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REVIEW

Immune dysfunction and chronic inflammation following spinal cord injury

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Study design: Review article.
Objectives: The objective of this study is to provide an overview of the many factors that contribute to the chronic inflammatory state typically observed following spinal cord injury (SCI).
Methods: Literature review.
Results: Not applicable.
Conclusion: SCI is typically characterized by a low-grade inflammatory state due to a number of factors. As bidirectional communication exists between the nervous, endocrine and immune systems, damage to the spinal cord may translate into both endocrinal and immune impairment. Damage to the autonomic nervous system may induce immune dysfunction directly, through the loss of neural innervation of lymphoid organs, or indirectly by inducing endocrinal impairment. In addition, damage to the somatic nervous system and the corresponding loss of motor and sensory function increases the likelihood of developing a number of secondary health complications and metabolic disorders associated with a state of inflammation. Lastly, numerous related disorders associated with a state of chronic inflammation have been found to be at a substantially higher prevalence following SCI. Together, such factors help explain the chronic inflammatory state and immune impairment typically observed following SCI. An understanding of the interactions between systems, both in health and disease, and the many causes of chronic inflammation may aid in the effective future treatment of immune dysfunction and related disorders following SCI.
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INTRODUCTION

Spinal cord injury (SCI) is a condition commonly associated with immune impairment and a state of chronic inflammation. This has been demonstrated by elevated levels of circulating proinflammatory cytokines and autoantibodies, which are apparent in individuals who are symptomatic or asymptomatic for secondary health complications.[1–5] As such, this population is often found to be in a perpetual low-grade inflammatory state, which is elevated to an even further extent when other health complications and associated disorders are present.

Owing to the complex bidirectional communication between the immune and neuroendocrine systems, damage to the spinal cord often results in the widespread dysfunction in other systems.[6] Both the endocrine and immune system may be affected due to respective dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and a loss of direct sympathetic innervation of lymphoid organs. There is ample evidence demonstrating that despite an elevated inflammatory state, SCI is associated with a state of immunosuppression and a heightened susceptibility to infection.[6–9] Suppressed function of natural killer cells, neutrophils, macrophages and lymphocytes have each been documented following SCI.[6,10,11] The loss of motor and sensory function also contribute to this population's greater susceptibility to a number of acute infections, including urinary tract infection (UTI) and pressure ulcers, as well as metabolic disorders associated with a more sedentary lifestyle such as obesity, atherosclerosis and type 2 diabetes.[12–14] A number of related disorders found to be significantly more prevalent following SCI such as depression and neuropathic pain may also contribute to a heightened systemic inflammatory state.[15–17]

It has yet to be definitively established whether or not such elevations in proinflammatory mediators are beneficial to this population or if they are in fact surrogate markers of further neurological and endocrinal impairment. Such mediators have critical roles in the elimination of invading pathogens and the repair of damaged tissue; however, there is also evidence to suggest a number of pathological roles. As such, an understanding of the bidirectional influence concerning the ability of inflammatory mediators to both influence, and be influenced by, a variety of disorders and secondary health complications following SCI may aid in future treatment strategies.

Rationale for immune impairment and chronic inflammation following SCI

Autonomic nerve damage. The immune system is under neuromodulatory control via the direct innervation of primary and secondary lymphoid tissues by autonomic nerve fibers of the sympathetic nervous system.[10] Preganglionic sympathetic neurons originating from the spinal column synapse in the ganglia with peripheral sympathetic neurons. These nerve fibers are responsible for innervating several lymphoid organs and their blood vessels including the spleen, thymus and lymph nodes, whereby they act to regulate blood flow as well as

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communicate directly with immune cells.[10] Within these organs, postganglionic noradrenergic fibers release catecholamines, such as norepinephrine, for direct communication with lymphocytes, which bear receptors for various neurally active hormones, neurotransmitters and neuropeptides.[18] The initial release of catecholamines has been shown to induce a rapid, transient increase in blood lymphocytes; however, prolonged exposure induces a number of anti-inflammatory effects including reduced circulating lymphocyte numbers and suppressed natural killer cell activity.[8] Prolonged exposure to catecholamines also seem to inhibit proinflammatory cytokine production by Th1 cells, while having no effect or even acting to enhance the production of anti-inflammatory cytokines by Th2 cells.[8]

As lymphoid organs such as the spleen and adrenal gland are innervated by sympathetic neurons that originate from regions throughout the thoracolumbar spinal cord, an injury at or above this region may be expected to induce immune suppression.[9] Damage to the cervical spine would interfere with supraspinal control over preganglionic neurons below the injury, whereas damage at the mid-thoracic region would damage preganglionic sympathetic neurons directly.[7] Level-dependent impairment in B-cell function has been demonstrated in mice subjected to high (T3) versus mid-thoracic (T9) SCI. It was shown that only after high thoracic SCI (causing disruption of autonomic control of the spleen) was splenic norepinephrine elevated and immune function suppressed,[9] whereas mid-thoracic SCI (leaving autonomic control of the spleen intact) has been shown to induce B-cell activation, increase the synthesis of autoantibodies[19] and activate autoreactive T cells.[20] Catecholamines such as noradrenaline have also been shown to be significantly reduced in humans with cervical or high thoracic injuries and have been attributed to a loss of adrenal gland innervation and dysfunction in sympathetic pathways.[21,22] Alternatively, certain aspects of post SCI immune alterations appear to be independent of injury level. Similar alterations in natural killer cell and T-cell cytotoxic activity have been demonstrated in humans with both high- and low-level injuries,[11,23] as have elevations in viral load following infection in mouse models of high and low thoracic SCI.[7] It may be possible that the level of injury has a greater impact on certain aspects of immunity than others. Additional factors such as autonomic completeness of injury and time since injury may also explain some of the variability in findings.

Damage to the sympathetic nervous system may also contribute to reduced immune function due to a loss of afferent signaling from the adrenal gland to the hypothalamus. A loss of such afferent pathways would reduce facilitation of hypothalamic nuclei and may ultimately induce dysfunction in the HPA axis.[6] Lesions on the anterior hypothalamus have been shown to lead to diminished numbers of nucleated spleen cells and thymocytes, as well as diminished antibody production, while lesions on the medial hypothalamus have been shown to lead to diminished T- and B-cell numbers.[6] It may be possible to speculate that damage to sympathetic afferents and corresponding reductions in the facilitation of hypothalamic nuclei could produce similar effects to that observed under conditions of hypothalamic lesions and contribute to the HPA axis dysfunction commonly reported following SCI.

Endocrine dysfunction

The HPA axis provides an additional immunoregulatory pathway whereby the immune response may be influenced hormonally. Within this pathway, the release of corticotropin releasing hormone from the hypothalamus induces the release of adrenocorticotropic hormone (ACTH) from the pituitary, which ultimately stimulates the release of glucocorticoids such as cortisol from the adrenal gland. Glucocorticoids induce immunosuppressive effects by acting on leukocytes equipped with receptors for various stress hormones. Once bound, glucocorticoids induce the upregulation of anti-inflammatory cytokines as well as the suppression of proinflammatory cytokines and other proinflammatory mediators.[24] Glucocorticoids also suppress the maturations, differentiation and proliferation of a number of immune cells. Owing to this critical hormonal influence, an imbalance in the HPA axis in either direction may result in immune dysfunction. Excessive glucocorticoid production may result in immunosuppression and an increased risk of infection, whereas a non-responsive HPA axis may result in a lack of suppression, resulting in an elevated inflammatory state.

Proinflammatory cytokines possess the ability to upregulate the HPA axis and as such, may contribute to HPA axis overactivation under conditions of chronic inflammation as typically observed following SCI. Such an influence may lead to the excessive production of glucocorticoids from the adrenal gland causing elevated circulating levels and a greater immunosuppressive influence. Increased levels of urine-free cortisol, stimulated by elevated plasma ACTH, have been demonstrated in humans following SCI and have been shown to remain elevated for 3 months post injury.[6,25] This process may induce the hormonally driven suppression of both the innate and adaptive immune systems and explain, in part, the increased susceptibility to infection and reduction in wound-healing capabilities observed following SCI.[26] Such an influence has been demonstrated within the innate immune system by reductions in natural killer cell function as well as in the adaptive immune system by reductions in T-cell function, which were shown to be inversely related to cortisol levels.[6] The majority of studies demonstrating this upregulation of the HPA axis and elevated levels of cortisol have, however, typically been performed under acute SCI conditions. It may be possible that under chronic conditions, the ongoing stress placed on the HPA axis could result in adrenal insufficiencies. Several studies performed on individuals with chronic SCI have eluded to such an effect.

Individuals with chronic SCI have been shown to have reduced basal cortisol levels and a reduced cortisol response to exogenous corticotropin releasing hormone administration.[27] A similar blunted cortisol response has also been demonstrated following intramuscular injection of ACTH.[28] Interestingly, in a similar study performed under acute SCI conditions, ACTH injection was shown to produce a normal elevation in plasma hydroxycorticosteroid levels.[29] These results may further support the theory that SCI results in adrenal insufficiencies, which take time to develop and are not apparent until the chronic stages. Such effects have been suggested to be the result of mild adrenocortical atrophy and/or a reduction in the sensitivity of corresponding adrenal receptors.[27] Of note, an increased adrenal volume within chronic SCI has been demonstrated in individuals with impaired adrenal reserves, suggesting a reduction in adrenal receptor sensitivity may be the more likely cause.[30] However, due to a limited sample size, further studies are required to make any definitive conclusions regarding the true cause of adrenal insufficiency following SCI. Regardless of the cause, if the adrenal gland does not sufficiently respond to ACTH released by the pituitary, adrenal insufficiencies may result, causing reduced levels of circulating glucocorticoids and a lack of immunosuppression, resulting in an elevated inflammatory state.[24]

Therefore, whether due to an elevation in glucocorticoid production caused by overstimulation of the HPA axis, or an eventual reduction in glucocorticoid production caused by desensitization of the ACTH receptors on the adrenal gland, immune dysfunction may result. This may explain, in part, an endocrine role in chronic inflammation following SCI (see Figure 1).

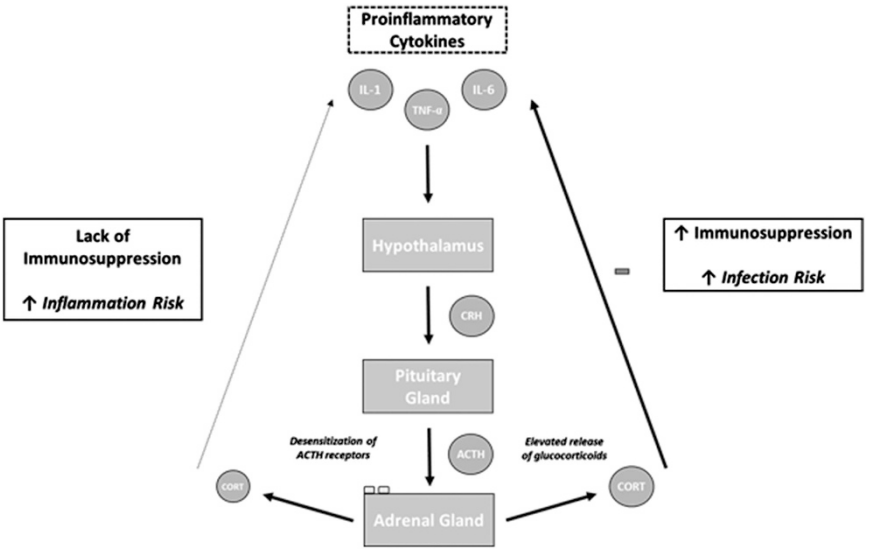

Figure 1 The HPA axis and inflammation. Proinflammatory cytokines have the capability of upregulating the HPA axis. This stimulates a cascade whereby corticotropin releasing hormone (CRH) induces the pituitary gland to release ACTH, which then induces the release of glucocorticoids such as cortisol (CORT) from the adrenal gland. Glucocorticoids induce immunosuppressive effects. Therefore, under conditions of chronically elevated proinflammatory cytokines, elevated levels of circulating glucocorticoids and a corresponding immunosuppression may result. Alternatively, prolonged overactivation of the HPA axis may result in a desensitization of ACTH receptors on the adrenal gland resulting in a reduction in glucocorticoid release and a lack of immunosuppression, allowing for elevated levels of proinflammatory mediators.

Somatic nerve damage

A loss of motor and/or sensory function following SCI places individuals at a heightened risk for the development of a variety of acute infections. Secondary health complications such as UTIs and pressure ulcers are common occurrences in this population, resulting in frequent spikes in inflammatory mediators. A recent study by Street *et al.*[31] followed a group of 171 patients receiving acute care for traumatic SCI and found 77% experienced an adverse event during their stay including UTIs, pneumonia, neuropathic pain, pressure ulcers and delirium. Of these complications, UTIs were found to be the most common occurrence.[31]

A loss of voluntary motor control of the bladder and/or the ability to sense when the bladder is full may result in insufficient bladder voidance. This results in the accumulation of stagnant urine within the bladder, allowing for an increase in bacterial growth and a resulting risk of infection.[2] UTIs have been consistently shown to be the most frequent cause of re-hospitalization in the SCI population, accounting for ~24–54% of cases.[32] This indicates that UTIs are a common occurrence, not only during the acute stages of SCI but also in the long term as well.

Both paralysis and atrophy of skeletal muscle, in combination with a loss of functioning dermatomes, also increases the risk of tissue damage and infection via pressure ulcer development. An inability to shift one's body weight and/or sense the pain and pressure associated with remaining in the same seated or supine position for an extended period of time may lead to the occlusion of blood flow to an area of tissue. As such, various areas of the body, particularly the gluteal and sacral regions, may be at risk for oxygen deprivation and necrosis.[2] Individuals with SCI are at a particularly high risk for pressure ulcer development with ~40% of individuals developing a pressure sore within any three-year period.[32]

Acute secondary health complications such as these result in an acute inflammatory response characterized by a spike in proinflammatory mediators.[33,34] The frequent occurrence of such complications paired with slower healing times makes this population prone to frequent and prolonged elevations in inflammatory mediators, further compounding the already elevated basal inflammatory state.

Metabolic disorders

Following SCI, the loss of motor function typically leads to inactivity and increases the likelihood of living a sedentary lifestyle. Further, the additional physical, psychological and biochemical demands placed on the body makes proper diet even more crucial to meet the body's elevated nutrient requirements. Unfortunately, a lack of awareness in this area combined with the cost and effort involved in maintaining a healthy diet places this population at high risk for nutrient deficiencies. Together, this places the SCI population at a higher risk for the development of metabolic disorders such as obesity, type 2 diabetes and atherosclerosis;[12–14] each of which are independently associated with a chronic inflammatory status.[12,35]

Obesity is now classified as an inflammatory disorder due to the discovery that adipose tissue acts as an endocrine organ, possessing the ability to secrete proinflammatory mediators, termed adipokines, such as TNF (tumor necrosis factor)-α, IL (interleukin)-1 and IL-6.[36] As such, an abundance of adipose tissue, as seen in obesity, may result in the overproduction of proinflammatory mediators and contribute to a low-grade inflammatory state. Adipose tissue is also known to secrete adiponectin, a protein with a critical role in fatty acid oxidation and glucose regulation.[37] Elevated concentrations of proinflammatory cytokines have however been shown to blunt the release of adiponectin, thereby limiting its ability to induce fatty acid oxidation and aid in glucose regulation by means of enhanced insulin sensitivity. This decrease in fatty acid oxidation further contributes to the overabundance of adipose tissue, which in turn leads to a greater secretion of proinflammatory cytokines, creating a viscous inflammatory cycle. A reduction in plasma concentrations of adiponectin has been reported in individuals with obesity, as well as in those with type II diabetes and cardiovascular disease.[38]

Closely related to this obesity-induced inflammatory state is a state of insulin resistance associated with the development of type-2

diabetes. Several cross-sectional studies using non-diabetic subjects have demonstrated that those with impaired glucose tolerance displayed elevated concentrations of proinflammatory cytokines such as C-reactive protein, sialic acid, TNF-α and IL-6. In addition, each were shown to be positively correlated with insulin resistance.[39–41] In addition to adiponectin-related mechanisms, a number of proinflammatory cytokines including TNF-α, IL-1 and IL-6 have each been suggested to have a role in insulin resistance via the downregulation of GLUT 4 gene transcription and translocation, as well as the inhibition of insulin receptors by mechanisms related to the upregulation of the suppressors of cytokine signaling proteins.[42,43] Insulin resistance may in turn result in elevated blood glucose concentrations placing excess strain on the kidneys and ultimately resulting in tissue damage and further inflammation.

Atherosclerotic plaques associated with cardiovascular disease are also influenced by, and further induce, elevations in proinflammatory mediators. A variety of proinflammatory mediators have the ability to induce vasoconstriction, thereby increasing shear force on vessels and the likelihood of endothelial damage. In addition, proinflammatory mediators act to increase chemotaxis and the production of adhesion molecules, thereby increasing leukocyte infiltration and platelet aggregation at the site of endothelial damage.[44] Together, these mechanism act to increase the risk of plaque formation in the form of an atherosclerotic plaque. Such plaques are treated similar to that of any other form of tissue damage with the elicitation of an inflammatory response. However, in the case of an atherosclerotic plaque, the inflammatory response is unable to repair the damaged tissue. Instead, migrating immune cells become trapped within the plaque and release inflammatory mediators contributing to an even greater inflammatory response and state of low-grade inflammation[44] (see Figure 2).

For these reasons, among others, the highly sedentary lifestyle often adopted following SCI, in combination with a lack of necessary dietary alterations may contribute to the chronic low-grade inflammatory response.

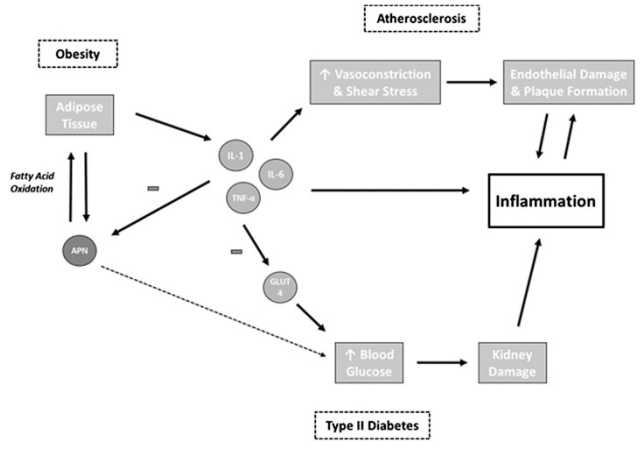

Figure 2 Influence of metabolic disorders on inflammatory state. Obesity results in the excess production of proinflammatory cytokines termed adipokines. These adipokines blunt the release of adiponectin (APN), which may reduce fatty acid oxidation and result in further elevations in adipose tissue and proinflammatory mediators. Reductions in adiponectin as well as the downregulation of GLUT 4 may lead to elevated blood glucose concentrations, ultimately placing excess strain on the kidneys. Lastly, as proinflammatory cytokines induce vasoconstriction they may contribute to vascular damage by increasing the shear force placed on vessels. The potential endothelial damage and plaque formation may lead to an ongoing inflammatory response.

Related disorders

A number of disorders including depression and neuropathic pain are associated with a state of chronic inflammation. Individuals diagnosed with major depression have been consistently reported to demonstrate elevated levels of proinflammatory cytokines,[45,46] and those with neuropathic pain have been shown to have altered levels of inflammatory mediators with elevations in the proinflammatory cytokines TNF, IL-6 and IL-2 along with reductions in anti-inflammatory cytokines such as IL-10 and IL-4.[1,47] As these disorders have a highly elevated prevalence following SCI, they too may contribute to the elevated inflammatory status observed in this population. The prevalence of depression following SCI is estimated to be five times greater in comparison with the general population with rates of ~20–40%.[15,16] Neuropathic pain is also far more prevalent, affecting an estimated 29–75% of the SCI population.[17] Although the inflammatory mechanisms behind these disorders are not fully understood, the ability of proinflammatory cytokines to act as neuromodulators allows them to contribute to these disorders via both direct and indirect influences.[48]

Cytokines have the ability to directly influence the central nervous system and have a role in a variety of responses including behavior modification by accessing the brain through leaky sites of the blood brain barrier via the circumventricular organs[48], or using specific active transporters to cross the blood brain barrier.[49] Alternatively, cytokines can communicate by acting on the vagal afferents, thereby avoiding the need to cross the blood brain barrier.[50] Proinflammatory mediators have also been suggested to directly influence nociceptors, by reducing ion-channel activation thresholds leading to peripheral sensitization.[51]

Proinflammatory cytokines also possess the ability to indirectly influence neuronal function via their ability to alter the regulation of key enzymes. The chronically elevated levels of proinflammatory cytokines often reported following SCI may therefore result in chronically upregulated enzyme activity, leading to potential protein imbalances related to both depression and neuropathic pain. For example, a number of proinflammatory cytokines have been shown to upregulate the enzyme indoleamine 2,3-dioxygenase of the kynurenine pathway. As this enzyme is responsible for the degradation of tryptophan, a critical precursor in the synthesis of serotonin, its chronic upregulation may result in serotonin deficiencies and related depressive symptoms.[52] Proinflammatory cytokines have also been shown to upregulate the enzyme cyclooxygenase. This enzyme is responsible for the production of potent, proinflammatory eicosanoids with established pain inducing properties such as prostaglandin 2.[53] An upregulation of cyclooxygenase may therefore result in greater and far more frequent neuropathic pain.

It is debated whether an elevated inflammatory status is the product of, or rather the cause of, such disorders. However, as both psychological stress and neurological damage would be expected to result in an elevation in proinflammatory mediators, it is likely a combination of effects.

CONCLUSION

The chronic low-grade inflammatory response and immune impairment observed following SCI is likely the result of a combination of factors due to the complex bidirectional communicatory pathways between systems. The involvement of many systems makes the effective treatment of immune dysfunction an extremely difficult task, requiring a multi-tiered approach. However, it may also provide the opportunity to develop novel treatment strategies for a variety of disorders by targeting immune impairment. The re-establishment of

immune homeostasis may not only help to improve the body's ability to fight infection and reduce unnecessary energy expenditure, but may also induce beneficial alterations in enzyme regulation, protein balances, hormone levels and neural function. An understanding of the interactions between systems, both in health and disease, and the many causes of chronic inflammation may aid in the effective future treatment of immune dysfunction and related disorders following SCI.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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