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Targeting neurotrophin and nitric oxide signaling to promote recovery and ameliorate neurogenic bladder dysfunction following spinal cord injury – Mechanistic concepts and clinical implications

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Abstract

This review summarizes the presentations made to a workshop entitled “Targeting Neurotrophin and Nitric Oxide Signaling to Promote Recovery and Ameliorate Neurogenic Bladder Dysfunction following Spinal Cord Injury – Mechanistic Concepts and Clinical Implications” at the International Continence Society (ICS) 2022 Vienna Meeting. Spinal cord injury (SCI; T8-T9 contusion/transection) causes impaired mobility, neurogenic detrusor overactivity (NDO), detrusor sphincter dyssynergia (DSD) and subsequent decreased quality of life. This workshop discussed the potential of future therapeutic agents that manage the lesion and its consequences, in particular possibilities to reduce the lesion itself and manage pathophysiological changes to the lower urinary tract (LUT). Attenuation of the spinal cord lesion itself was discussed with respect to the potential of a trio of agents: LM11A-3, a p75 neurotrophin receptor modulator to counter activation of local apoptotic pathways; LM22B-10 to promote neuronal growth by targeting tropomyosin-related kinase (Trk) receptors; and cinaciguat, a soluble guanylate cyclase (sGC) activator as an agent promoting angiogenesis at the injury site. The workshop also discussed targets on the bladder to block selectivity sites associated with detrusor overactivity and poor urinary filling profiles, such as purinergic pathways controlling excess contractile activity and afferent signaling, as well as excess fibrosis. Finally, the importance of increased mechanosensitive signaling as a contributor to DSD was considered, as well as potential drug targets. Overall, an emphasis was placed on targets that help restore function and reduce pathological LUT consequences, rather than downregulate normal function.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anthony J. Kanai is on the editorial board of Continence, Christopher H. Fry is a Co-Editor of Continence, and Karl-Erik Andersson is on the Advisory Board of Continence.

Keywords

Spinal cord injury (SCI); Detrusor sphincter dyssynergia (DSD); Neurogenic detrusor overactivity (NDO); Neural cord repair; Bladder wall metabolism; Mechanosensitive afferents

1. Introduction

The following review is a summary of the workshop cited above. Current therapeutic options to treat LUT dysfunction after SCI were reviewed. This was followed by a description of two future targets that may be amenable to interventions; firstly, repair of damage to the cord itself and secondly, normalization of bladder wall functions that contribute to abnormal LUT function. In addition, there were more in depth discussions of the pathophysiology of NDO and DSD that help to shed more insight into the mode of action of current and emergent therapies.

2. Current and future pharmacological treatments for SCI-Induced LUT disorders

Approximately 90% of individuals with SCI have neurogenic LUT dysfunction [2]. NDO and DSD are the major urological symptoms of neurogenic LUT dysfunction after SCI, and often cause high pressure in the bladder that can result in upper urinary tract and renal damage. The main treatment objectives are protection of the urinary tract, improvement of urinary continence, recovery of normal LUT function, and consequent improvement in the patient's quality of life. The current therapeutic drugs for neurogenic LUT dysfunction include antimuscarinics, α_1 -adrenoceptor antagonists, β_3-adrenoceptor agonists, and toxins. Antimuscarinics are used in first-line treatment, as a monotherapy or in combination with other drug classes. However, adverse events including dry mouth, constipation, and cognitive impairment sometimes necessitate treatment discontinuation [3] and several studies reported the efficacy of β_3-adrenoceptorceptor agonists, mirabegron and vibegron to treat NDO [4]. α_1-adrenoceptor antagonists are used to treat storage and voiding symptoms, as well as autonomic dysreflexia [5]. Toxins such as intravesical capsaicin and resiniferatoxin have shown efficacy but have adverse effects [6], are difficult to handle and are currently not used. Intradetrusor botulinum toxin is an effective treatment and an alternative option for patients with NDO who have an inadequate response to oral anticholinergics and/or β_3-adrenoceptor agonists and are able to carry out clean intermittent catheterization, if necessary [7]. Future alternatives, still in development for clinical use, include *e.g.*, small molecule transient receptor potential channel antagonists [8] and inosine [9]. Drugs acting by the nitric oxide (NO•) pathway are of particular potential interest, as the actions of NO• are mediated through sGC that generates cyclic guanosine monophosphate (cGMP) and is considered in detail below. Phosphodiesterase 5 (PDE5) inhibitors that increase cellular cGMP through inhibition of degradation have shown efficacy in proof-of-concept studies [10]. sGC activators, such as cinaciguat, offer interesting alternatives, especially when sGC activity is downregulated under conditions of oxidative stress. Thus far, much attention has been directed to manage the bladder and outflow tract, but other domains remain less explored: considered in the workshop were other targets,

including: attenuation of spinal cord damage itself; and, in the case of DSD, regulation of mechanosensitive afferent activity.

3. Treatment of SCI-induced LUT dysfunction with neurotrophin/NO• signaling promoters

Therapeutic benefits may result by treating distinct stages of SCI-induced pathology using a combination of pharmacological agents to improve the functional outcomes after SCI. Neural differentiation, growth and survival are supported by a variety of trophic factors and neurotrophins have been implicated in neurodegenerative conditions, including SCI. This family of polypeptide growth factors includes nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) acting through p75 and Trk receptors. Neurotrophins are stored in intracellular vesicles as proneurotrophins that are proteolytically cleaved to their mature form before release. However, in pathological conditions or injury, proteolytic cleavage of proneurotrophins cannot keep pace with their increased generation which leads to their premature release and binding to the low affinity p75 neurotrophin-sortilin complex. Activation of p75 neurotrophin receptors ($p75^{NTR}$) by proneurotrophins triggers apoptotic signaling pathways that contribute to degenerative processes following SCI in a mouse model. If administered within a few days of damage [1,16,17], the small molecule $p75^{NTR}$ modulator, LM11A-31, binds to $p75^{NTR}$-sortilin complex as a protective agent to lessen cell death that occurs in the first stage of SCI (Fig. 1). Additionally, LM22B-10, administered afterwards over several weeks [1], activates TrkB/C receptors to promote neural remodeling and help repair spinal cord scarring that can improve LUT function following SCI (Fig. 2).

The actions of NO• are mediated through sGC that generates cGMP leading to various processes including angiogenesis, increased spinal cord perfusion and reduction of tissue scarring. However, sGC activity may be downregulated by a negative feedback action of NO• itself, as well as injury-associated oxidative stress. In this context, sGC activators, such as cinaciguat, could play an essential role, as they boost cGMP production even when sGC activity mediated by NO• is reduced by oxidative stress. The high metabolic activity of neurons and surrounding cells in the central nervous system is sustained by an extensive network of blood vessels. However, chronic stages of SCI are associated with infiltration of inflammatory cells and an added local demand for oxygenation when perfusion is already compromised by the original injury. Incomplete vascularization can lead to focal ischemia that can limit neural regeneration. Therefore, increased vascular perfusion in later stages of SCI may help promote functional recovery. Tissue damage and ischemia correlate with mitochondrial dysfunction which boosts the generation of reactive oxygen species perpetuating cellular damage and expanding the epicenter of the injury. Accordingly, treatment with the heme-independent sGC activator, cinaciguat, in mice with SCI improved mitochondrial respiratory control ratios in spinal cord tissues from the injury site as well as increased vessel formation around the scar (Fig. 3), suggesting an additional novel therapeutic mechanism to protect against secondary damage following SCI [1].

The next two sections are concerned with identification of potential targets in the LUT dysregulated by SCI.

4. Mechanism and pathophysiology of SCI-induced NDO

Two pathological features of the neuropathic bladder (NPB) are enhanced spontaneous contractions and a change to passive wall stiffness and are present in the human bladder, as well as various animal models used to parallel or mimic human conditions. Nerve-evoked contractions from rodent detrusor preparations [11] exhibit a frequency-dependent purinergic component as evidenced by a frequency-dependent release of both acetylcholine (ACh) and ATP, with ATP release occurring at lower frequencies. Purinergic components of the contraction are largely absent in normal human bladder but re-emerge in tissue from humans with SCI, as seen by the leftward shift of the frequency-response curve [12] (Figs. 4, 5A, B). Pathology-induced atropine resistance is attributed to decreased metabolism of ATP by ectonucleotidases [18] and increased basal and stretch-evoked release from non-neuronal sources such as the urothelium [19,20]. The increased levels of ATP can also potentiate autonomous contractions of the detrusor that increase in amplitude due to enhanced gap junction coupling (Fig. 5c), [13,21]. This detrusor activity can in turn stimulate mechanosensitive nerves [22] to cause reflex bladder contractions.

Neurogenic injury is also associated with urinary retention and inflammation, leading to bladder wall remodeling, specifically excess deposition of collagen to alter tissue compliance and bladder capacity. Bladder fibrosis is found not only to occur in SCI but in congenital conditions such as myelomeninocoele [23,24]. Thus, studying NPB of varying etiologies, using *in vivo* and *in vitro* methodologies, will provide a more structured approach to developing solutions that may not just minimize symptoms but provide more targeted solutions to alleviate these conditions.

5. Mechanism and pathophysiology of SCI-induced DSD

The LUT has two main functions, storage and voiding of urine. During the voiding phase supraspinal and spinal mechanisms control relaxation of the outlet urethral sphincter relaxes as well as bladder contraction to promote efficient voiding of urine. SCI rostral to the lumbosacral level eliminates the voluntary and supraspinal control of voiding, initially inducing an areflexic bladder leading to urinary retention [15]. Later, as NDO develops, the loss of detrusor and urethral sphincter coordination, termed DSD, results in inefficient voiding, bladder hypertrophy, and high intravesical pressure (Fig. 6A-D). Although anticholinergics, botulinum toxin and neuromodulation have been available for NDO, a specific treatment targeting DSD is unavailable. Recent studies [25,26] have demonstrated that upregulation of neurotrophic factors such as BDNF is involved in SCI-induced DSD and inefficient voiding (Fig. 7), due to activation of mechanosensitive Aδ-fiber afferent pathways rather than C-fiber afferents whose hyperexcitability contribute to NDO. Thus, anti-neurotrophic factor therapies, those that target Aδ-fiber afferents using subpopulation-specific viral vectors, and/or mechanosensitive channel blockers targeting acid sensing ion channels (ASIC), or Piezo2 channels (Fig. 6E), [14] that are abundantly expressed in dorsal root ganglion [27] offer themselves as new modalities to alleviate inefficient voiding due to SCI-induced DSD.

6. Summary and conclusion

There are multiple factors that influence the response to SCI that results in NDO and DSD. Most current therapies are designed to reduce symptoms associated with these secondary symptom complexes and are directed to control the activity of the LUT. The presentations from this workshop discussed a different approach that targets either repair of the SCI itself in a staged approach, or pathophysiological changes to LUT function.

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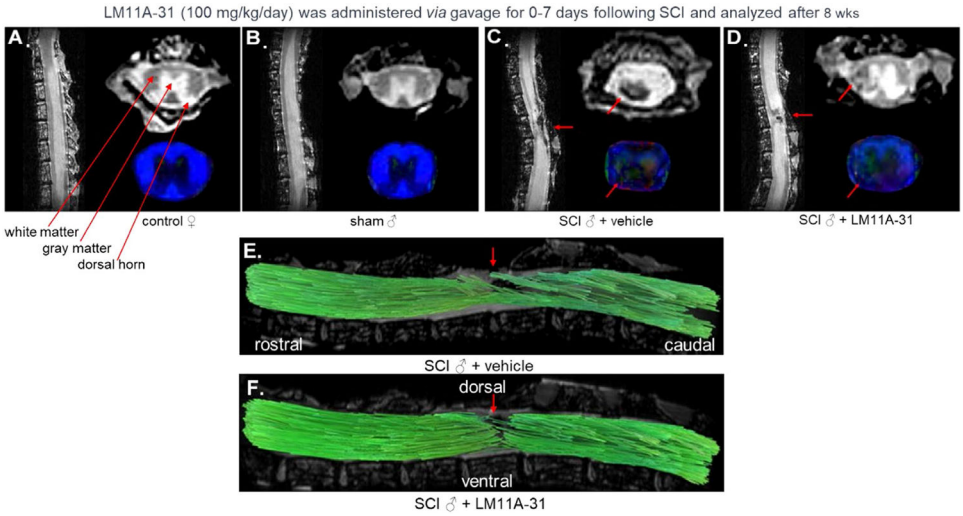

Fig. 1. Magnetic resonance and diffusion tensor imaging from mouse model of SCI (contusion) and the effect of LM11A-31 treatment on neural degeneration at the injury site.

Magnetic resonance images overlaid with directionally encoded color maps for orientation of fractional anisotropy in spinal columns from (A) Control female, (B) sham male, (C) SCI male, and (D) SCI male, given daily LM11A-31 (100 mg/kg/day, gavage, starting within three hours after injury). Anterior/posterior fractional anisotropy is indicated by blue and changes in fractional anisotropy orientation are indicated by green and red prominent in the SCI cords (red arrows) suggesting changes in tissue integrity and cellular orientation. Fiber tracking from (E) vehicle and (F) LM11A-31 treated SCI mouse cords showed decreased continuity in axons through the injury site in vehicle *versus* LM11A-31 treated animals. *Source:* Figure adapted from [1].

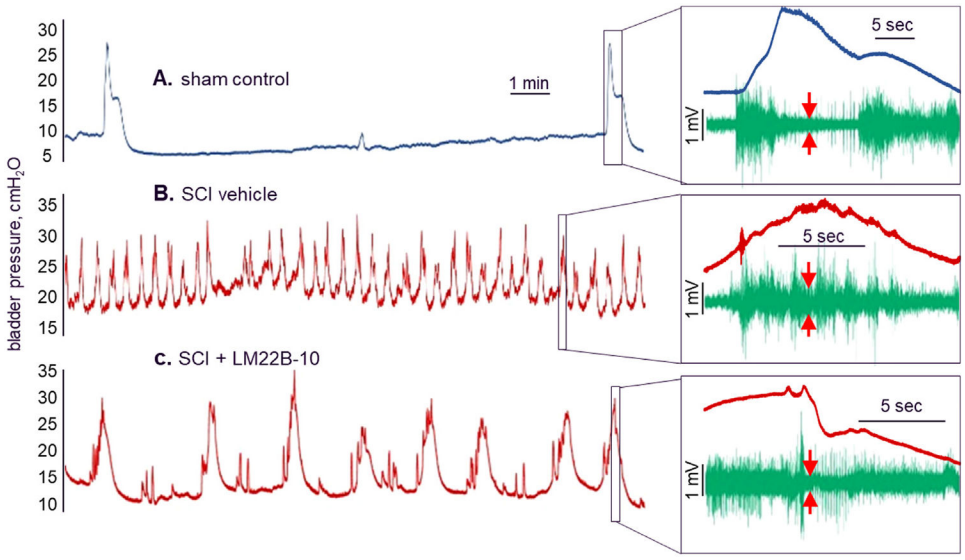

Fig. 2. LM22B-10 treatment improves NDO, and DSD in SCI (contused) mice.

LM22B-10 (5 mg/kg/day/28 days) was administered to female mice *via* osmotic pumps implanted immediately following SCI and decerebrate cystometrogram-external urethral sphincter-electromyogram (CMG-EUS-EMG) recordings were performed 28 days after injury. (A) CMG trace from sham control female with expanded time base inset to the right showing simultaneous EUS-EMG. Note the decrease in tonic EUS firing during voiding concurrent with decrease in bladder pressure. (B) CMG trace from SCI female with vehicle treatment with EUS-EMG recording to inset on right. (C) Trace from SCI female given LM22B-10 treatment and EUS-EMG trace inset to the right.

Source: Figure adapted from [1].

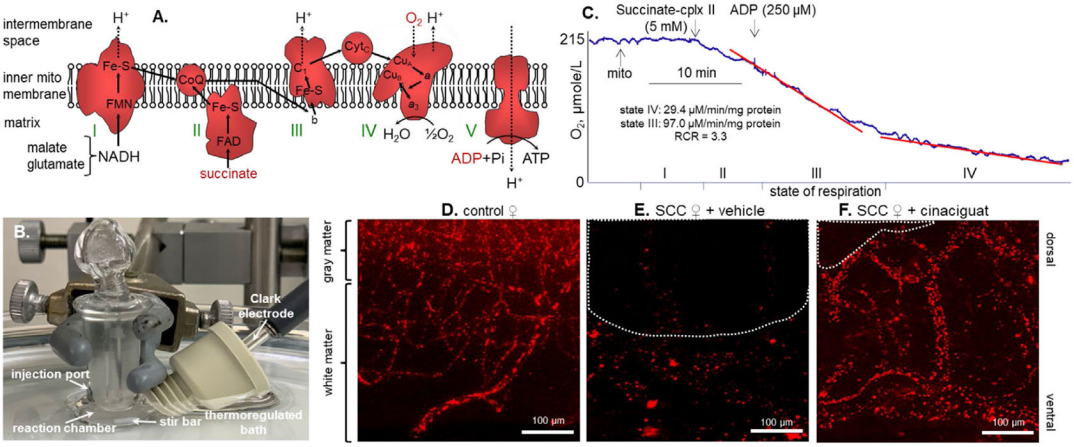

Fig. 3. Cinaciguat improves spinal cord mitochondrial respiration and blood vessel density in mice with SCI (contusion).

(A) Schematic of key membrane proteins of the mitochondrial electron transport chain. (B) Image of setup for measurement of respiratory control ratio from isolated mitochondria. (C) Example trace of oxygen concentration from isolated mitochondria from mouse spinal cord. Vascular illumination was performed by perfusion of mice with fluorescent microbeads (0.02 µm diameter) after which the spinal cord was isolated and sectioned to 50 µm for confocal microscopy. Blood vessels from T8-T9 spinal cord segment of (D) control, (E) SCI mouse given vehicle and (F) SCI mouse give daily cinaciguat for first 7 days (10 mg/kg/day, gavage) after injury then analyzed at four weeks.

Source: Figure adapted from [1].

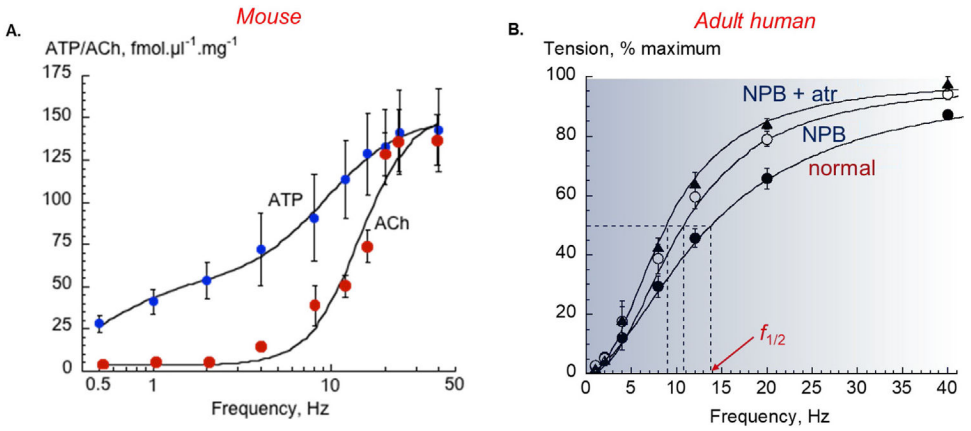

Fig. 4. Differential neurotransmitter release from mouse and adult human detrusor strips in response to electrical field stimulation (EFS).

(A) Force frequency response curve of ATP and acetylcholine (Ach) released from a normal mouse bladder strip demonstrating frequency-dependent release of transmitters. (B). Force frequency response curve of % maximal tension generated to EFS in normal human adult and neuropathic bladder (NPB) detrusor strips. NBP show lower half-maximal stimulation frequencies compared to normal adults. NBP show further leftward shift in the presence of atropine indicating a greater extent of ATP release.

Source: Fig. 4A adapted from [11] and 4B from [12].

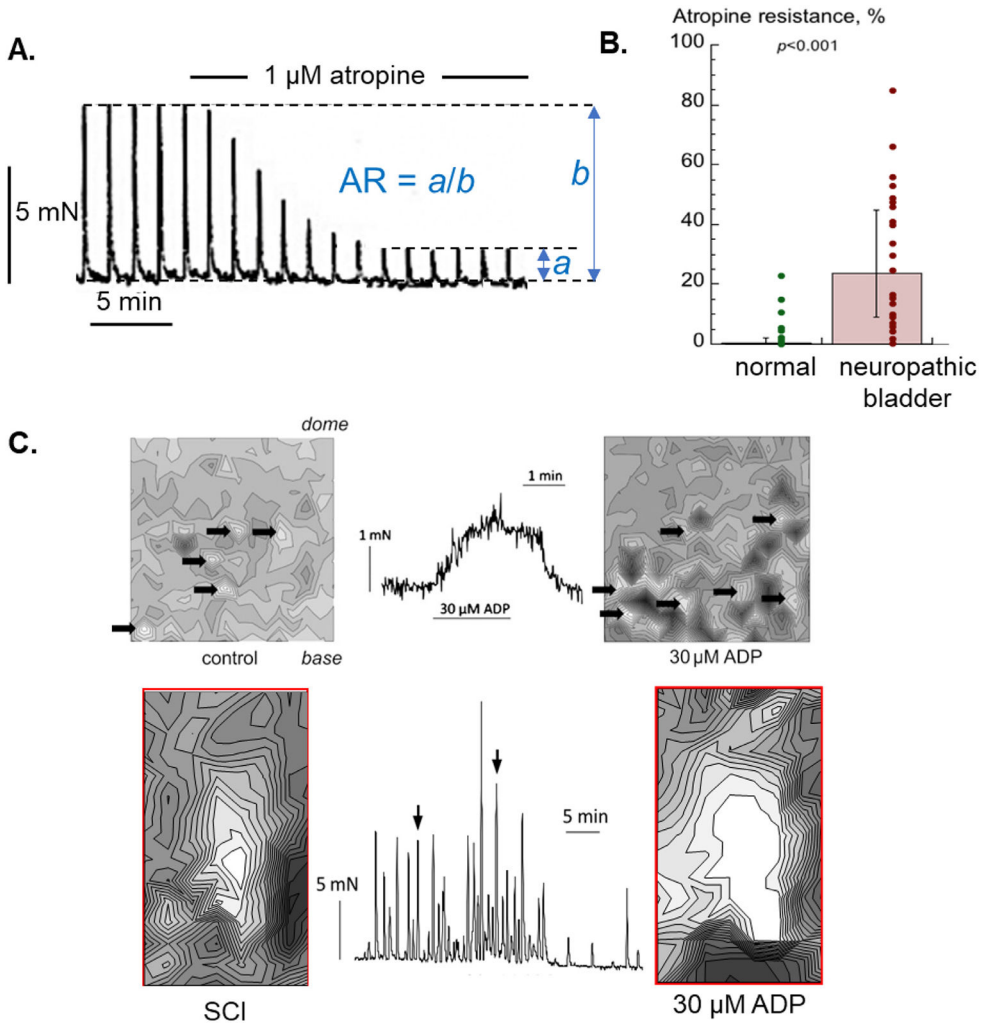

Fig. 5. Atropine resistance in human neuropathic bladders and consequences to detrusor overactivity.

(A) Example tension trace from isolated normal human bladder strip stimulated by EFS before and after addition of atropine to superfusate. Atropine resistance is defined as percentage of remaining EFS contraction compared to control conditions. (B) Percentage atropine resistance of EFS contractions in normal and neuropathic human bladder strips. (C) Optical mapping of Ca^{2+} transients across the mucosal surface of a control mouse bladders show multiple initiation sites of activity (black arrows pointing to white regions on the map indicate earliest conduction delay with respect to imaged area and darker gray shades indicate later conduction delays). Simultaneous tension recordings show addition of ADP increases the number of initiation sites on Ca^{2+} isochrone maps and a slight rise in tension. Conversely, SCI (transected) mouse bladders show a stable single initiation site and large amplitude spontaneous contractions that could be potentiated by ADP. These support a purinergic mechanism for amplifying spontaneous contractions of the detrusor and a role in SCI-induced NDO.

Source: Fig. 5A and B adapted from [12] and 5C adapted from [13].

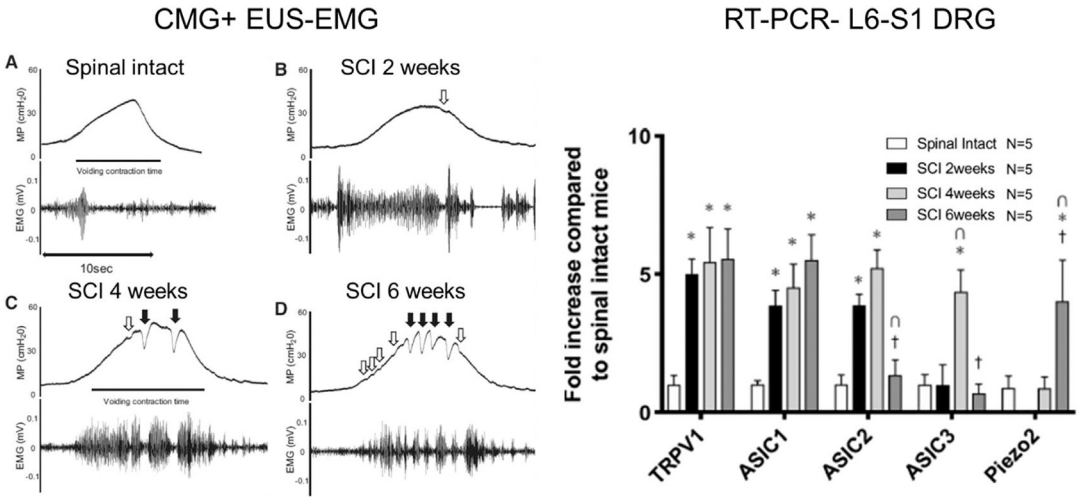

Fig. 6. Time course for development of DSD following SCI (transection) and temporal changes in mechanosensitive channel expression within L6-S1 dorsal root ganglia (DRG) in female mice.

Simultaneous CMG-EUS-EMG recordings from (A) spinal cord intact, (B) two weeks, (C) 4 weeks and (D) 6 weeks post SCI. (E) Bar chart of mRNA expression profile for mechanosensitive channels in the L6-S1 DRG from spinal cord intact and two, four and six weeks after SCI.

Source: Figure adapted from [14].

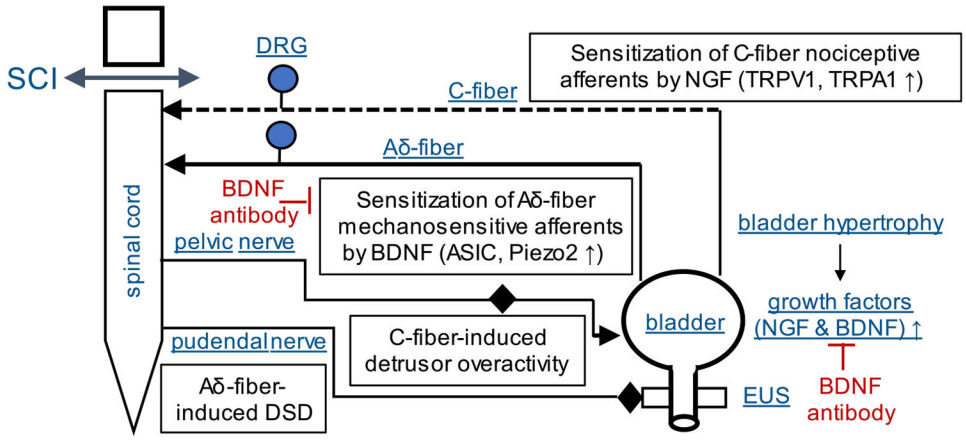

Fig. 7.

Schematic for pathological mechanism of BDNF on LUT dysfunction following SCI (transection).

Source: Figure adapted from [15].