● **INVITED REVIEW**

Autonomic dysreflexia: a cardiovascular disorder following spinal cord injury

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Abstract

Autonomic dysreflexia (AD) is a serious cardiovascular disorder in patients with spinal cord injury (SCI). The primary underlying cause of AD is loss of supraspinal control over sympathetic preganglionic neurons (SPNs) caudal to the injury, which renders the SPNs hyper-responsive to stimulation. Central maladaptive plasticity, including C-fiber sprouting and propriospinal fiber proliferation exaggerates noxious afferent transmission to the SPNs, causing them to release massive sympathetic discharges that result in severe hypertensive episodes. In parallel, upregulated peripheral vascular sensitivity following SCI exacerbates the hypertensive response by augmenting gastric and pelvic vasoconstriction. Currently, the majority of clinically employed treatments for AD involve anti-hypertensive medications and Botox injections to the bladder. Although these approaches mitigate the severity of AD, they only yield transient effects and target the effector organs, rather than addressing the primary issue of central sympathetic dysregulation. As such, strategies that aim to restore supraspinal reinnervation of SPNs to improve cardiovascular sympathetic regulation are likely more effective for AD. Recent pre-clinical investigations show that cell transplantation therapy is efficacious in reestablishing spinal sympathetic connections and improving hemodynamic performance, which holds promise as a potential therapeutic approach.

Key Words: autonomic dysreflexia; hyper-reflexia; sympathetic dysfunction; C-fibers; propriospinal axons; α-adrenoceptors; stem cell transplantation

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Introduction

Execution of normal autonomic activity is vital for all bodily systems to operate in a synchronous and harmonious manner. An insult to autonomic centers can therefore have a multitude of detrimental effects where physiological systems become incapable of responding to internal and/or external provocations, thus resulting in perpetual functional degradation. Spinal cord injury (SCI) is a unique disorder where almost every physiological system is compromised. Interrupted supraspinal regulatory signals to their target organs is the major cause for autonomic failure following SCI, which typically leads to reduced autonomic tone, maladaptive intraspinal plasticity and inappropriate reflexive responses to afferent input. Depending on the level and severity of the injury, individuals with SCI may experience respiratory disorders, sexual dysfunction, lower urinary tract complications, impaired thermoregulation, gastrointestinal disturbance, and cardiovascular dysfunction. It is therefore not surprising that individuals with SCI consider recovery of autonomic function to be paramount for improving quality of life (Anderson, 2004).

Cardiovascular dysfunction following SCI is of particular importance, as it is one of the leading causes of morbidity and mortality in this population (Myers et al., 2007). Although many of the cardiovascular ailments that manifest following SCI are associated with increased risk of death, special attention must be given to autonomic dysreflexia (AD), as it is the only cardiovascular condition to directly cause death or irrevocable damage to individuals with SCI

(Dolinak and Balraj, 2007). AD is characterized by sudden episodic increases in blood pressure accompanied by baroreceptor-mediated bradycardia in response to noxious visceral or cutaneous stimulation below the injury level (Karlsson, 1999). Although approximately 90% of individuals with complete tetraplegia experience AD (Curt et al., 1997), there remains no effective permanent treatment for this disorder, partly due to our limited understanding of its pathophysiology. Nevertheless, studies show that AD is related to complex interactions between maladaptive intraspinal and peripheral plasticity that occur following SCI. Therefore, in order for researchers to circumvent previous impediments and develop clinically relevant and viable treatments for AD, it is imperative to have a comprehensive and up to date understanding of the purported mechanisms as well as previously employed treatments for AD. Accordingly, this review will discuss cardiovascular autonomic regulation and how it changes after SCI, followed by a detailed overview on the central and peripheral mechanisms underlying AD, as well as treatment considerations.

Autonomic Regulation of Cardiovascular Function

Cardiovascular function is regulated through the constant balance between sympathetic and parasympathetic function, which generally have opposing effects to one another. Sympathetic activity is excitatory, as it increases heart rate, cardiac contractility and blood pressure, while parasympathetic activity reduces heart rate and elicits a reflexive decrease in

blood pressure. Under normal conditions, baroreceptors relay excitatory and/or inhibitory afferents to the nucleus tractus solitarus (NTS) in the brainstem, *via* the vagus and glossopharyngeal nerves. From the NTS, secondary neurons project directly to cardiovascular centers which formulate appropriate modulatory signals, the net output of those commands, *via* the NTS, are a balance of inhibitory and excitatory efferents towards the heart and vasculature (Freire-Maia and Azevedo, 1990). For example, when arterial pressure is elevated, baroreceptors distend and increase their firing rate to supraspinal centers, which subsequently causes reflexive inhibition of sympathetic activity thus reducing heart rate and blood pressure. Conversely, when baroreceptors sense low arterial pressures, their slow firing rate prompts supraspinal centers to increase sympathetic outflow in order to induce compensatory tachycardia and raise blood pressure. Therefore, the machinery required for successful cardiovascular autonomic regulation involves reciprocal interplay between central and peripheral pathways. Damage to any part of this intricate system can result in tremendous cardiovascular autonomic impairments.
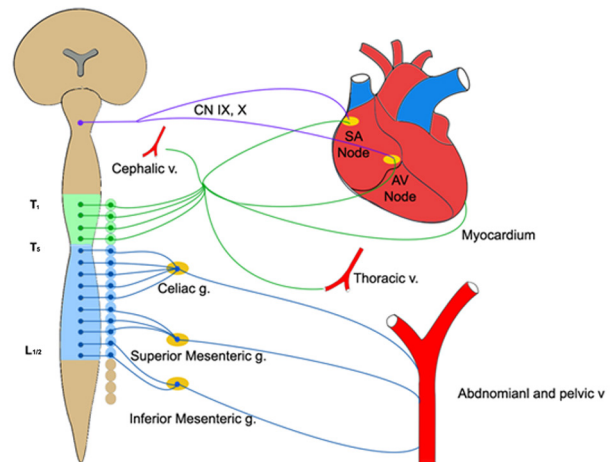
Sympathetic cardiovascular regulation

sympathetic preganglionic neurons (SPNs) involved in cardiovascular regulation are located in the intermediolateral cell column (IML) of the lateral horn and gray commissure along T_1–L_2 spinal levels. The SPNs between T_{1-4} are essential for cardiac sympathetic modulation, and they exit the spinal cord and synapse with the sympathetic chain ganglion to connect with sympathetic postganglionic neurons. During sympathetic stimulation, nicotinic receptors in the post galgniolinc neurons are stimulated by cholingergic transmission, which result in norepinephrine release from the postganglionic neuron terminals. The released norepinehphrine binds onto β_1-adrenoceptors in the sino-atrial and atrio-ventricular nodes, which augments depolarization rate and action potential propagation throughout the cardiac conduction pathways, thus increasing heart rate. Additionally, norepinephrine binds to myocardial β_1-adrenoceptors to increase cardiac contractility by enhancing intracellular calcium release and subsequent formation of actin-myosin cross bridges. The SPNs between T_5–L_2 connect with the collateral ganglia to then synapse directly onto the sympathetic postganglionic neurons. From there, norepinephrine is released and binds onto α_1-adrenoceptors expressed in smooth muscles of the splanchnic bed and the lower limbs. Sympathetic stimulation of the abdominal and splanchnic vasculature specifically plays a major role in increasing systemic blood pressure. Conversely, β_2-adrenoceptors are also found in smooth muscles but cause vasodilation when stimulated to increase organ blood perfusion (**Figure 1**). This organization is imperative for the sole purpose of the fight or flight response, which is to direct blood towards the most critical regions during autonomic excitement and shunt it away from the less critical areas. For example, at times of danger, vasoconstriction of the splanchnic vessels increases blood pressure, but also directs blood away from the area, as the abdominal organs are not needed to function during times of stress. As such, blood gets redirected towards skeletal muscles, that contain vasodilated blood vessels through stimulated α_2-adrenoceptor, which increases oxygen delivery and metabolic fuel utilization to enhance performance.

Parasympathetic cardiovascular regulation

Cardiac parasympathetic neurons are located in the dorsal motor nucleus of the vagus nerve and the nucleus ambiguous in the medulla oblongata. Parasympathetic preganglionic neurons project through the vagus and glossopharyngeal nerves, synapsing with postganglionic cells that in turn synapse onto the heart (**Figure 1**). Therefore, unlike sympathetic neurons, cardiac parasympathetic fibers are anatomically independent of the spinal cord. Acetylcholine is used as a messenger between the pre and post ganglionic neurons and is also released from the vagal neural terminals to exert its effects on target organs. Following acetylcholine release from postganglionic terminals; the neurotransmitter binds onto muscarinic receptors in the sinoatrial (SA) node to hyperpolarize the membrane potential, thus slowing down the rate of action potential formation and heart rate (Gordan et al., 2015). Although parasympathetic nerves do not have a direct effect on blood vessels, they can stimulate nitric oxide release, which results in vasodilation of smooth muscles.

Figure 1 Illustration of normal cardiovascular autonomic control.
For cardiac parasympathetic modulation, long parasympathetic preganglionic neurons within the vagus and glossopharyngeal nerves (Cranial nerves (CN) IX & X) exit from the medulla oblongata, synapsing with short parasympathetic preganglionic neurons which terminate on the sinoatrial (SA) and atrioventricular (AV) nodes to decrease heart rate through the action on acetylcholine. Peripheral blood vessels (v.) are not directly innervated by parasympathetic nerves. Conversely, for cardiac sympathetic regulation, short sympathetic preganglionic neurons from T_{1-4} synapse with the autonomic chain, which then connects with long sympathetic postganglionic neurons that terminate on the sinoatrial and atrioventricular nodes, as well as myocardial tissue to increase heart rate and contractility. These nerves also innervate blood vessels of the head, neck and thoracic region in order to regulate blood flow to the upper body. Sympathetic preganglionic neurons below the T_4 segment bypass the sympathetic chain, travel through the collateral ganglia (celiac, superior mesenteric and inferior mesenteric ganglions (g.)) and synapses with sympathetic postganglionic neurons. These neurons terminate on blood vessels of the abdomen, pelvic region and lower limbs and cause vasoconstriction to increase blood pressure.

Supraspinal cardiovascular regulation

In an intact body, blood pressure and heart rate are in constant synchronous fluctuation within a physiological range, which is balanced by continuous excitatory and inhibitory drive over cardiovascular activity. Such a balance promotes normal basal vasomotor tone as well as appropriate pressor and depressor responses to autonomic perturbations. The brainstem contains several key regions that regulate pressor and depressor responses when stimulated and inhibited, respectively. The 5 main regions in the brainstem that do so are the 1) rostral ventrolateral medulla (RVLM), 2) rosral ventromedial medulla, 3) caudal raphe nuclei, 4) A5 cells in the pons and 5) paraventricular nucleus (PVN) of the hypothalamus (Chalmers et al., 1994). Basal and reflexive sympathetic tones are primarily provided by the lateral tegmental field (LTF) and the RVLM. The LTF projects and drives sympatho-excitatory signals to the RVLM, however, the RVLM plays a chief role in increasing sympathetic outflow to the SPNs. Axons from the RVLM project directly towards the SPNs in the IML within the thoracolumbar spinal cord, which synapses with postganglionic sympathetic neurons, releasing norepinephrine to increase vasomotor tone, heart rate and cardiac contractility. Although the sources of excitatory and inhibitory drive to the RVLM remains unclear, anatomical studies suggest that numerous supraspinal regions converge and project to the RVLM to activate and/or dampen its activity (Dampney, 2016). Two of the most prominent regions that modulate RVLM activity are the caudal ventrolateral medulla (CVLM) and the caudal pressor area (CPA). The CVLM, located inferior to the RVLM, is the primary inhibitor of RVLM activity, thus causing a depressor response when activated (Campos et al., 2008). In contrast, the CPA primarily activates the RVLM by impeding the CVLM's sympatho-inhibitory signals towards the RVLM, thus maintaining sympathetic tone (Ghali, 2017). Sympatho-modulation can also occur independently of the RVLM through regions such as the medullocervical pressor area and the gigatecullar depressor area (GDA). The medullocervical pressor is to increase blood pressure through direct activation of the SPNs within the IML (Ghali, 2017), bypassing the RVLM. Similarly, axons from the GDA extend to and depress several autonomic modulatory regions in the brainstem and the IML, causing inhibition of sympathetic activity, thus reducing blood pressure, chronotropy and inotropy (Aicher, 2003).

Cardiovascular Performance after SCI

The loss of supraspinal control over the SPNs controlling heart and blood vessels is the principal underlying cause of impaired cardiovascular function in individuals with SCI. Although modulatory descending signals from the brain are disrupted following SCI, spinal and peripheral cardiovascular circuitry caudal to the injury are not abrogated, but rather undergo maladaptive plasticity that initiates disordered activities. These include abnormal basal and orthostatic hemodynamics, cardiac arrhythmias, cardiac vagal dysfunction, and the focus of this paper, AD.

Hypotension and orthostatic hypotension

Recent guidelines for acute management of SCI consider hypotension as basal systolic blood pressure lower than 90 mmHg in humans (Walters et al., 2013). However, the goal mean arterial pressure in acute management of SCI is > 80–85 mmHg. Higher levels of SCI directly correlate with frequency and severity of hypotension, by compromising vascular sympathetic outflow, basal vascular tone, and thus, arterial pressure (Krassioukov and Claydon, 2006). In the chronic stage of SCI, prolonged hypotension can be asymptomatic, but nevertheless it is associated with chronic fatigue (Lucas et al., 2004), reduced health-related quality of life (Carlozzi et al., 2013), neurological deficits (Catapano et al., 2016) and increased risk of mortality.

Moreover, individuals with high level SCI often experience orthostatic hypotension, which is a drop in systolic blood pressure by at least 20 mmHg and diastolic by 10 mmHg upon the assumption of an upright position (Freeman et al., 2011). Such a drop in blood pressure is attributed to failed vascular sympathetic activation due to interrupted descending excitatory transmission. Failure to vasoconstrict during an orthostatic challenge results in reduced venous return and stroke volume, as well as excessive venous pooling in the lower limbs. Secondary mechanisms that contribute to orthostatic hypotension include hypovolemia, absence of skeletal pump activity, cardiovascular deconditioning and upregulation of vasodilatory agents (Claydon et al., 2006; Wecht et al., 2007). Classic symptoms of orthostatic hypotension include blurred vision, light headedness, dizziness, fatigue and syncope (Claydon et al., 2006). Additionally, orthostatic hypotension in individuals sustaining SCI may substantially limit a person's ability to accomplish their activities of daily living and successfully participate and complete physical rehabilitation.

Cardiac arrhythmias and vagal dysfunction

Heart rate is tightly regulated by synchronous vagal and sympathetic modulatory outflow, therefore a high level SCI that disrupts such a balance may result in disordered heart rate activity. Almost all individuals with severe tetraplegia experience life-threatening bradycardia immediately after SCI, which is a resting heart rate of < 60 beats/min (Collins et al., 2006). This is mainly attributed to disrupted cardiac sympathetic outflow in conjunction with cardiac vagal dominance (Lehmann et al., 1987). Furthermore, injuries to the mid thoracic spine that cause hypotension may elicit tachycardia as a compensatory attempt to ameliorate basal hypotension. Such tachycardia is mediated by increased cardiac sympathetic arborization (Lujan et al., 2012) and altered ventricular calcium handling capacity (Rodenbaugh et al., 2003), both of which are conducive for arrhythmogenesis.

In theory, cardiac parasympathetic activity should be preserved after SCI because vagus efferents travel directly from the medulla to effector orgars. However, recent electrophysiological and animal studies show disordered cardiac vagal modulation after SCI. For example, head-up tilt experiments, which normally cause vagal withdrawal, fail to elicit a reduction in cardiac vagal activity in individuals with SCI (Wecht et

al., 2006). Conversely, cardiac vagal stimulation does not result in an expected drop in heart rate following SCI (Wecht et al., 2009). Moreover, the QT-variability index, a gauge of cardiac vagal activity when sympathetic tone is low (Sharif et al., 2015), is suggestive of reduced cardiac parasympathetic outflow in individuals with SCI (Ravensbergen et al., 2012). Recent clinical studies demonstrated impaired vagal modulation over ventricular diastolic function following SCI (Sharif, unpublished), which might be explained by morphological changes in vagal preganglionic neurons (De Carlo, unpublished). These studies suggest a paradoxical impairment in cardiac vagal control following SCI, which merits further investigation.

Autonomic Dysreflexia

AD is a condition characterized by transient bursts of massive sympathetic discharges that result in dangerous episodic hypertension in response to a noxious stimulus below the level of injury (Karlsson, 1999). Clinically, AD is indicated when systolic blood pressure rises above baseline by at least 20 mmHg. However, since individuals with SCI are typically hypotensive, a rise of blood pressure towards "normal" ranges could also suggest a dysreflexic event. AD manifests in both acute and chronic stages of SCI, and although it is more prevalent in complete injuries above T_6 (Mathais, 1992), individuals with incomplete SCI are prone to developing it as well (Helkowski et al., 2003). Noxious cutaneous and visceral stimuli below the neurological level trigger AD, but bladder and colorectal distention (CRD) are the most potent triggers for this response. Accordingly, CRD-induced AD *via* an inflatable balloon tipped catheter has become a well-established method for studying the hyper-reflexive response in animal studies (Krassioukov and Weaver, 1995; Krenz and Weaver, 1998a). However, a major limitation to this method is that it is not natural, as in these investigations, AD is stimulated in an artificial manner. Therefore, another method of evaluating AD in pre-clinical studies is by detecting the frequency of spontaneous AD, which refers to the number of hyperreflexic episodes experienced in a given period of time. Typically, blood pressure and heart rate are simultaneously measured over a 24-hour period *via* implantable telemetry, and whenever blood pressure spikes instantaneously by more than 20 mmHg, AD is signified (**Figure 2**).

The exact mechanisms underlying AD are still unknown, but formation of new intraspinal circuitry paralleled with peripheral vascular plasticity contribute to such a disorder (**Figure 3**). When afferent fibers below the injury transmit noxious inputs *via* the dorsal horn, SPNs caudal to the injury that undergo maladaptive plasticity respond by reflexively releasing massive amounts norepinephrine to the splanchnic region, which consequently causes severe hypertension. Due to damaged bulbospinal pathways, inhibitory efferent signals cannot reach and neutralize the activated SPNs below the injury, which results in rostral vasodilation and sustained caudal vasoconstriction. The presentation of AD can range from asymptomatic (Ekland et al., 2008) to mildly symptomatic to life-threatening (Vallès et al., 2005). Classic symptoms include sudden hypertension,

Table 1 Signs and symptoms of autonomic dysreflexia

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|---|
| Elevated blood pressure by at least 20 mmHg from baseline |
| Pounding headache |
| Face and neck flushing |
| Profuse sweating above the level of injury |
| Shivering |
| Cutis ansernia (goose bumps) |
| Blurred vision |
| Dizziness |
| Nausea |
| Eyes watering |
| Pronounced bradycardia/irregular heart beats |
| Rapid breathing |

throbbing headache, face flushing and sweating above injury level (**Table 1**). More severe consequences of AD include seizures (Fausel and Paski, 2014), cardiac arrhythmias (Pine et al., 1991), cerebrovascular hemorrhage (Vallès et al., 2005) and death (Dolinak and Balraj, 2007).

Interruption of supraspinal regulation

As discussed in the previous sections, neurons in the brainstem and hypothalamus project to the spinal cord to modulate sympathetic activity and control basal and reflexive hemodynamics. For example, neurons in the C_1 region of the RVLM release epinephrine for the tonic discharge of SPNs to sustain sympathetic outflow within a normal range (Guyenet et al., 1989), while those in the caudal raphe nuclei secrete serotonin to increase sympathetic activity (Marina et al., 2006). If the majority of serotonergic inputs are abolished, basal blood pressure decreases (Coote, 1990). Following SCI, these descending vasomotor pathways are partially or completely damaged. Resultant decrease in sympathetic activity and plasma levels of catecholamine cause hypotension at rest and during a postural challenge (Mathias, 2006). Moreover, the loss of descending regulation of sympathetic activity is the initial and primary cause of AD (**Figure 3A**), which leads to the development of central and peripheral changes (discussed below) that exacerbate the hyper-reflexive episodes. It is still unknown, however, if alterations in supraspinal regions following SCI contribute to AD. Supraspinal plasticity has been reported to occur after SCI, as a neural adaptation to paralysis. Such plasticity could theoretically impact supraspinal vasomotor networks, making them more conducive for hyper-reflexive bursts or sympathetic disinhibition, thus facilitating AD. However, research on supraspinal plasticity within the autonomic regions and its potential contribution to AD is certainly warranted.

Pelvic afferent fiber sprouting

Both pelvic myelinated and unmyelinated afferent fibers are upregulated after SCI, however only the unmyelinated C-fibers, which highly express neuropeptide calcitonin gene related peptide (CGRP) (Keast and De Groat, 1992), play an exclusive role in eliciting AD (Hou et al., 2008). C-fiber
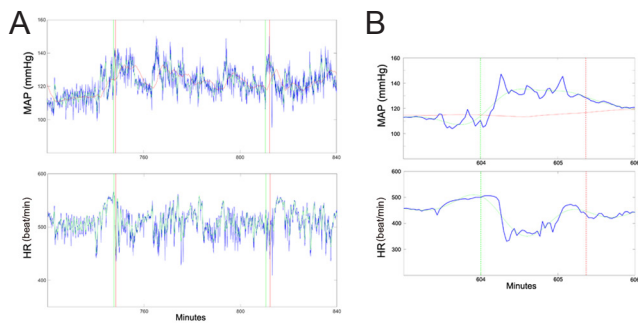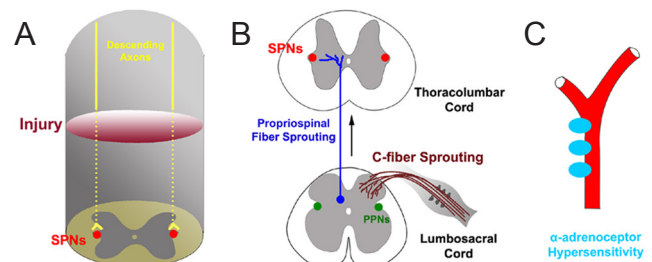
Figure 2 Graphic examples of spontaneous AD following SCI.
The spinal cord was completely transected at T_4 in a Fischer 344 rat. Using a radio-telemetric system connecting with an implantable probe inserted into the descending aorta, resting hemodynamics was recorded every 2 seconds for 24 hours 2 weeks post-injury. The event of spontaneous AD was subsequently detected in data analysis with a program written in Matlab (The Math Works, Inc.), in which MAP peak exceeds the baseline at least 15 mmHg whereas HR must drop by at least 15 beats/min. (A) The blue lines show MAP or HR tracers in a 120-minute period. The vertical green lines indicate the beginning of an AD event, while red dotted lines coincide with the end of the event. The horizontal red lines represent the baseline trace and horizontal green lines are smoothened traces. (B) A representative time-stretched tracer indicates a typical AD response manifested by suddenly increased MAP and simultaneously decreased HR. MAP: Mean arterial pressure; HR: heart rate; AD: autonomic dysreflexia; SCI: spinal cord injury.

Figure 3 Schematic of the pathophysiology of autonomic dysreflexia (AD).
(A) Loss of supraspinal control over sympathetic preganglionic neurons is the primary cause of disordered blood pressure regulation and AD after spinal cord injury (SCI). (B) Increased sprouting of C-fibers (CGRP) within the dorsal horn of the sacral region enhances noxious inputs from the pelvic region. Corresponding propriospinal neuron sprouting transmits these noxious signals rostrally to SPNs within the thoracolumbar region. The sympathetic preganglionic neurons (SPNs) within the thoracolumbar region also undergo morphological changes that render them unstable and supersensitive when stimulated, causing them to release massive surges of sympathetic discharge which markedly increases blood pressure. (C) α-Adrenoceptors within the peripheral vasculature become hypersensitive to sympathetic stimulation resulting in a greater degree of vasoconstriction and smooth muscle contraction when activated by catecholamines thus further augmenting the hypertensive responses.

sprouting in the dorsal root ganglia is instrumental for the development of AD following SCI. Compared to their myelinated counterpart, C-fibers are smaller in diameter, unmyelinated and are primarily involved in conveying thermal and nociceptive signals to supraspinal centers (Keast and De Groat, 1992). Notably, since CGRP-fibers express the high nerve growth factor (NGF) affinity receptor, TrK (Averill et al., 1995), elevation in NGF content following SCI substantially exacerbates CGRP-axonal sprouting (Korsching and Thoenen, 1985; Lindsay and Harmar, 1989) which exaggerates the degree of noxious sensory input.

Experimental mid-thoracic SCI causes considerable enlargements in CGRP terminal arbors within the dorsal horn, which represents increased sprouting of unmyelinated C-fibers within sensory neurons (Krenz and Weaver, 1998b; Krenz et al., 1999; Marsh et al., 2002) (**Figure 3B**). This has also been demonstrated in clinically relevant models of SCI (Weaver et al., 2001). The proliferation of CGRP-fibers within the dorsal roots exaggerates transmission of sensory inputs from peripheral sources, which over-excites the SPNs and consequently results in an augmented hyper-reflexive sympathetic response. Although CGRP-fibers undergo similar degrees of sprouting in all spinal segments following SCI (Krenz and Weaver, 1998b; Ondarza et al., 2003), sprouting in the lumbosacral region, specifically, plays a chief role in eliciting AD (Cameron et al., 2006; Rabchevsky, 2006; Hou et al., 2008). This is likely because lumbosacral segments contain afferent neurons innervated by the pelvic organs, which convey the most sensitive noxious stimuli for AD (bladder and colon distension). Moreover, elevated CGRP immunoreactivity in the dorsal horn occurs 2 weeks post injury (Krenz and Weaver, 1998b; Wong et al., 2000; Weaver et al.,

2001), which is when AD becomes fully established (Krenz and Weaver, 1998a; Krassioukov et al., 1999). Correlational observations show a strong relationship between CGRP-fiber distribution in the dorsal horn and the magnitude of CRD-induced AD following increased NGF release after SCI (Krenz et al., 1999; Cameron et al., 2006; Rabchevsky, 2006). More direct evidence shows that neutralizing intraspinal NGF with a NGF-antibody or a TrK anatagonist prevents sprouting of CGRP-fibers and consequently mitigates the hypertensive response during CRD (Krenz et al., 1999; Marsh et al., 2002). Conversely, experimental overexpression of NGF further increases CGRP-fiber sprouting and exacerbates CRD-induced AD, while abrogating CGRP-fibers with Semaphorin 3A mitigates hyperreflexia (Cameron et al., 2006). These studies provide strong evidence that NGF-induced CGRP sprouting likely elicits AD by enhancing sensory input to the SPNs.

Plasticity of propriospinal neurons
Although there is a paucity of literature regarding the relationship between propriospinal neurons (PN) and autonomic dysfunction following SCI, some evidence suggests that PN plasticity may facilitate AD. A PN is defined as an interneuron of which the cell body is located in the spinal cord and its axon terminals project to different spinal segments (Flynn et al., 2011). Anatomically, PNs are considered either long or short based on the length of their axons. Short PNs are those whose axons span over one to six spinal segments, whereas long PNs stretch over more than six segments (Contana, 2009). Anterograde tracing revealed that PNs extend along the entire length of the spinal cord *via* lamina X/dorsal gray commissure (Matsushita, 1998; Petkó and Antal, 2000). In motor function, this anatomical orientation serves as a basis

for the reciprocal connection between cervical and lumbar motor circuits to enable synchronous activity between upper and lower limbs during ambulation (Juvin et al., 2005).

Similar to C-fiber sprouting, PNs also undergo similar alterations following SCI that contribute to the genesis of AD (**Figure 3B**). This was initially hypothesized by Cameron et al. (2006), who employed anterograde tracing from the lumbosacral spine to reveal increased PN projections around the thoracic SPNs at 2 weeks post SCI, the time-point when AD was evident. These findings were later corroborated by studies reporting elevated lumbosacral PN axonal density around the dorsal gray commissure after SCI (Hou et al., 2008). Sacral PNs convey noxious inputs from the CGRP-fibers rostrally towards SPNs in the thoracolumbar segments, which causes them to produce a reflexive sympathetic discharge (Hou et al., 2008). Furthermore, intermittent CRD caused a marked increase in c-fos levels around the lumbosacral dorsal gray commissure, indicating activation of lumbosacral interneurons during AD (Hou et al., 2008). This is in agreement with previous reports that showed a 3-fold increase in the amount of c-fos labelled neurons in the lumbosacral cord after similar treatments (Landrum et al., 2002). These findings suggest that plasticity of lumbosacral NPs may relay the increased sensory signal input towards thoracolumbar SPNs to elicit a dysreflexic episode.

Morphological changes in SPNs
Following SCI, SPNs in the IML undergo morphological alterations that are pivotal for the development of AD. At 1 week post-injury, SPNs caudal to the injury become severely atrophied, as evidenced by reduced somal size as well as loss and retraction of neurite dendritic arborizing (Krassioukov and Weaver, 1995, 1996; Llewellyn-Smith et al., 2006). Such morphological decaying is not evident in the SPNs rostural to the injury, suggesting that loss of supraspinal input plays a key role in mediating such maladaptive plasticity after SCI. By 2 weeks post-injury, SPN atrophy is completely reversed, as somal size and dendritic density are regained, while dendritic projections are restored towards their normal terminal points (Krassioukov and Weaver, 1996; Krenz and Weaver, 1998a). These temporal alterations in the SPNs are also confirmed by human studies (Krassioukov et al., 1999). Interestingly, re-establishment of SPN size at 2 weeks post-injury coincides with the time point of AD manifestation. At 1 week post-injury when SPNs are atrophied, CRD does not elicit AD, however when SPNs regain their size at 2 weeks post-injury, CRD results in dramatic hypertensive episodes (Krassioukov and Weaver, 1995; Krenz and Weaver, 1998a). This implies that as SPNs regain their normal size and dendritic arborization, new inappropriate synapses are formed which instigate reflexive sympathetic responses to noxious sensory input.

It is unknown how new intraspinal connections that mediate AD are created, however upregulation of neural regulatory signals following SCI may account for their formation. For instance, synaptophysin is a presynaptic vesicle phosphoprotein involved in fiber outgrowth and synaptogenesis (Masliah et al., 1991) and is highly expressed around caudal SPNs 1

week post SCI (Krassioukov and Weaver, 1995). Although this is the time point prior to restoration of SPN morphology and development of AD, it suggests that neurotrophic factors that form new unfavorable synapses are activated well before the establishment of AD, which could provide a window of opportunity for early neuroprotective treatments (Krassioukov and Weaver, 1996). Moreover, growth associated protein-43 (GAP-43) is another phosphoprotein involved in nerve regeneration and new neurite path formation (Neve et al., 1998) that may be implicated in AD. Following SCI, GAP-43 is overexpressed around the SPNs in the IML and extends throughout the intermediate gray matter, suggesting sprouting of new intraspinal axons that are possibly implicated in the initiation of AD (Weaver et al., 1997). Additionally, despite disruption of supraspinal input to spinal autonomic regions, SPNs caudal to the injury sustain detectable amounts of glutamate, GABA and catecholamines, all of which may provide anatomic substrates for exaggerated sympathetic reflexes during AD (Cassam et al., 1997; Llewellyn-Smith et al., 1997).

Peripheral vascular alterations
In addition to central neural plasticity, the vasculature also undergoes adaptive alterations following SCI that are highly implicated in AD (**Figure 3C**). Mathias et al. (1976) was the first to report changes in vascular function following SCI, where individuals with SCI demonstrated greater increases in blood pressure compared to able-bodied individuals after administration of an α-receptor agonist. This invoked the idea that after SCI, α-adrenoceptors may become hypersensitive to sympathetic stimulation, thus augmenting vasoconstriction and hypertension during AD. These findings were later confirmed by a series of studies, which confirmed that α-adrenoceptors, on the receptor level, become hyper-sensitive to sympathomimetics in systemic (Krum et al., 1992a, b) and local blood vessels (Arnold et al., 1995) after SCI. There is currently no evidence suggesting an upregulation or increase in the amount of vascular receptors after SCI. Hyper-responsiveness of α-adrenoceptors following SCI is thought to be a physiological compensation to the sustained low levels of plasma nor-adrenaline following sympathetic denervation (Krum et al., 1992a, b). However, this postulate is somewhat contentious, as β2-adrenoceptors are also subjected to low levels of catecholaminergic stimulation following SCI, but do not demonstrate such hyper-excitability (Krum et al., 1992b). Similarly, rats with SCI exhibit super-sensitivity to angiotensin II agonists, despite upregulation of this hormone (Groothuis et al., 2010; Al Dera and Brock, 2015) and its enzyme precursor, renin (Mathias et al., 1976). Therefore, attenuated sympathetic tone following SCI may not completely explain the reason behind α-adrenoceptor hyper-sensitivity.

Recent *in vitro* studies propose different potential mechanisms for vascular super-reactivity after SCI. These studies typically reported enhanced and/or prolonged vascular contractions in response to peripheral nerve stimulation (Yeoh et al., 2004; Brock et al., 2006; Rummery et al., 2010; Tripovic et al., 2011) or α-adrenoceptor agonists (Yeoh et al., 2004; Brock et al., 2006; Laird et al., 2008). However, such vascular

responses are attributed to altered smooth muscle morphology (Yeoh et al., 2004), impaired neural re-uptake of norepinephrine (Brock et al., 2006; Laird et al., 2008), or disruption in the relative proportion of α-adrenoceptor subtypes (Laird et al., 2008). In addition, there still remains much discrepancy regarding the location (Laird et al., 2008; Rummery et al., 2010) and type of blood vessels (McLachlan and Brock, 2006) that become super-sensitive following SCI. It is noteworthy to mention that elevated vascular reactivity to sympathetic stimulation provides a secondary mechanism that exacerbates AD, whereas central plasticity is the primary cause. As such, reversing these vascular alterations could reduce the severity of hypertension during a dysreflexic episode, but would not completely eliminate it. Successful lasting treatments should focus on ameliorating central mechanisms, while peripheral strategies may serve as a temporary solution.

Applicable Treatments and Experimental Therapeutic Approaches for AD

Recent alarming reports show a substantial gap of knowledge regarding AD within medical emergency personnel (Jackson and Acland, 2011), individuals with SCI and even their caregivers (McGillivray et al., 2009; Schottler et al., 2009). It is therefore imperative that clinicians, individuals with SCI and those living with them to be educated on the necessary measures required to prevent, detect and manage AD. The best approach for managing AD is for SCI individuals to become well aware of the specific noxious stimuli that trigger an episode and to avoid such situations (Rabchevsky and Kitzman, 2011). There are currently no permanent effective treatments for AD, as the most commonly used interventions only have transient and fleeting effects. During a dysreflexic episode, non-pharmacological measures should be employed first in order to alleviate the symptoms and decrease the hypertensive spikes. If non-pharmacological measures are ineffective in doing so, pharmacological agents with rapid anti-hypertensive properties should be implemented (Consortium for Spinal Cord Medicine, 2002; Krassioukov et al., 2009). Which if are also unsuccessful in reducing blood pressure, then the individual must be taken to the hospital immediately.

Nonpharmacological management
A step-by-step protocol for acute and immediate management of AD is outlined in the *Guidelines of the Consortium for Spinal Cord Medicine* (Consortium for Spinal Cord Medicine, 2002) (**Figure 4**). First, prompt recognition of symptoms is a must, which can also be confirmed by obtaining a blood pressure measurement. Second, the individual must be kept in an upright position, as this could facilitate blood pooling in the lower limbs due to orthostatic gravitation. In addition, keeping a patient in supine during AD can increase the risk for cerebrovascular hemorrhage and/or hypertensive encephalopathy. The next step is to loosen any tight clothing or constricting devices caudal to the injury to improve lower limb blood pooling, but also, tight clothing may act as a noxious stimulus in overly sensitive individuals. This is followed by rapid investigative work to identify and remove the source of noxious stimulation
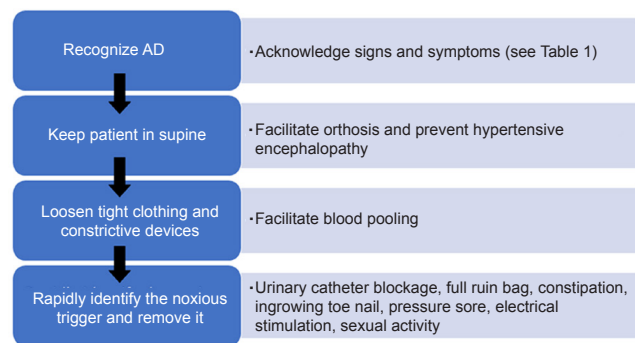
Figure 4 Schematic illustration of the step-by-step protocol for non-pharmacological and acute management of autonomic dysreflexia (AD).

triggering AD, however, in 85% of cases it is related to bladder distension or fecal impaction (Krassioukov et al., 2009). In this case, indwelling urinary catheters should be examined for possible blockages, urinary bags must be emptied and steps must be taken to facilitate voiding. Elimination of the noxious trigger usually eliminates AD immediately, however, if elevated blood pressure is sustained, then pharmacological interventions become necessary.

Pharmacological interventions
In a recent systematic review, Krassioukov et al. (2009) discussed in detail the most commonly used drugs to alleviate symptoms of AD. Nifedipine, a calcium channel blocker traditionally used to treat hypertension and angina, is the most widely used drug for immediate treatment of AD. It has been the preferred method by patients due to its instant effects on reducing blood pressure and ameliorating minor and major symptoms (Krassioukov et al., 2009). It is typically administered *via* a 'bite and swallow' method at a dose of 10 mg, which ensures rapid release and absorption of its contents. The same dose may be taken again within 30–60 minutes if blood pressure has not completely subsided back to normal (Ferguson and Vlasses, 1986). Nifedipine is also effective in reducing blood pressure spikes during noxious procedures such as cystometry (Thyberg et al., 1994), cystoscopy (Dykstra et al., 1987) and vibro-ejaculation (Steinberger et al., 1990). Nitrates are the second most commonly used agents for acute treatment of AD in individuals with SCI (Krassioukov et al., 2009). In contrast to Nifedipin, nitrates are potent vasodilators that work directly on vascular smooth muscle, and are also primarily used for the treatment of angina. Sublingual administration of nitrates is the preferred method, as it has rapid onset of action and longer lasting effects compared to inhalation (Braddom and Rocco, 1991). Besides anecdotal observations and expert opinions, no studies have provided empirical evidence for the effectiveness of nitrates on AD. Although not validated in clinical trials yet, acute administration of neuropathic pain medication, gabapentin, was recently shown to alleviate CRD-induced AD in SCI rats (Rabchevsky et al., 2011, 2012). Gabapentin is thought to exert its positive effects by decreasing presynaptic glutamatergic release, as glu-

tamate neurotransmission may contribute to the development of AD (Rabchevsky et al., 2012). However, further studies are required to establish gabapentin's efficacy for treating AD in humans with SCI. Other drugs that are commonly used to reduce hypertensive episodes during AD include α-adrenoceptor blockers, angiotensin I converting enzyme inhibitors, ganglionic blockers, and sildenafil (viagra) (Krassioukov et al., 2009).

Botulinum toxin (Botox, BT)

BT is a potent neurotoxin produced by the anaerobic gram-positive bacterium *Clostridium botulinum* (Nigam and Nigam, 2010). It contains 8 subtypes, however, subtype A (BTA) is most commonly used in clinical practice due to its potent propensity to cause temporary paralysis of skeletal muscles. Thus, BTA has been widely used as a means for treating abnormal muscle contractions and spasms in a wide range of neuromuscular disorders. It exerts effects by blocking the release of acetylcholine into the neuromuscular junction, thereby inhibiting post-synaptic uptake of the neurotransmitter and preventing muscle contractions. Due to BTA's ability to cause temporary muscle paralysis, it has been an effective strategy for treating hyper-reflexive bladders and detrusor-sphincter dyssynergia (DSD) in individuals with SCI (Khera et al., 2004). Both DSD and bladder hyper-reflexia are well appreciated triggers for AD, as obstruction of the urethral outlet during detrusor muscle contractions increases intravesical pressure, thereby resulting in robust transmission of noxious bladder sensations. Several human studies reported dramatic reductions or disappearance of AD secondary to improved DSD and detrusor hyperreflexia after administration of BTA (Gallien et al., 1998; Schurch et al., 2000). In addition, more recent clinical trials reported decreased severity and frequency of AD during urodynamics after administration treatment with BTA, which was related to increased bladder volume, compliance and voiding threshold (Tsai et al., 2009; Fougere et al., 2016). However, these results are not universal, there is a need to resolve literature dispute as one study showed exacerbation of AD in a subpopulation of SCI individuals following BTA injections (Chen and Kuo, 2012).

Capsaicin

Capsaicin is a neurotoxin extracted from red peppers and has a selective inhibitory effect on sensory C-fibers through their vanilloid receptors. Low doses of capsaicin initially excite and depolarize C-fibers in the dorsal root, while prolonged application eventually desensitizes and damages the sensory fibers, thus inhibiting transmission of noxious sensations (Lynn, 1990). As C-fiber sprouting plays an important role in the pathogenesis of AD (see mechanisms section), it is plausible that ablating them with capsaicin would reduce the severity of the hyper-reflexia. One study demonstrated elimination of AD during bladder distension following capsaicin treatment in patients with SCI (Igawa et al., 2003), while another showed exacerbation of AD (Giannantoni et al., 2002). In the latter study, however, resiniferatoxin RXT, a more selective and potent C-fiber desensitizer, eliminated AD. These findings suggest that capsaicin must be administered in sufficiently high doses to eliminate C-fibers, since low doses could alternatively stimulate a hyper-reflexive event.

Anti-CD11d antibody

Anti CD-11d antibody is an anti-inflammatory agent specific to the CD11d/CD18 integrin. It has a neuroprotective immunomodulatory effect by blocking the interaction between CD11d and vascular cell adhesion molecule 1 (VCAM), thus preventing pro-inflammatory cytokines from being released and further damaging the spinal cord (Weaver et al., 2015). Administration of CD11d antibody acutely after experimental SCI markedly reduced CRD-induced AD by at least 50%, which persisted for 6 weeks (Gris et al., 2004). These improvements were not related to changes in CGRP-fiber content, but possibly due to enhanced preservation of neural tissue over several segments caudal to the injury site (Gris et al., 2005). Moreover, CD11d administration within the first 6 hours of an injury substantially reduced the magnitude of the hypertensive reflex during CRD, suggesting an early window of opportunity for this form of treatment with clinical relevance, as humans typically get to a hospital after a SCI within 6–12 hours (Ditor et al., 2006).

Cell transplantation

Cell transplantation has been extensively studied for its therapeutic potential to restore sensory/motor function following SCI, however, little is known about its ability to improve autonomic deficits in this population. Only recently pre-clinical studies started to examine the effects of cell transplantation on cardiovascular autonomic function in SCI. In the first study to do so, Kalincík et al. (2010) showed that transplanting olfactory ensheathing cells (OEC) following SCI did not alleviate the severity of AD, but accelerated blood pressure recovery time during a hyper-reflexive episode by approximately 50%. Although OEC transplantation did not promote nerve regeneration across the graft, there was evidence for morphological alterations in the SPNs caudal and rostral to the injury site, which may have mediated the partial autonomic recovery. In contrasts, transplantation of neural stem cells (NSCs) may be a more promising strategy for restoring cardiovascular autonomic function after SCI. Recently, Hou et al. (Hou et al., 2013) transplanted embryonic rat brainstem neural stem cells into a complete T_4 transection, which improved resting hemodynamics and dramatically reduced CRD-induced AD. These improvements were in conjunction with robust long-distance axonal growth and subsequent topographic reinnervation of caudal SPNs (Hou et al., 2013). Moreover, since spinal serotonergic depletion caudal to the injury contributes to the initiation of AD (Cormier et al., 2010), transplantation of serotonergic cells from fetal raphe nucleus reduced the frequency and magnitude of AD in rats with SCI (Hou, unpublished).

Future Perspectives and Considerations

It is clear that AD is a very complex disorder mediated by maladaptive central and peripheral reorganization. The multifaceted nature of AD pathophysiology makes it difficult to

develop focused and long lasting treatments. For example, this report provided evidence for collective plasticity within the SPNs, CGRP-fibers, PNs, and peripheral vasculature, all of which contribute to the exaggerated hypertensive sympathetic reflex. Therefore, successful interventions may have to implore a comprehensive approach to address all of these issues. So far, clinical interventions used to treat AD are temporary means as they only provide a "Band-Aid" solution to the problem. This is not unexpected, as much remains unknown about the pathology of AD, but also, we do not know how all of the separate components leading to AD conjugate with one another. The majority of our knowledge stems from animal studies in the acute or sub-acute stages of SCI, hence we also do not know how the purported mechanisms change or contribute to AD chronically after SCI. Therefore, examination of the putative causes underlying AD is warranted. Moreover, most pre-clinical investigations of AD are based on completely transected injury models. Although transection models provide a great deal of insight to understand SCI and are also more pleasant for experimental evaluation, they are not clinically relevant. Accordingly, studies may simulate preclinical models as closely as possible to clinical situations to better understand AD.

Animal studies show that intraspinal plasticity facilitates AD development within 2 weeks of SCI. However, trophic and inflammatory factors mediating such plasticity are typically activated immediately following SCI, preceding the initiation of AD. This implies that neuroprotective strategies to block these negative factors could potentially prevent formation of unfavorable pathways, thus inhibiting the development of AD. Therapeutic approaches aimed at reestablishing supraspinal autonomic control are certainly required in the chronic stages of SCI. Although very novel, recent evidence from our laboratory suggests that stem cell transplantation, using different types of cells, may be efficacious in improving disordered cardiovascular autonomic regulation and reducing the severity of AD. We hope that by further refining and enhancing cell transplantation methods, we could find a permanent and effective treatment for AD.

Conclusion

AD is experienced by the majority of individuals with high severe SCI, which could have detrimental and life-threatening outcomes. Although there have been considerable advancements in the field, much remains unknown about the pathology of AD, hence we still do not have lasting effective treatments for this disorder. Disrupted supraspinal regulation over sympathetic spinal centers results in the formation of new intraspinal circuitry, in concert with peripheral vascular alterations, which are key for the development of AD. As such, strategies aimed at permanently treating AD should focus on restoring supraspinal connection and regulation of cardiovascular sympathetic activity.

References

Aicher SA (2003) The gigantocellular depressor area revisited. Cell Mol Neurobiol 23:479-490.

Al Dera H, Brock JA (2015) Spinal cord injury increases the reactivity of rat tail artery to angiotensin II. Front Neurosci 8:435.

Anderson KD (2004) Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 21:1371-1383.

Arnold JM, Feng QP, Delaney GA, Teasell RW (1995) Autonomic dysreflexia in tetraplegic patients: evidence for alpha-adrenoceptor hyper-responsiveness. Clin Auton Res 5:267-270.

Averill S, McMahon SB, Clary DO, Reichardt LF, Priestley JV (1995) Immunocytochemical localization of trkA receptors in chemically identified subgroups of adult rat sensory neurons. Eur J Neurosci 7:1484-1494.

Braddom RL, Rocco JF (1991) Autonomic dysreflexia. A survey of current treatment. Am J Phys Med Rehabil 70:234-241.

Brock JA, Yeoh M, McLachlan EM (2006) Enhanced neurally evoked responses and inhibition of norepinephrine reuptake in rat mesenteric arteries after spinal transection. Am J Physiol Heart Circ Physiol 290:H398-405.

Cameron AA, Smith GM, Randall DC, Brown DR, Rabchevsky AG (2006) Genetic manipulation of intraspinal plasticity after spinal cord injury alters the severity of autonomic dysreflexia. J Neurosci 26:2923-2932.

Campos RR, Carillo BA, Oliveira-Sales EB, Silva AM, Silva NF, Futuro Neto HA, Bergamaschi CT (2008) Role of the caudal pressor area in the regulation of sympathetic vasomotor tone. Braz J Med Biol Res 41:557-562.

Carlozzi NE, Fyffe D, Morin KG, Byrne R, Tulsky DS, Victorson D, Lai JS, Wecht JM (2013) Impact of blood pressure dysregulation on health-related quality of life in persons with spinal cord injury: development of a conceptual model. Arch Phys Med Rehabil 94:1721-1730.

Cassam AK, Llewellyn-Smith IJ, Weaver LC (1997) Catecholamine enzymes and neuropeptides are expressed in fibres and somata in the intermediate gray matter in chronic spinal rats. Neuroscience 78:829-841.

Catapano JS, John Hawryluk GW, Whetstone W, Saigal R, Ferguson A, Talbott J, Bresnahan J, Dhall S, Pan J, Beattie M, Manley G (2016) Higher mean arterial pressure values correlate with neurologic improvement in patients with initially complete spinal cord injuries. World Neurosurg 96:72-79.

Chalmers J, Arnolda L, Llewellyn-Smith I, Minson J, Pilowsky P, Suzuki S (1994) Central neurons and neurotransmitters in the control of blood pressure. Clin Exp Pharmacol Physiol 21:819-829.

Chen SF, Kuo HC (2012) Improvement in autonomic dysreflexia after detrusor onabotulinumtoxinA injections in patients with chronic spinal cord injuries. Ci Ji Yi Xue Za Zhi 24:201-204.

Claydon VE, Steeves JD, Krassioukov A (2006) Orthostatic hypotension following spinal cord injury: understanding clinical pathophysiology. Spinal Cord 44:341-351.

Collins HL, Rodenbaugh DW, DiCarlo SE (2006) Spinal cord injury alters cardiac electrophysiology and increases the susceptibility to ventricular arrhythmias. Prog Brain Res 152:275-288.

Consortium for Spinal Cord Medicine (2002) Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities. J Spinal Cord Med 25 Suppl 1:S67-88.

Contana AC (2009) The Propriospinal System. London: Academic Press.

Coote JH (1990) Bulbospinal serotonergic pathways in the control of blood pressure. J Cardiovasc Pharmacol 15 Suppl 7:S35-41.

Cormier CM, Mukhida K, Walker G, Marsh DR (2010) Development of autonomic dysreflexia after spinal cord injury is associated with a lack of serotonergic axons in the intermediolateral cell column. J Neurotrauma 27:1805-1818.

Curt A, Nitsche B, Rodic B, Schurch B, Dietz V (1997) Assessment of autonomic dysreflexia in patients with spinal cord injury. J Neurol Neurosurg Psychiatry 62:473-477.

Dampney RA (2016) Central neural control of the cardiovascular system: current perspectives. Adv Physiol Educ 40:283-296.

Ditor DS, Bao F, Chen Y, Dekaban GA, Weaver LC (2006) A therapeutic time window for anti-CD 11d monoclonal antibody treatment yielding reduced secondary tissue damage and enhanced behavioral recovery following severe spinal cord injury. J Neurosurg Spine 5:343-352.

Dolinak D, Balraj E (2007) Autonomic dysreflexia and sudden death in people with traumatic spinal cord injury. Am J Forensic Med Pathol 28:95-98.

Dykstra DD, Sidi AA, Anderson LC (1987) The effect of nifedipine on cystoscopy-induced autonomic hyperreflexia in patients with high spinal cord injuries. J Urol 138:1155-1157.

Ekland MB, Krassioukov AV, McBride KE, Elliott SL (2008) Incidence of autonomic dysreflexia and silent autonomic dysreflexia in men with spinal cord injury undergoing sperm retrieval: implications for clinical practice. J Spinal Cord Med 31:33-39.

Fausel RA, Paski SC (2014) Autonomic dysreflexia resulting in seizure after colonoscopy in a patient with spinal cord injury. ACG Case Rep J 1:187-188.

Ferguson RK, Vlasses PH (1986) Hypertensive emergencies and urgencies. JAMA 255:1607-1613.

Flynn JR, Graham BA, Galea MP, Callister RJ (2011) The role of propriospinal interneurons in recovery from spinal cord injury. Neuropharmacology 60:809-822.

Fougere RJ, Currie KD, Nigro MK, Stothers L, Rapoport D, Krassioukov AV (2016) Reduction in bladder-related autonomic dysreflexia after onabotulinumtoxina treatment in spinal cord injury. J Neurotrauma 33:1651-1657.

Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, et al. (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 21:69-72.

Freire-Maia L, Azevedo AD (1990) The autonomic nervous system is not a purely efferent system. Med Hypotheses 32:91-99.

Gallien P, Robineau S, Verin M, Le Bot MP, Nicolas B, Brissot R (1998) Treatment of detrusor sphincter dyssynergia by transperineal injection of botulinum toxin. Arch Phys Med Rehabil 79:715-717.

Ghali MGZ (2017) The brainstem network controlling blood pressure: an important role for pressor sites in the caudal medulla and cervical spinal cord. J Hypertens doi: 10.1097/HJH.0000000000001427.

Giannantoni A, Di Stasi SM, Stephen RL, Navarra P, Scivoletto G, Mearini E, Porena M (2002) Intravesical capsaicin versus resiniferatoxin in patients with detrusor hyperreflexia: a prospective randomized study. J Urol 167:1710-1714.

Gordan R, Gwathmey JK, Xie LH (2015) Autonomic and endocrine control of cardiovascular function. World J Cardiol 7:204-214.

Gris D, Marsh DR, Dekaban GA, Weaver LC (2005) Comparison of effects of methylprednisolone and anti-CD11d antibody treatments on autonomic dysreflexia after spinal cord injury. Exp Neurol 194:541-549.

Gris D, Marsh DR, Oatway MA, Chen Y, Hamilton EF, Dekaban GA, Weaver LC (2004) Transient blockade of the CD11d/CD18 integrin reduces secondary damage after spinal cord injury, improving sensory, autonomic, and motor function. J Neurosci 24:4043-4051.

Groothuis JT, Thijssen DH, Rongen GA, Deinum J, Danser AH, Geurts AC, Smits P, Hopman MT (2010) Angiotensin II contributes to the increased baseline leg vascular resistance in spinal cord-injured individuals. J Hypertens 28:2094-2101.

Guyenet PG, Haselton JR, Sun MK (1989) Sympathoexcitatory neurons of the rostroventrolateral medulla and the origin of the sympathetic vasomotor tone. Prog Brain Res 81:105-116.

Helkowski WM, Ditunno JF, Jr., Boninger M (2003) Autonomic dysreflexia: incidence in persons with neurologically complete and incomplete tetraplegia. J Spinal Cord Med 26:244-247.

Hou S, Tom VJ, Graham L, Lu P, Blesch A (2013) Partial restoration of cardiovascular function by embryonic neural stem cell grafts after complete spinal cord transection. J Neurosci 33:17138-17149.

Hou S, Duale H, Cameron AA, Abshire SM, Lyttle TS, Rabchevsky AG (2008) Plasticity of lumbosacral propriospinal neurons is associated with the development of autonomic dysreflexia after thoracic spinal cord transection. J Comp Neurol 509:382-399.

Igawa Y, Satoh T, Mizusawa H, Seki S, Kato H, Ishizuka O, Nishizawa O (2003) The role of capsaicin-sensitive afferents in autonomic dysreflexia in patients with spinal cord injury. BJU Int 91:637-641.

Jackson CR, Acland R (2011) Knowledge of autonomic dysreflexia in the emergency department. Emerg Med J 28:866-869.

Juvin L, Simmers J, Morin D (2005) Propriospinal circuitry underlying interlimb coordination in mammalian quadrupedal locomotion. J Neurosci 25:6025-6035.

Kalincík T, Choi EA, Féron F, Bianco J, Sutharsan R, Hayward I, Mackay-Sim A, Carrive P, Waite PM (2010) Olfactory ensheathing cells reduce duration of autonomic dysreflexia in rats with high spinal cord injury. Auton Neurosci 154:20-29.

Karlsson AK (1999) Autonomic dysreflexia. Spinal Cord 37:383-391.

Keast JR, De Groat WC (1992) Segmental distribution and peptide content of primary afferent neurons innervating the urogenital organs and colon of male rats. J Comp Neurol 319:615-623.

Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP (2004) Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int 45:987-993.

Korsching S, Thoenen H (1985) Nerve growth factor supply for sensory neurons: site of origin and competition with the sympathetic nervous system. Neurosci Lett 54:201-205.

Krassioukov A, Claydon VE (2006) The clinical problems in cardiovascular control following spinal cord injury: an overview. Prog Brain Res 152:223-229.

Krassioukov A, Warburton DE, Teasell R, Eng JJ; Spinal Cord Injury Rehabilitation Evidence Research Team (2009) A systematic review of the management of autonomic dysreflexia after spinal cord injury. Arch Phys Med Rehabil 90:682-695.

Krassioukov AV, Weaver LC (1995) Reflex and morphological changes in spinal preganglionic neurons after cord injury in rats. Clin Exp Hypertens 17:361-373.

Krassioukov AV, Weaver LC (1996) Morphological changes in sympathetic preganglionic neurons after spinal cord injury in rats. Neuroscience 70:211-225.

Krassioukov AV, Bunge RP, Pucket WR, Bygrave MA (1999) The changes in human spinal sympathetic preganglionic neurons after spinal cord injury. Spinal Cord 37:6-13.

Krenz NR, Weaver LC (1998a) Changes in the morphology of sympathetic preganglionic neurons parallel the development of autonomic dysreflexia after spinal cord injury in rats. Neurosci Lett 243:61-64.

Krenz NR, Weaver LC (1998b) Sprouting of primary afferent fibers after spinal cord transection in the rat. Neuroscience 85:443-458.

Krenz NR, Meakin SO, Krassioukov AV, Weaver LC (1999) Neutralizing intraspinal nerve growth factor blocks autonomic dysreflexia caused by spinal cord injury. J Neurosci 19:7405-7414.

Krum H, Louis WJ, Brown DJ, Howes LG (1992a) Pressor dose responses and baroreflex sensitivity in quadriplegic spinal cord injury patients. J Hypertens 10:245-250.

Krum H, Louis WJ, Brown DJ, Howes LG (1992b) A study of the alpha-1 adrenoceptor blocker prazosin in the prophylactic management of autonomic dysreflexia in high spinal cord injury patients. Clin Auton Res 2:83-88.

Laird AS, Finch AM, Waite PM, Carrive P (2008) Peripheral changes above and below injury level lead to prolonged vascular responses following high spinal cord injury. Am J Physiol Heart Circ Physiol 294:H785-792.

Landrum LM, Jones SL, Blair RW (2002) The expression of Fos-labeled spinal neurons in response to colorectal distension is enhanced after chronic spinal cord transection in the rat. Neuroscience 110:569-578.

Lehmann KG, Lane JG, Piepmeier JM, Batsford WP (1987) Cardiovascular abnormalities accompanying acute spinal cord injury in humans: incidence, time course and severity. J Am Coll Cardiol 10:46-52.

Lindsay RM, Harmar AJ (1989) Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. Nature 337:362-364.

Llewellyn-Smith IJ, Weaver LC, Keast JR (2006) Effects of spinal cord injury on synaptic inputs to sympathetic preganglionic neurons. Prog Brain Res 152:11-26.

Llewellyn-Smith IJ, Cassam AK, Krenz NR, Krassioukov AV, Weaver LC (1997) Glutamate- and GABA-immunoreactive synapses on sympathetic preganglionic neurons caudal to a spinal cord transection in rats. Neuroscience 80:1225-1235.

Lucas KE, Rowe PC, Coresh J, Klag MJ, Meoni LA, Ford DE (2004) Prospective association between hypotension and idiopathic chronic fatigue. J Hypertens 22:691-695.

Lujan HL, Janbaih H, DiCarlo SE (2012) Dynamic interaction between the heart and its sympathetic innervation following T5 spinal cord transection. J Appl Physiol (1985) 113:1332-1341.

Lynn B (1990) Capsaicin: actions on nociceptive C-fibres and therapeutic potential. Pain 41:61-69.

Marina N, Taheri M, Gilbey MP (2006) Generation of a physiological sympathetic motor rhythm in the rat following spinal application of 5-HT. J Physiol 571:441-450.

Marsh DR, Wong ST, Meakin SO, MacDonald JI, Hamilton EF, Weaver LC (2002) Neutralizing intraspinal nerve growth factor with a trkA-IgG fusion protein blocks the development of autonomic dysreflexia in a clip-compression model of spinal cord injury. J Neurotrauma 19:1531-1541.

Masliah E, Fagan AM, Terry RD, DeTeresa R, Mallory M, Gage FH (1991) Reactive synaptogenesis assessed by synaptophysin immunoreactivity is associated with GAP-43 in the dentate gyrus of the adult rat. Exp Neurol 113:131-142.

Mathais CJ (1992) The cardiovascular sysem in tetraplegia and paraplegia. In: Handbook of Clinical Neurology. New York: Elsevier Science.

Mathias CJ (2006) Orthostatic hypotension and paroxysmal hypertension in humans with high spinal cord injury. Prog Brain Res 152:231-243.

Mathias CJ, Frankel HL, Christensen NJ, Spalding JM (1976) Enhanced pressor response to noradrenaline in patients with cervical spinal cord transection. Brain 99:757-770.

Matsushita M (1998) Ascending propriospinal afferents to area X (substantia grisea centralis) of the spinal cord in the rat. Exp Brain Res 119:356-366.

McGillivray CF, Hitzig SL, Craven BC, Tonack MI, Krassioukov AV (2009) Evaluating knowledge of autonomic dysreflexia among individuals with spinal cord injury and their families. J Spinal Cord Med 32:54-62.

McLachlan EM, Brock JA (2006) Adaptations of peripheral vasoconstrictor pathways after spinal cord injury. Prog Brain Res 152:289-297.

Myers J, Lee M, Kiratli J (2007) Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. Am J Phys Med Rehabil 86:142-152.

Neve RL, Coopersmith R, McPhie DL, Santeufemio C, Pratt KG, Murphy CJ, Lynn SD (1998) The neuronal growth-associated protein GAP-43 interacts with rabaptin-5 and participates in endocytosis. J Neurosci 18:7757-7767.

Nigam PK, Nigam A (2010) Botulinum toxin. Indian J Dermatol 55:8-14.

Ondarza AB, Ye Z, Hulsebosch CE (2003) Direct evidence of primary afferent sprouting in distant segments following spinal cord injury in the rat: colocalization of GAP-43 and CGRP. Exp Neurol 184:373-380.

Petkó M, Antal M (2000) Propriospinal afferent and efferent connections of the lateral and medial areas of the dorsal horn (laminae I–IV) in the rat lumbar spinal cord. J Comp Neurol 422:312-325.

Pine ZM, Miller SD, Alonso JA (1991) Atrial fibrillation associated with autonomic dysreflexia. Am J Phys Med Rehabil 70:271-273.

Rabchevsky AG (2006) Segmental organization of spinal reflexes mediating autonomic dysreflexia after spinal cord injury. Prog Brain Res 152:265-274.

Rabchevsky AG, Kitzman PH (2011) Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. Neurotherapeutics 8:274-282.

Rabchevsky AG, Patel SP, Duale H, Lyttle TS, O'Dell CR, Kitzman PH (2011) Gabapentin for spasticity and autonomic dysreflexia after severe spinal cord injury. Spinal Cord 49:99-105.

Rabchevsky AG, Patel SP, Lyttle TS, Eldahan KC, O'Dell CR, Zhang Y, Popovich PG, Kitzman PH, Donohue KD (2012) Effects of gabapentin on muscle spasticity and both induced as well as spontaneous autonomic dysreflexia after complete spinal cord injury. Front Physiol 3:329.

Ravensbergen HJ, Walsh ML, Krassioukov AV, Claydon VE (2012) Electrocardiogram-based predictors for arrhythmia after spinal cord injury. Clin Auton Res 22:265-273.

Rodenbaugh DW, Collins HL, Nowacek DG, DiCarlo SE (2003) Increased susceptibility to ventricular arrhythmias is associated with changes in Ca^{2+} regulatory proteins in paraplegic rats. Am J Physiol Heart Circ Physiol 285:H2605-2613.

Rummery NM, Tripovic D, McLachlan EM, Brock JA (2010) Sympathetic vasoconstriction is potentiated in arteries caudal but not rostral to a spinal cord transection in rats. J Neurotrauma 27:2077-2089.

Schottler J, Vogel L, Chafetz R, Mulcahey MJ (2009) Patient and caregiver knowledge of autonomic dysreflexia among youth with spinal cord injury. Spinal Cord 47:681-686.

Schurch B, Stöhrer M, Kramer G, Schmid DM, Gaul G, Hauri D (2000) Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol 164:692-697.

Sharif H, Cotie LM, La Fountaine MF, Ditor DS (2015) The influence of cardiac autonomic activity on the QT-variability index in able-bodied and incomplete spinal cord injured individuals. Auton Neurosci 190:46-52.

Steinberger RE, Ohl DA, Bennett CJ, McCabe M, Wang SC (1990) Nifedipine pretreatment for autonomic dysreflexia during electroejaculation. Urology 36:228-231.

Thyberg M, Ertzgaard P, Gylling M, Granerus G (1994) Effect of nifedipine on cystometry-induced elevation of blood pressure in patients with a reflex urinary bladder after a high level spinal cord injury. Paraplegia 32:308-313.

Tripovic D, Al Abed A, Rummery NM, Johansen NJ, McLachlan EM, Brock JA (2011) Nerve-evoked constriction of rat tail veins is potentiated and venous diameter is reduced after chronic spinal cord transection. J Neurotrauma 28:821-829.

Tsai SJ, Ying TH, Huang YH, Cheng JW, Bih LI, Lew HL (2009) Transperineal injection of botulinum toxin A for treatment of detrusor sphincter dyssynergia: localization with combined fluoroscopic and electromyographic guidance. Arch Phys Med Rehabil 90:832-836.

Vallès M, Benito J, Portell E, Vidal J (2005) Cerebral hemorrhage due to autonomic dysreflexia in a spinal cord injury patient. Spinal Cord 43:738-740.

Walters BC, Hadley MN, Hurlbert RJ, Aarabi B, Dhall SS, Gelb DE, Harrigan MR, Rozelle CJ, Ryken TC, Theodore N, American Association of Neurological Surgeons, Congress of Neurological Surgeons (2013) Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. Neurosurgery 60 Suppl 1:82-91.

Weaver LC, Cassam AK, Krassioukov AV, Llewellyn-Smith IJ (1997) Changes in immunoreactivity for growth associated protein-43 suggest reorganization of synapses on spinal sympathetic neurons after cord transection. Neuroscience 81:535-551.

Weaver LC, Verghese P, Bruce JC, Fehlings MG, Krenz NR, Marsh DR (2001) Autonomic dysreflexia and primary afferent sprouting after clip-compression injury of the rat spinal cord. J Neurotrauma 18:1107-1119.

Weaver LC, Bao F, Dekaban GA, Hryciw T, Shultz SR, Cain DP, Brown A (2015) CD11d integrin blockade reduces the systemic inflammatory response syndrome after traumatic brain injury in rats. Exp Neurol 271:409-422.

Wecht JM, Weir JP, Bauman WA (2006) Blunted heart rate response to vagal withdrawal in persons with tetraplegia. Clin Auton Res 16:378-383.

Wecht JM, Weir JP, Krothe AH, Spungen AM, Bauman WA (2007) Normalization of supine blood pressure after nitric oxide synthase inhibition in persons with tetraplegia. J Spinal Cord Med 30:5-9.

Wecht JM, Weir JP, DeMeersman RE, Schilero GJ, Handrakis JP, La-Fountaine MF, Cirnigliaro CM, Kirshblum SC, Bauman WA (2009) Cold face test in persons with spinal cord injury: age versus inactivity. Clin Auton Res 19:221-229.

Wong ST, Atkinson BA, Weaver LC (2000) Confocal microscopic analysis reveals sprouting of primary afferent fibres in rat dorsal horn after spinal cord injury. Neurosci Lett 296:65-68.

Yeoh M, McLachlan EM, Brock JA (2004) Tail arteries from chronically spinalized rats have potentiated responses to nerve stimulation in vitro. J Physiol 556:545-555.