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The effects of vaccine timing on the efficacy of an acute eccentric exercise intervention on the immune response to an influenza vaccine in young adults

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ABSTRACT

An acute bout of exercise prior to vaccination can improve the antibody and cell-mediated responses to influenza vaccination. The mechanisms underpinning this adjuvant effect remain unclear, and further investigation to determine the optimal exercise protocol is warranted. The aim of the current study was to determine whether exercise augmented the immune response to vaccination, and whether the timing of exercise relative to vaccination affected the efficacy of the intervention. One hundred and fifty-six (76 men) healthy participants were randomly assigned to a control group or one of three intervention groups who exercised immediately, 6 h or 48 h prior to administration of a standard trivalent influenza vaccine. The exercise groups performed 50 repetitions of the eccentric portion of both the bicep curl and lateral raise movements at an intensity eliciting 85% of each participant's pre-determined concentric one repetition maxima. Antigen-specific serum antibody titres were measured at baseline and 28 days post-vaccination as indicators of the humoral response. All three viral strains elicited strong antibody responses; however, eccentric exercise did not further augment any antibody responses compared to the control group. Cell-mediated immunity at 28 days post-vaccination was determined by measuring the IFN-γ response to *in vitro* stimulation of the blood with whole vaccine. There were no differences in cell-mediated immunity among the groups. Although these null findings were unexpected, they are consistent with previous research showing that exercise-induced immunoenhancement was only observed when the control group had relatively poor responses. In conclusion, it is likely that the robust immune responses to the vaccine observed in this study may have limited any further immune enhancement by exercise.

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1. Introduction

Influenza is a major cause of morbidity and mortality resulting in the death of up to half a million people annually worldwide (WHO Influenza Position Paper, 2005). Vaccination is used to reduce the incidence of influenza infection but, as yet, is only effective at preventing illness in approximately two-thirds of the population (Villari et al., 2004). Low efficacy rates have prompted further research into the role of adjuvants that may enhance the immune response to vaccination (Aguilar and Rodriguez, 2007). In addition to the studies investigating exogenous adjuvants, research has begun examine the potential role of behaviourally-induced, endogenous adjuvants (Edwards et al., 2007b). For example, acute stress exposure prior to immunization has been shown to improve both humoral (Millan et al., 1996; Persoons et al., 1995; Silberman et al., 2003; Wood et al., 1993) and cell-mediated immunity in rodents (Blecha et al., 1982; Dhabhar and McEwen, 1996, 1997, 1999; Saint-Mezard et al., 2003, 2004).

Adjuvant effects of acute psychological stress and exercise have also been demonstrated in humans (Edwards et al., 2006, 2007a, 2008). For example, acute stress improved the antibody response to influenza vaccination in women (Edwards et al., 2006). In order to maximise the potential adjuvant effect of the acute exercise intervention, a resistance-based, eccentric exercise protocol was developed (Edwards et al., 2007a). During an eccentric contraction, the exercising muscle applies continuous force as it lengthens, causing damage to the internal structure of the muscle fibres (Proske and Morgan, 2001). This damage is greater than that ob-

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served with concentric (shortening) muscle contractions (Sorichter et al., 1999) and, in untrained individuals, leads to an inflammatory response in the muscle (Sorichter et al., 2006). For example, exercise elevates the levels of inflammatory mediators released from stressed cells within the damaged muscle tissue (Peake et al., 2005). Numerous cytokines are also released, and may play a role in augmenting immune interactions (Peake et al., 2005). Therefore, it possible that eccentric exercise, performed using the muscles located at the site of vaccine administration, improves the subsequent immune response by inducing a pro-inflammatory environment in the muscles. In support of this theory, the extent of the self-reported pain and the change in upper arm limb circumference following eccentric exercise, both indirect indicators of muscle damage, were significantly positively correlated with the subsequent cell-mediated immune response to the vaccination (Edwards, et al., 2007a).

In light of these promising findings, it is important to improve the exercise intervention further to achieve the maximum adjuvant effect possible. One factor that can be manipulated is the timing of the exercise relative to the vaccination. Within the local muscle tissue, the complex inflammatory response to muscle damage evokes a number of changes, occurring almost immediately after the onset of muscle damage, and lasting up to 7 days post-exercise (Peake et al., 2005). Therefore, a number of different timepoints in the post-exercise recovery period may provide the optimal environment for enhancing the immune response to vaccination. As well as having clear implications for future clinical applications of such an intervention, a timing manipulation may also help elucidate the mechanisms underlying the exercise-induced augmentation of vaccine responses.

Previously, an augmented vaccine response was successfully induced using a protocol in which participants were vaccinated 6 h post-exercise (Edwards et al., 2007a,b). This timepoint was selected to coincide with the peak response of the cytokine interleukin-6 (IL-6) to eccentric exercise (MacIntyre et al., 2001). High levels of IL-6 are associated with stronger antibody responses to live *Francisella tularensis* vaccination in humans (Krakauer, 1995) and co-administration of plasmids encoding IL-6 has been shown to enhance influenza vaccine efficacy in mice (Krakauer, 1995; Lee et al., 1999). Further, the extent of the antibody response to the A/Panama strain was positively correlated with the IL-6 response to the acute stress tasks (Edwards et al., 2006). Given these findings, the current study also included a group vaccinated 6 h post-exercise to coincide with a predicted peak in IL-6.

It is also important to include a group vaccinated at the point of peak muscle damage, as this is a key process that could underlie the eccentric exercise-induced augmentation of antibody responses. Peak muscle damage, defined by pain, swelling, loss of muscle function and the production of creatine kinase, is delayed after exercise cessation (Sorichter et al., 1999). At approximately 48 h post-exercise, there is a peak accumulation of inflammatory infiltrate comprised of cellular (e.g. neutrophils and mononuclear cells) (Fielding et al., 1993) and secreted (e.g. cytokines, heat shock proteins, uric acid) (Peake et al., 2005) factors. We propose that this heightened inflammatory environment may enhance antigenic recognition and clearance at the site of muscle damage. Therefore, in the current study, a second group were vaccinated 48 h after exercise.

Finally, a group were vaccinated immediately after exercise. From a pragmatic perspective, this would simplify any future clinical application of this intervention. There were also sound theoretical reasons to hypothesise that this might be effective. It has been hypothesised that a redistribution of immune cells (Kruger et al., 2008), and subsequent demargination into sites of tissue damage immediately following stress, may be one of the principle mechanisms behind the acute-stress immunoenhancement hypothesis (Dhabhar et al., 1995). Further, there is evidence that muscular contractions are associated with a short term increase in lymphatic drainage of the exercised muscle (Havas et al., 1997) which could subsequently enhance immune cell transport to and from the site of antigen administration (Swartz et al., 2008). As such, a third exercise group were vaccinated immediately post-exercise in the current study.

In summary, three exercise groups (immediate, 6 h, 48 h post-exercise) were compared to a non-exercising control group, in terms of their humoral and cell-mediated responses to influenza vaccination. We hypothesised that the exercise groups would show augmented immune responses to the influenza vaccine in comparison to the control group, and that the timing of vaccination would influence the efficacy of the exercise intervention.

2. Methods

2.1. Participants

One hundred and fifty-six healthy students (76 men, 80 women) at the University of Birmingham were recruited, and 155 completed the study (mean ± SD; age: 20.38 ± 2.35 years; body mass index: 22.82 ± 2.89 kg/m^2). None of the participants had received the influenza vaccine in the past year and none had reported influenza-like illness in the year prior to participation. Exclusion criteria included smoking, a history of immune or cardiovascular disease, current acute infection or illness, pregnancy or suspected pregnancy, and a history of vaccine-related allergies or side effects. Use of prescription medication within one month of participation was also an important exclusion criterion; but females taking the contraceptive pill were not excluded. In addition, none of the participants reported having performed any resistance training in the 6 months prior to testing. All participants were instructed to abstain from vigorous exercise and over-the-counter medication for at least 24 h, alcohol for at least 12 h, and food or caffeine for at least 2 h prior to each session. All participants provided written informed consent and the study protocol was approved by the Black Country Local Research Ethics Committee. All participants were paid £30 or given research credits upon completion of the study.

2.2. Procedure

Participants were pseudo-randomised, maintaining an even sex distribution, into one of four groups: immediate exercise group (n = 38), 6 h exercise group (n = 39), 48 h exercise group (n = 39) or a resting control group (n = 39). Groups did not differ for stressful life events exposure, perceived stress and health behaviours (data not reported here); these factors have been associated with the extent of antibody responses (Burns et al., 2003; Cohen et al., 2001). In the first session, baseline blood samples were taken, from an antecubital vein in the dominant arm, following a 20 min rest period. Participants then had height and weight measured, and a test of maximum muscle strength was conducted. In the second session, they completed either the eccentric exercise task (exercise groups) or remained quietly resting for 25 min (control group). Participants then returned to the laboratory at varying times, depending on group allocation, for session three; the resting control group received the vaccine immediately after task completion. During this session, a nurse administered the 2007/2008 northern hemisphere influenza vaccine (Inactivated Split Virion BP, Sanofi Pasteur MSD, Batch No. B9676-1) via intra-muscular injection into the deltoid muscle of the non-dominant arm. Participants returned to the laboratory at 28 days post-vaccination to provide blood samples for antibody and cell-mediated immunity measurement.

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