

Spinal cord injury: Known and possible influences on the immune response to exercise

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ABSTRACT

A spinal cord injury (SCI) can increase the risk of infection by impacting on many aspects of immune function; one particularly well-documented observation is a reduction in lymphocyte numbers. The vast majority of lymphoid cells express adrenergic receptors. Therefore, autonomic function loss and concomitant alterations in resting and post-exercise catecholamine concentrations, particularly so in individuals with a tetraplegia, may impact directly on immune cells and depress immunity. Other factors are further likely to contribute, examples including altered muscular, endocrine and cardiovascular function following SCI. However, some alterations, such as increases in natural killer cell cytotoxicity following exercise in those with a tetraplegia, are unrelated to the catecholamine response. Likewise, mucosal immunity in individuals with a tetraplegia appears to be similarly influenced by exercise as in the able-bodied population. Indeed, rehabilitation therapy and exercise can increase some measures of immunity and autonomic function in those with an SCI. It is therefore possible that compensatory mechanisms offset disability-related detriments. This may be by way of sympathetic reflex activity, receptor hypersensitivity, or parasympathetic and neuroendocrine adjustments. Future work needs to explore these mechanisms further to clarify the implications of an SCI on the immune response to exercise and susceptibility to infection.

In this article, we review the impacts of an SCI on immune, and specifically, exercise immune function. The relevant anatomical and physiological foundations of the immune system are first briefly laid out in order to understand the potential impacts of neural and neuroendocrine dysfunction on the immune system. With the limited number of human studies available, we have then aimed specifically to gather all relevant existing literature on exercise immunology in individuals with an SCI in patient, recreationally active and athlete populations. We believe that an understanding of the impacts of exercise can provide a tool to help maintain or improve health in individuals with an SCI.

A comprehensive literature search was conducted using the search engines PubMed, SPORTDiscus, Web of Science and Zetoc, search period June 2012 – February 2013. Key words employed included spinal cord injury, immunology, exercise, paraplegic, tetraplegic, upper body exercise, interleukin, immunoglobulin, sympathetic, and parasympathetic. All articles and articles derived from their reference lists were checked for their suitability.

Key words: Catecholamines, cytokines, natural killer cells, autonomic nervous system, mucosal immunity

1 INTRODUCTION

An SCI increases the risk of infection, and complications from infection are among the leading causes of re-hospitalization and death in the post-acute phase

following SCI (12, 76). Specifically, pneumonia, influenza, or other respiratory complications accounted for the majority of deaths in a large scale study conducted on 886 individuals with SCI between 1943 and 1990 (22). Heightened infection and illness susceptibility are acknowledged sequelae of acute, subacute and chronic SCI that challenge the activity, satisfaction, productivity, and health of its survivors (59). Apart from the deleterious consequences for the suffering individual, there are economic consequences and strain on health care providers.

Therapeutic exercise for individuals with SCI is actively encouraged and interest in wheelchair sports is increasing, particularly with the legacy of the London 2012 Paralympic Games. The advancements in wheelchair design (1), combined with greater funding opportunities and sports professionalism have resulted in a greater number of wheelchair athletes performing on recreational (36) and professional levels (31); likewise, the quality of the sports performance has improved. This is supported by analysis of objective markers of physical performance by both sports scientists and coaching support staff, which, when investigating peak oxygen uptake as an example, has increased around two-fold within 30 years (32, 38).

The able-bodied literature reports a higher prevalence of symptoms of respiratory illness in athletic than non-athletic populations, with a marked number of these infectious in nature (16, 77), which underlines the practical importance to analyse immune function in athletes with an SCI. Understanding the influence of exercise on immune functions is potentially critical for the management of infections in individuals with SCI, given the substantial impacts of exercise on immune functions (87). Furthermore, from a mechanistic point of view, SCI provides exercise immunologists with an ideal *in vivo* model with which to investigate the influences of the autonomic nervous system on the immune response to exercise.

2 PHYSIOLOGICAL BACKGROUND: COMMUNICATION BETWEEN THE IMMUNE SYSTEM AND THE BRAIN

2.1 Role of the autonomic nervous system

The central nervous system receives messages from the immune system and, vice versa, messages from the brain modulate immune functions (21). Some of these unconscious actions are modulated by the autonomic nervous system. Moynihan *et al.* (57) and Elenkov *et al.* (21) summarize three lines of evidence supporting sympathetic nervous system (SNS) involvement in immune regulation:

1. Lymphoid organs are innervated by sympathetic noradrenergic nerve fibres.
2. The vast majority of lymphoid cells express adrenergic receptors.
3. Noradrenaline, an important neurotransmitter of sympathetic nerves, is released in lymphoid organs following immunization.

The rapid, “real-time” brain control of innate immune mechanisms underlying inflammation is thought to be based on autonomic neuronal projections to sites of inflammation (65). Evidence accumulated in the last decades indicates that,

peripherally, both noradrenaline released from the non-synaptic sympathetic nerve terminals and adrenaline (and to a lesser extent, noradrenaline) released from the adrenal medulla are involved in immunomodulation (21), resulting in both activation and suppression of immune parameters (Table 1).

Table 1: Evidence of catecholamine action on immune cells.

References	Findings
Kappel <i>et al.</i> , 1991; Tonnesen <i>et al.</i> , 1987	Natural killer cell activity is increased following both infusion of adrenaline and exercise, which naturally increases catecholamine concentration.
Keller <i>et al.</i> , 1983	Stress-induced lymphopenia is adrenal-dependent: adrenaline correlates inversely with lymphocyte number, as shown in animal stress experiments (stressor: electrical shocks).
Landmann <i>et al.</i> , 1984	Even moderate physical stress (15 min, increasing up to 75% of maximum power output) results in an increase of adrenaline, which correlates negatively with the $T_{\text{helper}}/T_{\text{suppressor}}$ cell ratio. These authors suggest that adrenaline plays a role in the mobilisation of immunocompetent cells and may lead to a distribution pattern favouring immunosuppression during stress.
Nash, 1994	Adrenaline administration causes a transitory leuko- and monocytosis. Sympathectomy can lead to decreases in natural killer cell cytotoxicity, and reduce the $T_{\text{cytolytic}}/T_{\text{suppressor}}$ cell ratio and B cell numbers.
McHale & Thornbury, 1990	Sympathetic nerve stimulation increases lymphocyte output in anaesthetised sheep.

In addition to the sympathetic strand of the autonomic nervous system, efferent fibres of the vagus nerves are involved in immune responses. For example, they inhibit the release of pro-inflammatory cytokines and regulate inflammation, coining the term cholinergic anti-inflammatory pathway (65). Experimentally, peripheral vagus nerve stimulation in vagotomized rats prevents the development of acute inflammation (6). The importance of intact innervation on immune control is also evident in humans, as denervated skin has a greatly reduced leukocyte infiltration following local damage, which is associated with a ~70% reduction in the rate of wound healing compared with normal skin (20). In chronic SCI, it has further been suggested that those with low fibronectin levels may present impaired wound healing, whilst lower zinc levels have been found in those presenting pressure ulcers (17).

Salivary glands are involved in the defence of the mucosa, and salivary secretory immunoglobulin A (SIgA) is the predominant immunoglobulin in saliva. It plays an important role in mucosal immunity and has therefore been described as “first line of defence” against pathogens and antigens presented at the mucosa, such as cold-causing viruses (4, 87). In analogy to immune cells as described above, salivary glands are innervated by autonomic nerve fibres. These originate from the upper thoracic segments, although it remains unclear precisely where in this region (69). In rats, sympathectomy results in a decreased SIgA secretion (70). Conversely, both parasympathetic and sympathetic stimulation of rat salivary glands can increase salivary gland blood flow, saliva flow rate, and SIgA secretion (13, 14, 69). Similarly, infusion of sympathetic and parasympathetic agonists can increase SIgA secretion rate (71).

The autonomic nervous system is not only involved in the execution of immune responses, but has also a sensory component. Afferent vagus nerve fibres rapidly signal the brain to trigger immunomodulatory responses in the early phases of inflammation (65). Peripheral sensory nerves are further part of reflex pathways to contribute to proinflammatory function, which includes vasodilation and mast cell activation (20). These reflex pathways consist of sensory receptors, afferent pathways, integration centers in the central nervous system, efferent pathways, and effector organs (29). Reflex pathways may also be activated by causes other than injury or inflammation; for example, they are involved during static muscle contraction, which increases adrenal sympathetic nerve activity in rats (86).

2.2 Role of humoral factors

In addition to the neural pathways, humoral factors are involved in the communication between the brain and the immune system. One pathway that has been explored extensively is the hypothalamus-pituitary-adrenal (HPA) axis, where adrenocorticotrophic hormone (ACTH) released from the pituitary stimulates glucocorticoid secretion in the adrenal gland (30, 65). One of the most prominent glucocorticoids is cortisol, with generally immunosuppressive and anti-inflammatory effects (21). Importantly, humoral feedback mechanisms can inform the brain on immunologic actions in the body, and hence, modify its behaviour. For example, cytokines and other soluble factors secreted in response to infection or inflammation (such as the tumour necrosis factor, TNF- α), produced by immune cells, do not only attract and modulate other immune cells locally, but can act on sensory neurons or the brain directly. In the context of this review, it is important to note that not only immune cells can trigger a cascade of immune actions, also cytokines released by working muscle (myokines) in response to exercise are capable of triggering an immunologic response (67).

3 SPINAL CORD INJURY: IMPACTS ON AUTONOMIC FUNCTION

As outlined above, an important route of communication between the brain and the immune system is via autonomic pathways descending the spinal cord. Given that sympathetic neurons exit the spinal cord at the thoracic (T) and high lumbar (L) level (T1-L2) (29, 49), a complete SCI at the T level (resulting in paraplegia) partly interrupts sympathetic pathways, while a complete cervical SCI (resulting in tetraplegia) completely abolishes sympathetic communication between brain and effector cells/organs (Fig. 1). Autopsy findings in patients with cervical SCI show a marked loss of axons in the dorsal aspects of the lateral funiculus, which is thought to be the location of the descending vasomotor pathways (29). Only injuries below L1 have minimal effects of SNS dysregulation (29). Hence, sympathetically governed function is impaired in individuals with a tetraplegia (TETRA), and one obvious observation in a sporting context includes the reduced maximum heart rate, which is in the range of around 130 beats per minute in these individuals (3). Spinal segments T2 to T4 supply sweat glands of the head and neck, T2 to T8 of the upper limbs, T6 to T10 of the trunk, and T11 to L2 of the lower extremities (29), explaining the reduced ability to sweat in TETRA. Fur-

ther, basal systolic and diastolic blood pressure in TETRA is about 15 mm Hg lower than that in able-bodied subjects (29). This accompanies the loss of motor and sensory control below the level of lesion. These adaptations lead to reductions in peak oxygen uptake in TETRA, even though the fittest individuals with a complete tetraplegia still reach scores of over $30 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (51).

There is also evidence for an altered HPA axis function in SCI. Animal experiments show that an SCI acutely activates the HPA axis in mice, resulting in elevated circulating cortisol levels, even though cortisol returns to baseline values by 3 days post injury (54). It has been suggested that the acute trauma-induced activation of the HPA axis and the SNS (resulting in increased noradrenaline) axis helps prevent pathological autoimmune reactions, or prevents hyperactivation of

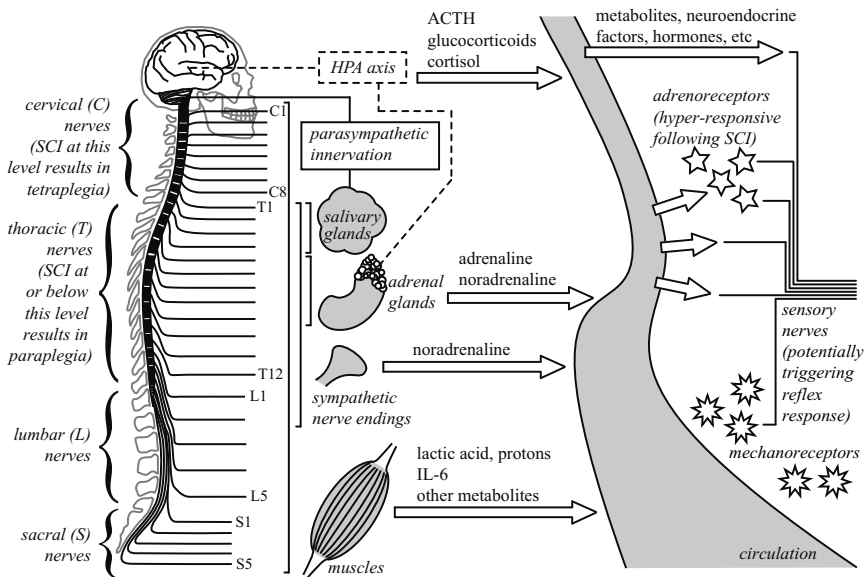


Figure 1: Anatomical and physiological basis for immunomodulatory processes potentially influenced by a spinal cord injury and/or exercise. For glands, sympathetic nerve endings and muscles, the origin of their nerves is shown. ACTH, adrenocorticotropic hormone; HPA, hypothalamus pituitary adrenal; IL-6, immunoglobulin-6; SCI, spinal cord injury.

the immune system (55). In chronic SCI, a number of studies in humans document an altered pattern of markers of the HPA axis (8, 37, 48, 89), discussed in detail in section 4.1.

4 SPINAL CORD INJURY: IMMUNE FUNCTION AND THE IMPACTS OF EXERCISE

The section above shows that individuals with an SCI present altered autonomic control due to a dysfunctional SNS and, potentially, an altered HPA axis, two sys-

tems which are known to regulate immune responses. It is therefore legitimate to assume that this is one of the reasons for the increased infection risk in SCI and has led researchers to measure markers of immune function, the autonomic nervous system and/or the HPA axis in a range of contexts. Immune responses have initially been investigated in resting conditions in individuals with an SCI. However, the amount of research on exercise immune function has grown steadily in recent years, not least as the association between resting immune dysfunction and low levels of fitness in persons without SCI (60) implies a negative influence of a sedentary lifestyle. Consequently, exercise has been suggested already two decades ago to be one intervention to reverse the negative immune alterations in TETRA (11).

4.1 Cortisol

4.1.1 Resting responses

Even though adaptations after an SCI include an increase in cortisol immediately after injury, urinary free cortisol concentration falls in normal range after 6 months post injury (17, 46). Kliesch et al. (46) further found a positive association between ACTH and cortisol in TETRA and in individuals with a paraplegia (PARA), indicating the normal function of the HPA axis despite an SCI. This work confirms the endocrine nature of ACTH action on cortisol secretion without the need of “hard-wired” neuronal mechanisms. Other researchers found a normal circadian rhythm of plasma cortisol concentration in TETRA, which further supports the concept of normal HPA axis function in this population (90).

However, there is evidence of a disturbed HPA axis following SCI, as indicated by elevated resting plasma cortisol levels in TETRA and PARA when compared with able-bodied controls, despite no differences in plasma ACTH (8). An impaired cortisol response to a corticotropin-releasing hormone (CRH) bolus in TETRA and PARA has further been observed (37). It must be noted, though, that this external CRH administration may cause a different response when compared with physiological changes of influencing metabolites, as, for example, found following exercise. The researchers of this project indeed point out that non-CRH or non-ACTH-dependent pathways may exist and compensate for their suggested HPA axis dysfunction in patients with an SCI (37).

4.1.2 Exercise responses

The plasma cortisol concentration in athletic TETRA is increased following strenuous exercise, such as simulated race conditions (88). Some studies suggest a minimal exercise duration required for cortisol concentration to change. A full marathon (26) increases plasma cortisol concentration in PARA, whereas a half-marathon does not alter plasma cortisol levels in either TETRA and PARA (2, 27). However, this contrasts other reports where increases in cortisol have been observed after exercise durations as little as 20 minutes (15, 48). The similar rise in plasma cortisol following exercise between TETRA and able-bodied controls (15, 48) further support the concept that cortisol is mainly governed by the HPA axis, with no or only little contribution of the SNS. It has also been suggested that the myokine interleukin-6 (IL-6) may give rise to increased cortisol production

(30), as documented by plasma cortisol rises following IL-6 infusion (62, 79). It has been proposed that this may be by way of secretion modulation via a neuroendocrine-immune loop involving the HPA axis (68). However, IL-6 does not seem to be the main modulator of cortisol: Brief acute exercise increases plasma cortisol in TETRA, PARA and non-spinal cord injured individuals, yet IL-6 levels only increase in PARA and non-spinal cord injured individuals, but not in TETRA (64).

Recently, it has been suggested that one of the benefits of exercise is the creation of an anti-inflammatory environment (30). As exercise gives rise to a range of anti-inflammatory cytokines, it can reduce the “reactivity” of immune cells, for example by downregulating TOLL-like receptor expression on immune cells. Exercise can also reduce fat mass, itself a producer of inflammatory agents (30). Cortisol, with its potent anti-inflammatory effects, has been shown to remain elevated for longer following exercise in TETRA when compared with able-bodied controls (48, 89) thus creating an anti-inflammatory environment for a longer duration. Again, this may be because of secretion modulation via a neuroendocrine-immune loop involving the HPA axis (68), which may be altered in TETRA.

4.2 Catecholamines

Sympathetic neurons exit the spinal cord between T1 and L2 (29, 49), and the majority of sympathetic neurons innervating the adrenal medulla originate from T5-T9 (29). Unsurprisingly, due to the abolition of neural pathways to the adrenal gland and dysfunction of sympathetic pathways, catecholamine release is therefore affected in individuals with a high-level SCI.

Resting plasma catecholamine concentrations are lower in TETRA when compared with able-bodied individuals and controls with a low paraplegia, and the exercise-induced increase is smaller in TETRA (47, 73, 74) or not present at all (48, 89). Plasma adrenaline and noradrenaline remain unchanged in TETRA following simulated racing conditions (88) and graded exercise tests to exhaustion (23, 64, 88), and plasma adrenaline following a half marathon does not increase in TETRA, whereas it does increase in individuals with T4-L1 lesions (2). Individuals with a lesion in the T1-T6 area present a reduced catecholamine response to a graded exercise test to exhaustion when compared to those with a T7-T12 lesion (81). Serum noradrenaline is significantly elevated after exercise in both these groups, whereas adrenaline is only elevated in the T7-T12 group (81), underpinning the physiological relevance of intact adrenal gland innervation.

It is worth noting that in contrast to volitional exercise, exercise-induced increases in adrenaline and noradrenaline have been observed in both TETRA and PARA when electrically stimulating paralysed muscles, even though the relative increase to resting levels was lower than in able-bodied individuals (5). Spinal reflexes have been thought earlier to be the potential candidate for these catecholamine responses (5, 74). It therefore appears that despite the central abolition of neural pathways, ways remain to exert responses normally centrally governed by the SNS. Exploring methods to exert catecholamine responses in those with an impaired SNS could hence be a promising way to modulate and improve immune

function in this population. Catecholamines are known to exhibit both immunodepressive and -stimulating characteristics (Table 1). However, Nash (60) suggests that periods of autonomic dysreflexia in SCI with the concomitant catecholamine boost and spikes in circulating glucocorticoids may be primarily immunodepressive, creating a "window of opportunity" in which opportunistic infections ensue. It has been suggested that suppressed immune function following autonomic dysreflexia (due to lymphocyte apoptosis) may explain why individuals with high level SCI are at high risk for recurrent infections throughout their lifetime (55). Indeed, a number of articles compiled by Nash (60) show the relationship between repeated catecholamine overstimulation and depression of immune function. Nash (60) further points out that adrenergic stress in experimental animals suppresses lymphocyte mitogen proliferation and natural killer cell (NK) and phagocytic activity and diminishes interferon producing capacity, a pattern of immune irregularities nearly matching that of humans with SCI.

Table 2: Adaptations of cellular immunity following an SCI and effect of level of injury

References	Findings
Campagnolo <i>et al.</i> , 2000; Cruse <i>et al.</i> , 2000; Kliesch <i>et al.</i> , 1996	PARA below the T10 level exhibit normal NK cell cytotoxicity. It has hence been suggested that the effects of adrenal hormones and neurotransmitters on NK cell function represent critical targets for future investigation (17). Likewise, neutrophil phagocytic function is decreased in TETRA but not in PARA below the T10 level (9).
Campagnolo <i>et al.</i> , 1994; Campagnolo <i>et al.</i> , 2000	Despite depressed NK cell levels in SCI, no difference in leucocyte counts, but increases in T and T _{helper} cells in SCI.
Campagnolo <i>et al.</i> , 1994	Depressed lymphocyte proliferative response in TETRA when compared to AB controls.
Held <i>et al.</i> , 2010	Increased susceptibility to a virus load and reduced macrophage activation and virus-specific T cells that control virus replication in animal SCI models.
Ibarra <i>et al.</i> , 2007	The T cell response to mitogen and antibody titre to antigen is reduced in animals with a chronic SCI (both at the T1 and T12 level). The immunosuppressive effect on both T cell and antibody reactions is stronger and lasts longer in the case of high (T1 level) and severe contusions, which gives rise to a higher risk to develop infectious diseases.
Iversen <i>et al.</i> , 2000	Reduced immunoglobulin G levels in TETRA and PARA when compared to AB controls.

AB, able-bodied; NK, natural killer cell; PARA, individuals with a paraplegia; SCI, spinal cord injury; T, thoracic; TETRA, individuals with a tetraplegia.

4.3 Leukocytes

4.3.1 Resting responses

Animal experiments show that an SCI at the T3 level acutely reduces the antigen-specific immunoglobulin following vaccination, and reduces spleen weight, dendritic, B, and T cell numbers (54). In humans, a reduced NK count has been

reported in both TETRA (89) and PARA (60, 84). It has been proposed that the NK number depression in TETRA is due to a production problem in normally sympathetically innervated bone marrow (10). NK cytotoxicity can also show reductions in SCI, especially in high level SCI (above T6, affecting autonomic innervation), with NK cytotoxicity in TETRA being about 40-60% of normal (9-11, 40, 46, 61). Further dysfunction in SCI has been reported for a variety of other resting immune measures (Table 2).

4.3.2 Exercise responses

It seems that exercise does not destroy NKs; rather, they are temporarily relocated to reservoir sites such as the walls of peripheral veins in response to the exercise-induced secretion of catecholamines (87) - the concomitant downmodulation of adhesion molecules releases them into the circulation (58). Since individuals with a high level SCI have an impaired sympatheticoadrenal activity, with lower catecholamine concentrations measured at rest and following exercise, these studies support the concept that catecholamines are responsible for recruitment of leukocytes to the circulation at rest and during exercise. Depressed leukocyte number elevation has also been demonstrated in persons without disability who exercise under beta-adrenergic blockade, underpinning this suggestion (78).

NK number and cytotoxicity and other aspects of immunity are influenced by acute exercise of various intensities and durations, and numerous studies have shown a depressed response in TETRA (Table 3). However, it has been shown early that rehabilitation therapy, including strength, endurance and mobility training, improves NK cytotoxicity in patient TETRA and PARA, whereas NK cytotoxicity stays at a low level in those not receiving therapy (46). Interestingly, increases in NK cytotoxicity in TETRA are unrelated to changes in NK number (2, 47, 89). Mechanisms other than catecholamine activation must be considered as responsible, as for example, NK cytotoxicity in both PARA and TETRA is elevated after a half-marathon despite no increases in adrenaline (2). It is hence possible that the altered, elevated cortisol response in TETRA (48, 89) modulates leukocyte function following exercise.

4.4 Cytokines

Appreciable numbers of individuals with SCI have abnormally high levels of pro-inflammatory cytokines whether or not they are symptomatic for infection. It is not surprising that these pro-inflammatory markers are further elevated in those with medical complications, such as urinary tract infection or pressure ulcers (18). Specifically, elevated plasma IL-6 concentrations and elevated soluble IL-2 receptor concentrations have been reported (60). Importantly, plasma IL-6 concentrations are related to reduced pulmonary function in SCI (28) and therefore may have some predictive power of health measures.

However, the manner of the acute cytokine response to strenuous exercise appears again to be lesion level dependent. Plasma IL-6 concentrations have been shown to increase in response to 20 minutes of upper body exercise (48) or a test to exhaustion (64) in PARA and AB, whereas it remains unaffected in TETRA (48, 64). It must be noted that IL-6 production is dependent on the duration of exer-

Table 3: Acute exercise effects on leukocyte number and activity in individuals with a spinal cord injury. Reported changes compare pre exercise with immediately after exercise values.

References	N	Impairment	Activity level	Exercise intervention	Immune measure	Change in immune measure
Banno <i>et al.</i> , 2012	6	TETRA (C6-C8)	recreational athletes	half marathon	NK cell number and cytotoxicity	number: no change (TETRA), 1.7-fold increase (PARA); cytotoxicity: 1.3-fold increase in both groups
	7	PARA (T5-L4)	recreational athletes		lymphocyte number leukocyte number	no change 1.8-fold increase in both groups
Furusawa <i>et al.</i> , 2003	7	PARA (T7-L1)	recreational athletes	half marathon	NK cell number and cytotoxicity lymphocyte number leukocyte number	number: no change, cytotoxicity: 1.2-fold increase no change 2-fold increase
	9	PARA (T5-T12)	elite athletes	marathon	NK cell number and cytotoxicity lymphocyte number leukocyte number	number: 2.4-fold decrease, cytotoxicity: 1.1-fold decrease no change 2.5-fold increase
Kawashima <i>et al.</i> , 2004	10	PARA (T5-T12)	patients	20 min orthotic gait exercise	NK cell number and cytotoxicity	number: no change, cytotoxicity: 1.4-fold increase
Klokner <i>et al.</i> , 1998	6	TETRA (C5-C7)	participating in on-going training programme	30 min functional electrical stimulation (maximal tolerable load for this duration)	NK cell number and cytotoxicity	number: no change (TETRA), 2-fold increase (PARA); cytotoxicity: increase in both groups (extent not stated)
	5	PARA (T4-T7)			lymphocyte number leukocyte number	increase in both groups (extent not stated) increase in both groups (extent not stated)
Kouda <i>et al.</i> , 2011	8	TETRA (C6-C7)	regularly active	20 min arm cranking at 60% $\dot{V}O_{2max}$	lymphocyte number leukocyte number prostaglandin E_2	no change (TETRA), 1.3-fold increase (AB) no change (TETRA), 1.5-fold increase (AB) 1.5-fold increase (TETRA), no change (AB)
	8	AB	not stated			

Nash, 1994	8	TETRA (no details given)	not stated	functional electrical stimulation elevating $\dot{V}O_2$ five-fold (duration not stated)	NK cell number and cytotoxicity lymphocyte and leukocyte numbers	number: 1.8-fold increase; cytotoxicity: 2.5-fold increase no change
Ueta <i>et al.</i> , 2008	7 6	PARA (T11-L4) AB	regularly active not stated	120 min arm cranking at 60% $\dot{V}O_{2max}$	NK cell number and cytotoxicity lymphocyte number leukocyte number prostaglandin E_2	number: no change in both groups; cytotoxicity: 1.1-fold decrease (PARA), 1.2-fold increase (AB) 1.9-fold increase (PARA), no change (AB) 1.6-fold increase in both groups 6-fold change (PARA), no change (AB)
Yamanaka <i>et al.</i> , 2010	8 6	TETRA (C6-C7) AB	regularly active not stated	20 min arm cranking at 60% $\dot{V}O_{2max}$	NK cell number and cytotoxicity lymphocyte number leukocyte number	number: no change (TETRA), 1.8-fold increase (AB); cytotoxicity: no change (TETRA), 1.4-fold increase (AB) no change (TETRA), 1.4-fold increase (AB) no change (TETRA), 1.3-fold increase (AB)

AB, able-bodied; C, cervical; L, lumbar; NK, natural killer cell; PARA, individuals with a paraplegia; T, thoracic; TETRA, individuals with a tetraplegia.

cise, with longer lasting activities resulting in more pronounced IL-6 level increases (30). Further, the IL-6 response is sensitive to the exercise intensity, directly representing the muscle mass involved, which decreases the higher the SCI lesion level. Upper body exercise per se (and even more pronounced when performed by persons with high level SCI), may therefore be insufficient to increase IL-6 above resting levels (68). Additionally, the before mentioned dysfunction of autonomic innervation could impact on IL-6 appearance in the blood, as catecholamines have been shown to influence cytokine production (65). Indeed, infusion of catecholamines can partly explain some of the rise in plasma concentrations of IL-6 found following exercise (24, 80), and administration of adrenergic antagonists can block adrenaline-stimulated IL-6 expression (24). This supports our finding that the plasma IL-6 response to strenuous exercise is associated with that of plasma adrenaline; responses of both are impaired in TETRA, but not in PARA or AB (64). This is an important issue as several immune responses are mediated by cytokines. For example, IL-6 infusion (amounts corresponding to levels of strenuous exercise) results in acute increases in neutrophils, cortisol, IL-10 and IL-1 receptor antagonist in healthy able-bodied individuals (79). Taken together, the combination of autonomic dysfunction impacting on cytokine production and less active, cytokine producing, muscle mass are the most likely reasons for the depressed production of IL-6 in TETRA. Given the messenger actions of IL-6, depressed levels may then impact on the production of other

cytokines/messenger molecules or alter immune cell number and function directly. Furthermore, an impaired IL-6 response to exercise may have downstream influences on metabolic responses, given the known glucoregulatory functions of IL-6 (68).

4.5 Salivary markers and upper respiratory symptoms

Mucosal immune function and its modulation by exercise have only recently been investigated in the SCI population. SIgA has been analysed in a number of studies to document the impact of chronic (53) and acute (51, 52) exercise in athletes with SCI. It was found that whilst slight differences in the SIgA response to exercise between TETRA and the control groups (PARA and able-bodied) exist (52), the overall pattern of the SIgA response is comparable between these groups. It was therefore suggested that the impact of sympathetic dysfunction on SIgA secretion in TETRA may be compensated by mechanisms such as reflex activity, by the parasympathetic nervous system, or by hypersensitivity of receptors (51).

A reduced SIgA secretion rate during periods of heavy training (53) is consistent with the positive relationship between post-race self-reported upper respiratory tract infections and training volume in athletes with an SCI (25). Epidemiological data from a large scale (N=18,693) study reveal that despite upper respiratory tract infections being the most prevalent acute respiratory condition in SCI, the annual outpatient visit rate is only 68/1000 – surprisingly, a lower rate when compared with the general population (155/1000) (75). Another epidemiological study investigating both TETRA and PARA reports a higher importance of pulmonary function, history of illness and smoking for chest illness than level or completeness of injury (82). In the case of pulmonary function, this may suggest a parameter that is trainable and that training may therefore decrease the risk of illness – indeed, very low incidences of upper respiratory symptoms were reported in wheelchair rugby athletes with tetraplegia during an observational study, with only 3 out of 14 athletes presenting light symptoms over 5 months (53).

5 IMPACTS OF MUSCULAR, VASCULAR, AND PSYCHOLOGICAL CHANGES AFTER SPINAL CORD INJURY

Apart from SNS and HPA dysfunction, it should be acknowledged that other disability-related factors may impact on immune function and further contribute to heightened illness susceptibility. For example, the colony-forming potential of progenitor cells from the bone marrow is reduced in SCI, which may be explained by inactivity characterising these individuals, possibly impairing blood flow through decentralized bone marrow (40). However, as long term adaptations to SCI include reductions in muscle mass, vessel diameter and blood flow below the level of lesion (63), this suggestion may not be limited to inactive individuals with an SCI but concern the SCI community as a whole. Furthermore, lesion level dependent paralysis of respiratory muscles can reduce respiratory function and the ability to cough and clear secretions that arise from respiratory infections (7). Respiratory training can improve respiratory parameters in SCI, such as maximum inspiratory and/or expiratory strength, vital capacity and maximum volun-

tary ventilation (19, 33, 85). Due to an improved ability to clear secretions, this may potentially reduce the risk of secondary complications, especially in individuals with high lesion levels. Finally, psychological stress and depression have known depressive effects on immune function, most likely via autonomic nervous and neuroendocrine system modulation (11). Given the psychological effects of SCI, this is likely to contribute to immune alterations in this population.

6 POTENTIAL COMPENSATORY MECHANISMS AFTER SPINAL CORD INJURY

Compensation of function loss is an intriguing field in exercise immunology in SCI populations. For example, receptors can adapt to an SCI and become hyper-responsive, as confirmed by adrenaline and noradrenaline injection in sympathectomized rats (66). It has also been observed that following SCI, spinal circuits are capable of generating some sympathetic activity, and a peripheral α -adrenoreceptor hyper-responsiveness may help to maintain normal function despite depressed circulating levels of catecholamines (29). Further studies during anaesthesia document increases in catecholamines, ACTH, and cortisol following functional electrical stimulation of anaesthetized limbs (45), suggesting that spinal reflexes and humoral feedback can potentially regulate immune responses during exercise. It has also been suggested that the blockade of IL-6 signalling after SCI in mice inhibits classic pathways and promotes an alternative pathway of macrophage activation (34). Likewise, the reported higher levels of dehydroepiandrosterone sulphate (which enhances IL-2 and has anti-glucocorticoid effects) in TETRA may be a compensatory response by the neurohormonal-immune axis to augment an injury-related impairment in the SNS or the immune response itself (8, 9). On a cellular level, increased fractions of T and T_{helper} cells in TETRA and PARA may be a compensatory change related to reduced numbers of NKs (10). Other mechanisms that may compensate for loss of sympathetic function include serotonin (synthesis known to increase during exercise and influence T cells, macrophages and NKs), vasoactive intestinal peptide, substance P or neuropeptide Y, all known to have immunomodulatory capacity (41). Yet for many of these substances, the link between exercise and altered immune function in humans or indeed individuals with an SCI has not been studied in detail (41).

7 CONCLUSION

An SCI, particularly above the T6 level, impacts on immune function, partly caused by the dysfunction of sympathetic pathways and possibly an altered HPA axis. Reduced resting levels and depressed exercise responses of the end products of the SNS and a number of immune measures have consistently been found in TETRA. However, even though a number of studies report depressed immune measures or depressed levels of immunomodulatory substances in response to exercise in high level SCI, there is very little empirical (rather than anecdotal) evidence reporting illness rates in TETRA athletes. The impact of high level SCI on immune responses to exercise is likely to be influenced by the redundancy of the

bidirectional talk between central nervous and the immune system, which seems to be able to compensate some of the lost function. Compensatory mechanisms are likely to include reflex activity, receptor hypersensitivity, or parasympathetic and neuroendocrine adjustments. Future work should address the influence of time since injury on the impact of exercise on immune measures (and infection frequency) as such compensatory mechanisms will likely develop over a period of months, or even years. Further, as participation in wheelchair exercise involves all levels of activity, from the recently injured to the Paralympian, the effect of activity on immune functions and the immune response to exercise should be considered when investigating optimal exercise intensities for both health and performance in SCI. Future work may further investigate the possibility of lesion-level/impairment-dependent individual exercise prescription to help counteract depressed immune function following SCI. Finally, individuals with SCI may serve as experimental models to better understand the impact of various levels of lesion and therefore help elucidate the mechanisms underlying the immune response to exercise.

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