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Editorials

Is exercise bad for the immune system?

It is probably not too surprising, in this age of contradictory health information, that something we once understood as being fairly obvious, the beneficial effects of exercise, has now been called into question. A review of the scientific literature reveals seemingly paradoxical reports on the effect of exercise on the immune system (Rowbottom and Green 2000). This is due, in part, to the fact that the effects of exercise on the immune system are complex and dependent upon several factors, including 1) the immune function or characteristic being analysed; 2) the intensity, duration and chronicity of exercise; and 3) the timing of the measurement of immune function in relation to the exercise bout (Woods *et al.* 1999; Mackinnon 2000). Perhaps the general conclusion that one can draw is that moderate exercise enhances immune responses, while prolonged and intensive exertion causes various decrements in immune function (Peters 1997; Nieman 2001). It is also clear that the physiological and immunological consequences of intensive exercise parallel the effect of other physical and psychological stressors (Pedersen and Hoffman-Goetz 2000; Clow and Hucklebridge 2001). But do these changes in immunological function measured *in vitro* correlate with increased susceptibility to disease *in vivo*? It has been suggested that impaired immune status following strenuous exercise may open a window of susceptibility to infectious agents (Perna *et al.* 1997). Indeed, several epidemiological surveys have now confirmed an increased incidence of upper respiratory tract infection symptoms in human athletes following participation in high intensity events, such as marathon races (Nieman 1994; Peters 1997; Kohut *et al.* 2001). While alterations in various *in vitro* immunological indices accompany this effect, the precise mechanism responsible for the increase in disease remains uncertain and is an area of continuing investigation (Bishop *et al.* 1999; Moseley 2000; Ostrowski *et al.* 2001).

Can we extend these findings to the horse? There have been a number of reports over the years that exercised horses exhibit alterations in various components of their immune responses (Rossdale *et al.* 1982; Snow *et al.* 1983; Kurcz *et al.* 1988; Wong *et al.* 1992; Keadle *et al.* 1993; Horohov *et al.* 1999; Raidal *et al.* 2000a; Folsom *et al.* 2001; Nesse *et al.* 2002), including a paper by Robson and colleagues in this issue (p 133). How exercise affects the horse's immune system appears to depend likewise upon the immune function being analysed, duration and intensity of exercise and timing of the measurement relative to the exercise. Most investigations on the effect of exercise on immune function have focused on the innate immune response in both horse and man (Hines *et al.* 1996; Nehlsen-Cannarella 1998). These initial responses to pathogens play a central role in disease resistance and the development of subsequent adaptive or specific immune responses. The innate immune response includes both cellular and humoral components, although most studies on the effect of exercise on this response have focused on the cellular components, namely neutrophil and natural killer (NK) cell function. Single bouts of moderate to intensive exercise are associated with an initial increase in NK cell function (Pedersen and Ullum 1994; Shephard *et al.* 1994; Horohov *et al.* 1996) and transiently impaired neutrophil antimicrobial functions in both horse and man (Wong *et al.* 1992; Pyne 1994). High intensity training has been associated with a general reduction in neutrophil function in both species (Smith and Pyne 1997; Raidal *et al.* 2000b). Endurance racing is likewise associated with changes in neutrophil function in both man and horse (Jensen-Waern *et al.* 1999; Robson *et al.* 2003). Similar effects of intensive exercise on bronchoalveolar macrophage function is also seen in horses (Wong *et al.* 1990; Raidal *et al.* 2000a), although in mice, there appears to be an enhancement of macrophage function following an exercise challenge (Su *et al.* 2001). As such, these studies indicate that equine innate immune responses, like those of man, can be adversely affected by intensive exercise.

While the effect of exercise on innate immune function is fairly uniform, its effect on specific immune response is more complex. Prolonged periods of intense training leads to an impairment of mucosal immunoglobulin levels in man (Tomasi *et al.* 1982; Pyne and Gleeson 1998; Gleeson *et al.* 2000; Mackinnon 2000). Unfortunately, there are no data on the effect of exercise on total serum or mucosal immunoglobulin levels in the horse, although recently we have reported no significant difference in anti-influenza virus antibody titres between exercised and rested ponies (Folsom *et al.* 2001). Actively exercising horses and human subjects produce similar levels of antibodies following vaccination as compared to unexercised controls (Gleeson 2000; Lunn *et al.* 2001); however, cell-mediated immunity following vaccination may be impaired (Bruunsgaard *et al.* 1997; Nielsen and Pedersen 1997; Folsom *et al.* 2001).

While much of our information regarding the adverse effect of exercise on equine immune function has been gathered from studies using treadmill-based exercise protocols (Wong *et al.* 1992; Keadle *et al.* 1993; Horohov *et al.* 1999; Raidal *et al.* 2000b), similar results have been obtained using samples collected from horses participating in racing (Snow *et al.* 1983; Nesse *et al.* 2002) and endurance riding events (Jensen-Waern *et al.* 1999). Similar to the human athlete experience (Woods *et al.* 1999), exercise-induced immune deviation in the horse also depends upon the intensity of the exercise. Therefore, relatively low intensity treadmill-based exercise is associated with little change in innate or adaptive immune responses, whereas high intensity exercise is associated with alterations in both innate and adaptive immunity (Horohov *et al.* 1999; Raidal *et al.* 2000a).

There are, therefore, clear parallels to the human experience. Nevertheless the central question remains, does exercise lead to increased susceptibility of horses to bacterial and viral infections? The marked susceptibility of racehorses to respiratory infections is widely recognized (Burrell *et al.* 1996; Morley *et al.* 2000a; Racklyeft *et al.* 2000). The reasons for this increased susceptibility remain unknown although probably include the immune status of the susceptible population as well as exposure to infected individuals (Christley *et al.* 2000; Morley *et al.* 2000b). Interestingly, a recent history of vaccination is not necessarily associated with a reduction in disease risk (Morley *et al.* 2000b). The possibility of training or racing schedules affecting the incidence of disease has not been widely considered (Christley *et al.* 2000). In a recent study, using a treadmill-based exercise protocol, it was shown that vaccinated ponies subjected to high intensity exercise were susceptible to influenza virus infection while nonexercised controls were protected (Folsom *et al.* 2001). This increased susceptibility was associated with alterations in the *in vitro* cell-mediated immune response to the virus (Folsom *et al.* 2001). Could a similar alteration in immune function account for influenza infections in vaccinated racehorses? Do alterations in neutrophil function likewise leave horses susceptible to bacterial infections? While there is little information currently available to support these concerns, the experience from human sports medicine indicates that there could be a similar window of vulnerability in our equine athletes.

Assuming that there is an association between exercise-induced immune suppression and increased incidence of respiratory disease in the horse, what can be done? The underlying mechanisms responsible for exercise-induced changes in immune function are poorly understood, but probably include neuroendocrinological and metabolic factors (Pedersen and Toft 2000). The working muscles or motor centres modify the response of the glands of the endocrine system, either directly via pituitary hormones or indirectly via the sympathoadrenal system. The secretion of pituitary hormones result in a reduction in the plasma concentration of insulin and a rise in virtually all other hormones including cortisol (Lucke and Hall 1980; Snow and Rose 1981; Thornton 1985; Hyyppa and Poso 1998; Caloni *et al.* 1999). Indeed, plasma cortisol response appears to be best correlated with both the duration and intensity of exercise as well as alterations in immune function in horses (Lassourd *et al.* 1996; Golland *et al.* 1999; Horohov *et al.* 1999; Nagata *et al.* 1999) and man (Suzuki *et al.* 2000). While the immunomodulatory effects of corticosteroids are widely known, it does not appear likely that cortisol alone is responsible for exercise-induced immune deviation, although it may be responsible for maintaining lymphopenia and neutrocytosis after exercise of long duration (Pedersen *et al.* 1997). Other possible mechanisms of exercise-induced immunomodulation include the so-called glutamine hypothesis which is based on the fact that physical activity directly affects the availability of glutamine and may therefore influence immune responses, since lymphocytes are dependent on glutamine for optimal growth (Pedersen *et al.* 1997). A similar case may also be made for other amino acids, vitamins, minerals and micronutrients (Cynober 2001; Nieman 2001). However, neither glutamine nor any other dietary supplements, with the possible exception of carbohydrate supplementation, has emerged as an effective countermeasure to exercise-induced immunosuppression in human athletes (Cynober 2001; Nieman 2001). Increased carbohydrate ingestion was associated with an attenuated cortisol, growth hormone, and epinephrine response and fewer perturbations in immune function (Nieman 2001). While dietary manipulation has been widely recognised as a means to meet the energetic needs of the equine athlete (Lawrence *et al.* 1993; Hintz 1994), the possible effect of diet on immunocompetency in the exercising horse has not yet been addressed.

While our understanding of the effect of exercise on the equine immune system is improving, a number of issues remain unresolved including the *in vivo* significance of some of the *in vitro* findings. Further work defining the mechanism and long-term consequences of exercise-induced immune modulation is needed before specific changes in current training or vaccination programmes may be contemplated. Nevertheless, evidence from the human literature indicates that such efforts could prove useful in protecting the health and welfare of the equine athlete.

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