Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation

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FROM ABSTRACT

Individuals with spinal cord injury (SCI) are highly susceptible to infection.

This post-traumatic immune suppression is thought to occur via alterations in sympathetic nervous system (SNS) or hypothalamic–pituitary–adrenal (HPA) axis function. Normally, the HPA axis and SNS help coordinate proper immune function.

After SCI, the HPA axis becomes activated and descending input to sympathetic preganglionic neurons (SPNs) is impaired.

Because lymphoid organs are innervated by SPNs distributed throughout the thoracolumbar spinal cord, we predicted level-dependent immune suppression after SCI due to activation of the HPA axis and loss of descending input to SPNs.

We tested this hypothesis by measuring indices of HPA (circulating corticosterone; CORT) and SNS function (norepinephrine (NE) in spleen) as well as antigen-specific antibody synthesis against an exogenous non-self protein following high- or low-level SCI. Using a mid-thoracic (T9) spinal contusion injury model, we found that CORT was elevated after SCI. However, splenic NE and antibody synthesis were similar to uninjured controls.

In contrast, high-level SCI (T3) caused sustained increases in CORT and splenic NE along with impaired antibody synthesis and elevated splenocyte apoptosis.

The immunosuppressive effects of T3 SCI were caused by NE acting at beta2-adrenergic receptors (beta2AR) and could be reversed using beta2AR blockers.

These data illustrate the immunosuppressive effects of the SNS after high-level SCI and indicate that immune deficits may be overcome using beta-blockers.

THESE AUTHORS ALSO NOTE:

“Clinical data show that human spinal cord injury (SCI) is accompanied by profound immunological impairment.”
“SCI-induced deficiencies in supraspinal control of the sympathetic nervous system (SNS) or hypothalamic-pituitary-adrenal (HPA) axis have long been suspected, but never proven, as mechanisms of post-traumatic immune suppression.”

“Activation of the HPA axis causes release of cortisol (humans) or corticosterone (CORT; rodents) from the adrenal cortex into the bloodstream. High or sustained levels of CORT suppress antibody production, cytokine synthesis and leukocyte proliferation.”

“In humans, urinary cortisol remains elevated for months after SCI suggesting prolonged dysregulation of HPA function.”

“Activation of the SNS causes the release of norepinephrine (NE).”

In spleen and lymph nodes, sympathetic nerves synapse on T and B cells. “This ‘hardwiring’ between the spinal cord and lymphoid tissue ensures proper immune function.” [Very Important]

Repeated or prolonged exposure of B cells to norepinephrine from the SNS is immunosuppressive. [Very Important]

“HPA/SNS responses are coordinated in the spinal cord via supraspinal projections and by afferent feedback from the periphery to sympathetic preganglionic neurons (SPNs).”

Preganglionic sympathetic neurons are found throughout the thoracic spinal cord and influence immune function through post-ganglionic noradrenergic projections to spleen and adrenal cortex.

Because preganglionic sympathetic neurons are influenced by descending input from the brain, “high-level SCI would cause greater dysfunction of the HPA axis and SNS and subsequently, greater immunological impairment than lower level SCI.”

This study shows that T9 spinal contusion injury causes acute disruption of HPA function. However, “T9 SCI is not associated with acute immune suppression.”

“HPA axis is a consequence of CNS injury but it alone is not responsible for post-traumatic immune suppression.”

“After SCI, the incidence of bacterial infection (e.g., pneumonia) is increased.”

T3 spinal cord injury induces splenocyte cell death and B cell apoptosis.
Although all splenic immune cells were decreased in number after T3 spinal cord injury, B cells were affected to the greatest extent.

DISCUSSION

“Here we show that immune suppression after spinal cord injury (SCI) is level dependent and involves norepinephrine (NE) acting at beta 2 adrenoreceptors.”

“Indeed, only in mice with high-level (T3) SCI was the concentration of splenic NE increased and antibody synthesis decreased relative to sham-injured or T9 SCI mice.”

“Infection is a leading cause of death after SCI.”

“Suppression of function in natural killer cells, neutrophils, macrophages and lymphocytes has been documented after SCI.”

“After a high thoracic (T3) SCI, when the majority of supraspinal control of sympathetic preganglionic neurons is disrupted, immune responses to exogenous antigens are impaired.”

“Massive and immediate activation of the sympathetic nervous system, with subsequent release of systemic (from adrenal glands) and tissue NE (from nerve fibers), is common to high-level SCI, stroke, traumatic brain injury and shock. In each case, NE is believed to be responsible for causing or exacerbating lymphocyte apoptosis and splenic atrophy.”

“Aberrant sympathetic reflexes and repeated exposure of peripheral immune cells to catecholamines could place individuals at increased risk for opportunistic infection.”

“Immune suppression and increased frequency of infection are common in individuals living with SCI.”

SCI-mediated suppression of antibody synthesis is caused in part by NE acting at beta2ARs.

KEY POINTS FROM DAN MURPHY

[Supraspinal influences inhibit the SNS. Spinal cord injury interrupts this inhibition, resulting in increased sympathetic tone, which causes immunosuppression.]

1) Individuals with spinal cord injury (SCI) are highly susceptible to infection.

2) “After SCI, the incidence of bacterial infection (e.g., pneumonia) is increased.”
3) Lymphoid organs are innervated by sympathetic neurons.

4) “Clinical data show that human spinal cord injury (SCI) is accompanied by profound immunological impairment.”

5) This study shows that increased sympathetic activity is immunosuppressive.

6) Activation of the HPA axis causes release of cortisol which also suppresses antibody production, cytokine synthesis and leukocyte proliferation.

7) Activation of the sympathetic nervous system causes the release of norepinephrine.

8) Leukocytes have a receptor for epinephrine, called the beta 2 adrenoreceptor.

9) In the spleen and lymph nodes, sympathetic nerves synapse on T and B cells. “This ‘hardwiring’ between the spinal cord and lymphoid tissue ensures proper immune function.” [Very Important]

10) Repeated or prolonged exposure of B cells to norepinephrine from the SNS is immunosuppressive. [Very Important]

11) Preganglionic sympathetic neurons are found throughout the thoracic spinal cord and influence immune function through post-ganglionic noradrenergic projections to the spleen and adrenal cortex.

12) High-level spinal cord injury causes greater immunological impairment than lower level spinal cord injury because more of the sympathetic nervous system function is impaired.

13) “Aberrant sympathetic reflexes and repeated exposure of peripheral immune cells to catecholamines could place individuals at increased risk for opportunistic infection.” [Catecholamines include norepinephrine from the sympathetic nervous system and epinephrine from the adrenal medulla. The adrenal medulla is innervated by the preganglionic sympathetic efferent neurons.]

COMMENTS FROM DAN MURPHY

This study shows that the increased sustained sympathetic tone caused by a high spinal cord injury results in immunosupression. Beta-blockers are drugs that interfere with the sympathetic nervous system chemical norepinephrine (they block the beta 2 adrenoreceptor that norepinephrine uses on the lymphocytes), thereby effectively causing sympathetic inhibition. These authors note that using beta-blockers enhances immunity. In the 9 years that we have been doing these Article Reviews, we have seen several studies that indicate that chiropractic spinal adjusting also inhibits the sympathetic nervous system, and we have reviewed several studies that indicate that chiropractic spinal adjusting improves immunity.