes in leukocyte subsets and stress hormones, especially in adrenaline and growth hormone, compared with a single bout of identical exercise at the same time of day. However, until recently the influence of nutritional interventions on the immuno-endocrine response to repeated bouts of ex-ercise is unknown. Therefore, some important questions that are discussed in the present review include: (1) Does an identical bout of exercise performed at different times of day

induce different immunoendocrine responses? (2) Does the second bout of exercise evoke higher immunoendocrine responses compared with an identical first exercise bout on the same day? (3) Does ingestion of carbohydrate (CHO) compared with placebo (PLA) during different periods of repeated exercise bouts attenuate immunoendocrine responses? (4) How much time is needed for the immune system to recover from the impact of repeated bouts of prolonged exercise?

Different times of day

Many physiological variables exhibit circadian rhythms (Petrovsky, McNair, & Harrison, 1998; Porterfield, 2001) and the best performance of elite athletes is often observed in the early evening (Atkinson & Reilly, 1996). However, in terms of the immune system, what time of day is best for exercising is still unknown. To understand and control for circadian variations is very important when the aim of a study is to compare the effects of exercise performed at different times of day on immunoendocrine responses. Cortisol is the major circulating human glucocorticoid and functions as a powerful natural immunosuppressant. Plasma cortisol exhibited a prominent circadian rhythm, maximal in the early morning hours just before awakening and reaching a nadir in the late evening until next early morning. This appeared to impose diurnal variation on immune function (Petrovsky et al., 1998). Plasma adrenocorticotropic hormone (ACTH) also showed a pronounced diurnal pattern, which peaked in the early morning and declined to a nadir in the evening (Porterfield, 2001). Circulating leukocyte and neutrophil counts demonstrated circadian rhythms increasing from early morning and peaking in the late evening (Haus, 1994), whereas lymphocyte counts were elevated during the night and decline after wakening (Dhabhar, Miller, Stein, McEwen, & Spencer, 1994). This relationship between cortisol and circulating leukocyte counts suggested that the endocrine system might play an important role in regulating immune cell turnover and/or redistribution between immune compartments (Dhabhar et al., 1994). Furthermore, saliva IgA concentration also showed diurnal variation (Dimitriou, Sharp, & Doherty, 2002), which was highest in the early morning, followed by a decline during the morning and then was stable from around noon onwards (Gleeson, Bishop, Sterne, & Hawkine, 2001a).

In order to compare the effects of exercise performed at different times of day on immunoendocrine responses, a study was conducted in our lab to investigate time-dependent changes in plasma stress hormones, interleukin-6 (IL-6), circulating numbers of leukocyte subsets, neutrophil function, saliva flow rate, and saliva IgA responses. The results confirmed that there were circadian variations in plasma concentrations of ACTH and cortisol, circulating counts of leukocytes, neutrophils and lym-

phocytes (Li & Gleeson, 2004c), and saliva IgA concentration (Li & Gleeson, 2004b). The observations are similar to previous findings (Dhabhar et al., 1994; Gleeson et al., 2001a; Haus, 1994; Porterfield, 2001) and support the notion that the diurnal variation must be considered when the aim of a study is to compare the effect of exercise performed at different times of day on the aforementioned parameters.

A comparison of immunoendocrine responses between a single bout of prolonged exercise in the morning (EX1) and in the afternoon (PMEX) are presented in Table 1 (EX1 vs. PMEX). The plasma concentrations of glucose, adrenaline, ACTH, cortisol, GH and IL-6 and the neutrophil degranulation response to stimulation with a standardized bacterial extract in vitro on a per cell basis in EX1 were similar to PMEX whereas the perturbations of circulating leukocytes and subsets in EX1 were lower compared with PMEX. The larger redistribution of leukocytes and subsets into the circulation at post-PMEX compared with post-EX1 might be caused by higher HPA activation since the percentage increase in plasma cortisol was significantly higher in PMEX (120 %) than EX1 (3 %). However, the responses of saliva flow rate, sIgA concentration and IgA secretion rate were similar in EX1 and PMEX.

In summary, a single bout of prolonged exercise performed in the afternoon induces a larger perturbation of leukocyte trafficking than an identical bout of morning exercise, which may be due to higher HPA activation and circadian rhythms. However, in terms of oral mucosal immunity, performing prolonged cycling at different times of day did not differently affect the salivary responses.

The first (EX1) vs. the second (EX2) of two bouts of prolonged exercise

Ronsen and his colleagues reported that the second exercise bout induced greater responses of stress hormones and circulating counts of leukocyte subsets compared with an identical first bout of intensive exercise on the same day (2001a, 2001b). However, in these studies the subjects were given standardised meals at regular times during the experimental protocol. In our lab we further compared the differences between the first and the second of two bouts of prolonged cycling on the aforementioned variables in individuals who remained fasted throughout or were given CHO at specific times during the trials. The comparisons of the immunoendocrine responses between the first and the second of two bouts of prolonged exercise are presented in Table 1 (EX1 vs. EX2).

Table 1 Comparison of immunoendocrine responses at different times of day and between the first and the second of two bouts of prolonged exercise

Parameters (References)	**EX1 *vs.* PMEX** (Li & Gleeson, 2004b)	**EX1 *vs.* EX2** (Li & Gleeson, 2004c)
Glucose	↔	↓
IL-6	↔	↔
Adrenaline	↔	↔
ACTH	↔	↑↑
Cortisol	↔	↑↑
GH	↔	↑
Leukocyte count	↓	↑
Neutrophil count	↓	↔
Lymphocyte count	↔	↑↑
Monocyte count	↓↓	↑↑
Degranulation per neutrophil	↔	↓↓
Saliva flow rate	↔	↔
Saliva IgA concentration	↔	↔
Saliva IgA secretion rate	↔	↔

PMEX: a single bout of exercise performed in the afternoon; EX1: the first of two bouts of exercise performed in the morning; EX2: the second of two bouts of prolonged exercise performed in the afternoon.

Significantly higher at post-EX2 than post-EX1 (↑ $p<.05$, ↑↑ $p<.01$); significantly lower at post-EX2 or post-PMEX than post-EX1 (↓ $p<.05$, ↓↓ $p<.01$); ↔ similar between post-EX2 or post-PMEX and post-EX1.

Muscle glycogen depletion and hypoglycaemia potentially caused fatigue (Costill & Hargreaves, 1992; Coyle et al., 1983) and elevate HPA and SNS stimulation during prolonged exercise (Mitchell et al., 1990). Low plasma glucose concentration itself may impair neutrophil function (Healy, Watson, & Newsholme, 2002; Leist, Single, Castoldi, Kuhnle, & Nicotera, 1997). The higher plasma concentration of adrenaline and cortisol released by elevated HPA and SNS stimulation evoked the redistribution of leukocytes from marginal pools and the bone marrow into the circulation (Gleeson & Bishop, 1999).

Plasma glucose concentration was significantly lower at post-EX2 compared with post EX1 when subjects ingested water throughout the experimental protocol, which appeared to subsequently induce larger elevations in circulating stress hormones and leukocyte counts (Li & Gleeson, 2004c). However, performing two bouts of prolonged cycling on the same day did not appear to alter sIgA transcytosis in either EX1 or EX2 (Li & Gleeson, 2004b).

In summary, the second compared with the first of two bouts of prolonged exercise on the same day induced a greater HPA activation, a larger leukocyte trafficking into the circulation, and a greater fall in neutrophil function; but did not increase plasma IL-6, or change sIgA secretion rate. The possible mechanisms have

been described in recently published review articles (Li, 2006, 2007).

Carbohydrate supplementation

In order to maintain the qualities of immunity and performance in subsequent exercise bout, it was particularly important for athletes to maintain immunocompetence (Gleeson & Bishop, 2000) and carbohydrate availability (Maughan, 2002) during daily training sessions. Nutritional strategies, particularly CHO supplementation, have been demonstrated to attenuate responses of the immune and neuroendocrine systems to exercise (Gleeson et al., 2001b). CHO ingestion compared with PLA better maintained plasma glucose concentration, attenuated HPA activation (Mitchell et al., 1990), plasma cytokines responses and immunological perturbations to an acute single bout of fixed duration exercise (Gleeson & Bishop, 2000). However, if exercise was continued to exhaustion, ingesting carbohydrate during exercise may enhance performance, but had little effect on minimising immunoendocrine responses (Bishop, Blannin, Walsh, & Gleeson, 2001).

The main findings from our studies concerning the effect of CHO ingestion on immunoendocrine responses during the second of two bouts of prolonged exercise are presented in Table 2. Ingestion of CHO compared with PLA during EX1 (Li & Gleeson, 2006) or EX2 (Li & Gleeson, 2005b) appeared consistently to better maintain the plasma glucose concentration, attenuate the activation of SNS and HPA, blunt the increase in circulating numbers of leukocytes and monocytes, and minimize the elevation of sIgA concentration during EX2 (Li & Gleeson, 2005a). CHO supplementation during EX2, moreover, attenuated the decline of neutrophil degranulation response to lipopolysaccharide (LPS) and oxidative burst activity to phorbol-12-myristate-13-acetate (PMA) on per cell basis compared with PLA. However, CHO ingestion during the recovery interval seemed less effective and only blunted the HPA activation and circulating lymphocyte count compared with PLA (Li & Gleeson, 2004a). Ingesting CHO-rich drinks during prolonged exercise was the most effective and common strategy applied to support CHO availability during exercise (Jeukendrup & Jentjens, 2000), which can attenuate activation of HPA and perturbation of the circulating numbers of leukocytes and subsets (Bishop, Blannin, Walsh, Robson, & Gleeson, 1999; Mitchell et al., 1990; Nieman et al., 1997).

Table 2 The effect of CHO ingestion on immunoendocrine responses during the second of two bouts of prolonged exercise

Parameters (References)	**NON-CHO** (Li & Gleeson, 2004b, 2004c)	**CHO-REC** (Li & Gleeson, 2004a, 2005a)	**CHO-EX1** (Li & Gleeson, 2005a, 2006)	**CHO-EX2** (Li & Gleeson, 2005a, 2005b)
Glucose	↓↓	↓↓	** ↔	** ↑↑
IL-6	↑	↑	↑	* ↑↑
Adrenaline	↑↑	↑↑	* ---	* ↑↑
ACTH	↑↑	* ↑	** ↑	* ↑↑
Cortisol	↑↑	* ↑	** ↑↑	** ↑↑
GH	↑↑	↑	↑↑	** ↔
Leukocyte count	↑	* ↑↑	** ↑↑	** ↑↑
Neutrophil count	↔	↔	↑↑	↑
Lymphocyte count	↑↑	↑↑	** ↑↑	↑↑
Monocyte count	↑↑	↑↑	* ↑↑	** ↑↑
Degranulation per neutrophil	↓↓	↔	* ↔	↔
Oxidative burst per neutrophil	---	---	* ↔	↔
Saliva flow rate	↓↓	↓↓	↓↓	↔
Saliva IgA concentration	↑↑	↑↑	* ↔	* ↔
Saliva IgA secretion rate	↔	↔	↔	↔

NON-CHO: no CHO supplementation (i.e. PLA or water); CHO-REC: CHO supplementation during the recovery interval; CHO-EX1: CHO supplementation during EX1; CHO-EX2: CHO supplementation during EX2.

Significantly different from PLA at post-EX2 (*p<.05, **p<.01); significantly higher at post-EX2 than pre-EX2 (↑p<.05, ↑↑p<.01); significantly lower at post-EX2 than pre-EX2 (↓ p<.05, ↓↓ p<.01); ↔ similar between post-EX2 and pre-EX2.

In contrast, the CHO ingestion during the recovery interval did not appear to attenuate the decline of plasma glucose concentration and was not effective in blunting the immuno-endocrine responses during EX2 compared with PLA. The findings suggest that the greatest benefit of CHO supplementation to attenuation of immunoendocrine responses during two bouts of prolonged exercise is obtained when CHO is consumed at the earliest opportunity since it allows more time for absorption and storage of glucose. For example, when CHO drink is consumed during EX1, some ingested CHO is emptied and absorbed

(~1 g·min^{-1}) to maintain plasma glucose concentration during the first bout of prolonged exercise, and some ingested CHO may provide substrate for glycogen synthesis in the liver and muscle during the recovery interval, and attenuate the decrease in CHO availability and immunoendocrine responses during the subsequent bout of exercise. However, if CHO is consumed during the recovery interval, there is less time available for absorption and glycogen synthesis and may also cause a rebound hypoglycaemia in the early stage of the subsequent exercise bout, inducing the activation of HPA. If CHO is consumed during the second exercise bout, some, but probably not all of the ingested CHO, is absorbed to maintain plasma glucose concentration but it is unlikely to be directed to resynthesis of liver and muscle glycogen during exercise.

In summary, ingestion of CHO compared with PLA during the recovery interval attenuated HPA activation to the second exercise bout to a small extent. If CHO was supplemented during the second exercise bout, the responses of SNS and HPA, plasma glucose, circulating leukocytosis and monocytosis, and sIgA level during the second exercise bout were blunted compared with PLA. Moreover, if CHO was ingested during the first of two bouts of prolonged exercise, the decline in neutrophil function can be prevented (compared with PLA) during the second exercise bout. It seemed that when two bouts of exercise were performed on the same day, the greatest benefit in terms of minimising circulating immunoendocrine responses was obtained by feeding CHO at the earliest opportunity.

Recovery Time

The findings from our studies about the recovery of immunoendocrine variables after prolonged exercise are presented in Table 3. It has been suggested that the alteration in immune cell function and leukocyte trafficking might last for several hours after exercise (Gleeson & Bishop, 1999). The results from the studies in our lab showed that the responses of activated SNS and HPA, circulating lymphocyte count, and oral immunity returned to pre-EX1 but plasma glucose and IL-6, circulating counts of leukocytes, neutrophils and monocytes, and neutrophil function did not recover to pre-EX values within 3 h after EX1 when subjects only ingested water or placebo during EX1 and the recovery interval (NON-CHO-3h and CHO-EX2-3h). However, if subjects ingested CHO during EX1 or the recovery interval, the decline in neutrophil function can be prevented (Li & Gleeson, 2004a, 2006). This may be because the ingestion of CHO compared with PLA attenuated the delayed neutrophilia that arised due to release of less mature neutrophils from the bone marrow into the circulation after EX1. Obviously, a 3-h interval was insufficient for recovery of leukocyte mobilization and neutrophil function but was long enough for

oral mucosal immunity (sIgA secretion rate) to recover from the impact of previous prolonged exercise. According to Ronsen et al. (2002a), a 6-h recovery interval may be better for athletes to recover their cellular immunity for the next training bout. Muns (1994) reported that nasal neutrophil function was depressed for 3 days after prolonged running. Moreover, Peters and Bateman (1983) suggested that the depression of sIgA concentration could last up to 18 h after marathon running and that repeated bouts of intense exercise may exert a cumulative effect on mucosal immunity (Mackinnon & Hooper, 1994). However, we did not observe a delayed effect of exercise on immunoendocrine variables 18 h after two bouts of prolonged exercise.

In summary, a 3-h interval was insufficient for recovery of leukocyte mobilization and neutrophil function from the impact of previous exercise whether subjects consumed placebo or CHO during exercise or recovery. However, an 18-h interval was sufficient for full recovery of all immunoendocrine variables that we measured in our studies from the impact of two bouts of prolonged exercise.

Conclusion

Following the above discussion, the present review concludes: (1) In terms of immunity performing exercise in the morning compared with the identical exercise bout in the afternoon may be beneficial to maintain immunocompetence since a smaller perturbation in leukocyte trafficking into the circulation was observed, which may be due to lower HPA activation and circadian rhythms. However, there was no effect of time of day on salivary responses to exercise. (2) The second compared with the first of two bouts of prolonged exercise on the same day induceed a greater HPA activation, a larger leukocyte trafficking into the circulation, and a greater fall in neutrophil function and a lower saliva flow rate; but did not increase plasma IL-6, or change sIgA secretion rate. (3) Furthermore, CHO ingestion during any period of two bouts of prolonged exercise showed limited beneficial effect to blunt these higher responses in the second exercise bout compared with the first identical exercise bout on the same day. When two bouts of exercise were performed on the same day, the greatest benefit in terms of circulating immunoendocrine responses was obtained by feeding CHO at the earliest opportunity. (4) A 3-h interval was insufficient for recovery of leukocyte mobilisation and neutrophil function from the impact of previous exercise whether subjects consumed placebo or CHO during exercise or recovery. However, an 18-h interval appeared sufficient for full recovery of immunoendocrine variables from the impact of two bouts of prolonged exercise.

Table 3 The immunoendocrine responses during recovery interval after two bouts of prolonged exercise

Parameters (References)	**NON-CHO-3** (Li & Gleeson, 2004b, 2004c)	**CHO-REC-3** (Li & Gleeson, 2004a, 2005a)	**CHO-EX1-3** (Li & Gleeson, 2005a, 2006)	**CHO-EX2-3** (Li & Gleeson, 2005a, 2005b)	**CHO-EX2-18** (Li & Gleeson, 2005a, 2005b)
Glucose	↔	↓↓	↓↓	↓	↔
IL-6	↑	↔	↔	↔	↔
Adrenaline	↔	---	---	↔	↔
ACTH	↓↓	↔	↔	↔	↔
Cortisol	↔	↓↓	↓↓	↔	↔
GH	↔	↔	↔	↔	↔
Leukocyte count	↑↑	↑↑	↑↑	↑↑	↔
Neutrophil count	↑↑	↑↑	↑↑	↑↑	↔
Lymphocyte count	↔	↓	↔	↔	↔
Monocyte count	↑↑	↑↑	↑↑	↑↑	↔
Degranulation per neutrophil	↓↓	↔	↔	↓	↔
Oxidative burst per neutrophil	---	---	↓	↓	↔
Saliva flow rate	↔	↔	↔	↔	↔
sIgA concentration	↔	↔	↔	↔	↔
sIgA secretion rate	↔	↔	↔	↔	↔

NON-CHO-3: The immunoendocrine responses at 3 h after the first of two bouts of prolonged exercise without CHO supplementation; CHO-REC-3: The immunoendocrine responses at 3 h after the first of two bouts of prolonged exercise with CHO supplementation during the recovery interval; CHO-EX1-3: The immunoendocrine responses at 3 h after the first of two bouts of prolonged exercise with CHO supplementation during EX1; CHO-EX2-3: The immunoendocrine responses at 3 h after the second of two bouts of prolonged exercise with CHO supplementation during EX2; CHO-EX2-18: The immunoendocrine responses at 18 h after the second of two bouts of prolonged exercise with CHO supplementation during EX2.

Significantly higher than pre-EX1 (↑ $p<.05$, ↑↑ $p<.01$); significantly lower than pre-EX1 (↓ $p<.05$, ↓↓ $p<.01$); ↔ similar from pre-EX1.

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單日重複性運動暨碳水化合物補充對免疫內分泌之影響

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摘要

單日重複性長時間運動暨不同時段運動對免疫系統之影響仍有待釐清。本綜評旨在探討單日重複性運動暨碳水化合物補充對人體免疫內分泌之影響。統整分析相關文獻後，獲致下列結語：一、在下午時段從事單次長時間運動較上午時段從事相同之運動引發更多之白血球再分配現象，其原因可能是受到較大之丘腦下部-腦垂體-腎上腺（hypothalamic-pituitary-adrenal, HPA）激活和週期性節律（circadian rhythms）之影響；但不同時段運動似乎不影響黏膜免疫（唾液免疫球蛋白 A）反應。二、單日重複長時間運動之第二次運動較第一次運動引發更大之 HPA 反應、更多之白血球移轉至循環、更嚴重之嗜中性球功能下降；但未進一步增加血漿介白素-6（interleukine-6）或改變唾液免疫球蛋白 A 之分泌速率。三、在單日重複長時間運動之任何時段補充碳水化合物對於減緩第二次運動引發（相較於第一次）更大免疫內分泌反應之效果有限；然而，越早補充碳水化合物，延緩效果越好。四、長時間運動後休息 3 小時，不足以讓白血球移轉和嗜中性球功能充分恢復，不論運動者在運動中或恢復期是否補充碳水化合物；但休息 18 小時則已足夠。

關鍵詞：重複性運動、白血球再分配、嗜中性球功能、壓力激素、碳水化合物補充