W17: Targeting Neurotrophin and Nitric Oxide Signaling to Promote Recovery and Ameliorate Neurogenic Bladder Dysfunction following Spinal Cord Injury—Mechanistic Concepts and Clinical Implications

Workshop Chair: Anthony Kanai, United States
8 September 2022 7:30 – 9:00

Start	End	Topic	Speakers
07:30	07:50	Current Pharmacological Options for Treating SCI-Induced LUT Dysfunction	Karl-Erik Andersson
07:50	08:10	Treating SCI-induced LUT Dysfunction Using Neurotrophin/NO• Signaling Promotors	Anthony Kanai
08:10	08:30	Mechanism and Pathophysiology of SCI-induced NDO	Christopher Fry
08:30	08:50	Mechanism and Pathophysiology of SCI-induced DSD	Naoki Yoshimura
08:50	09:00	Discussion	All Speakers

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Overview

Spinal cord injury (SCI) can cause impairment of mobility, neurogenic detrusor overactivity (NDO), detrusor sphincter dyssynergia (DSD) and decreased quality of life. This workshop will examine the therapeutic potential of three pharmacological agents in promoting functional recovery and amelioration of NDO and DSD after SCI and the rationale for their use: LM11A-31, a p75 neurotrophin receptor modulator to counter activation of cell death pathways; LM22B-10, to target tropomyosin-related kinase (Trk) receptors and promote neuronal growth; and cinaciguat, a soluble guanylate cyclase (sGC) activator to enhance spinal cord perfusion/oxygenation, support repair of spinal lesions to ameliorate NDO and DSD. LM11A-31 and cinaciguat have passed human safety tests and have potential for transitioning to clinical trials.

Aims & Learning Objectives

This workshop will examine the therapeutic potential of pharmacological agents in promoting functional recovery and amelioration of NDO and DSD after SCI and the rationale for their use.

1. Therapeutic benefits of anti-apoptotic p75 neurotrophin receptor modulator, LM11A-31, in limiting spinal cord lesions, paralysis, NDO and DSD in contusion injury.
2. Therapeutic window of proneuronal growth receptor TrkB/C agonist, LM22B-10, in promoting neural regeneration in spinal cord lesions.
3. Therapeutic benefits of sGC activator, cinaciguat, in promoting spinal cord revascularization and cellular viability.

Target Audience

Urologists, Urogynaecologists, Rehabilitation Therapists, Nurses and Basic Scientists.

Suggested Reading

1. Ikeda, Y., Zabbarova, I., Tyagi, P., Hitchens, K., Wolf-Johnston, A., Wipf, P., Kanai, A. Targeting neurotrophin and nitric oxide signaling to treat spinal cord injury and associated neurogenic bladder overactivity. Continence, 2022. https//doi.1016/j.cont.2022,100014.

2. Yao, C., Cao, X., Yu, B. Revascularization after traumatic spinal cord injury. Frontiers in Physiology, 2021. PMID: 33995118.

3. Rabchevsky, A., Michael, F., Patel, S. Mitochondria focused neurotherapeutics for spinal cord injury. Experimental Neurology, 2020. PMID: 32353464.

4. Zabbarova, I., Ikeda, Y., Carder, J., Wipf, P., Wolf-Johnston, A., Birder, L., Yoshimura, N., Getchell, S., Almansoori, K., Tyagi, P., Fry, C., Drake, M., Kanai, A. Targeting p75 neurotrophin receptors ameliorates spinal cord injury-induced detrusor sphincter dyssynergia in mice. Neurourology & Urodynamics, 37:2452-2461, 2018. PMID: 29806700.

5. Ryu, J., Tooke, K., Malley, S., Soulas, A., Weiss, T., Ganesh, N., Saidi, N., Daugherty, S., Saragovi, U., Ikeda, Y., Zabbarova, I., Kanai, A., Yoshiyama, M., Farhadi, H., de Groat, W., Vizzard, M., Yoon, S. Role of proNGF/p75 signaling in bladder dysfunction after spinal cord injury. Journal of Clinical Investigation, 128:1772-1786, 2018. PMID: 29584618.

6. Tep, C., Lim, T., Ko, P., Getahun, S., Ryu, J., Goettl, V., Massa, S., Basso, M., Longo, F., Yoon, S. Oral administration of a small molecule targeted to block proNGF binding to p75 promotes myelin sparing and functional recovery after spinal cord injury. Journal of Neuroscience, 33:397-410, 2013. PMID: 23303920.

Summary of the Presentations

Current Pharmacological Options for Treating SCI-induced LUTD (K-E. Andersson)

Approximately 90% of individuals with SCI have neurogenic lower urinary tract dysfunction (NLUTD). NDO and DSD, the major neuro-urological symptoms of NLUTD after SCI, often cause high pressure in the bladder, resulting in upper urinary tract dysfunction. The main treatment objectives are protection of the upper urinary tract, improvement of urinary continence,

restoration of the LUT function (or parts of it), and improvement in the patient's quality of life. The current therapeutic drugs for NLUTD include antimuscarinics, α_1 -adrenoceptor antagonists, β_3-adrenoceptor agonists, and toxins. Antimuscarinics are used in first-line treatment for NLUTD. They can be used as monotherapy or in combination with other drug classes. However, adverse events including dry mouth, constipation, and cognitive impairment sometimes necessitate treatment discontinuation. Several studies have reported the efficacy of β_3-adrenoceptorceptor agonists, mirabegron and vibegron, in the treatment for NLUTD. α_1-Adrenoceptor antagonists are used for treatment of storage symptoms, voiding symptoms and autonomic dysreflexia. Toxins such as intravesical capsaicin and resiniferatoxin have shown efficacy but have adverse effects, are difficult to handle and are today considered obsolete. Intradetrusor botulinum toxin is an effective treatment and alternative option for patients with NDO who have an inadequate response to oral anticholinergics and/or β_3-adrenoceptor agonists and are performing clean intermittent catheterization.

Future alternatives, still in development for clinical use, include *e.g.*, small molecule transient receptor potential (TRP) channel antagonists and inosine. Drugs acting by the nitric oxide (NO•) pathway may be of particular interest. The actions of NO• are mediated through soluble sGC that generates cyclic guanosine monophosphate (cGMP). Phosphodiesterase 5 (PDE5) inhibitors act by inhibiting cGMP degradation and have shown efficacy in proof-of-concept studies. Since sGC activity may be downregulated by a negative feedback action of NO• itself, sGC activators, such as cinaciguat, offer an interesting alternative.

Neurotrophin and Nitric Oxide Signaling in SCI-induced LUTD (A. Kanai)

There may be therapeutic benefits to treating the 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) to regulate various cellular processes through the 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 upregulated release which leads to their binding to the low affinity p75 neurotrophin-sortilin complex. Activation of p75 neurotrophin receptors by proneurotrophins triggers apoptotic signaling pathways that contribute to degenerative processes following SCI. Given early, LM11A-31 binds to p75 neurotrophin-sortilin receptors as a protective agent to lessen cell death that occurs in the first stage of SCI. Added later on, LM22B-10 activates Trk receptors to promotes neural remodeling to help repair spinal cord scarring.

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. 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 that perpetuates cellular damage and expands the epicenter of the injury.

Mechanism and Pathophysiology of SCI-induced NDO (C. Fry)

Two frequent pathological features of the neuropathic bladder are enhanced spontaneous contractions and a change to passive wall stiffness. One overriding question is whether these features are causative or merely associated with patient symptoms. This presentation will consider several aspects: are these phenomena consistent in the human bladder and in various animal models that are used to parallel or mimic human conditions; are they consistent in the juvenile and adult bladder; and what are the pathophysiological bases of these observations. Examples will be drawn from neuropathic bladders of varying aetiologies, using *in vivo* and *in vitro* methodologies. Together, answers to these questions should provide a more structured approach to develop solutions that may not just minimise symptoms but provide more targeted solutions to alleviate these conditions.

Mechanism and Pathophysiology of SCI-induced DSD (N. Yoshimura)

The lower urinary tract has two main functions, the storage and voiding of urine. During the voiding phase, the outlet urethral sphincter relaxes and the bladder contracts to promote efficient release of urine through the supraspinal and spinal mechanisms. SCI rostral to the lumbosacral level eliminates the voluntary and supraspinal control of voiding, inducing initially an areflexic bladder leading to urinary retention. Later, NDO develops, and loss of detrusor and urethral sphincter coordination (termed DSD) results in inefficient voiding, bladder hypertrophy, and high intravesical pressure. Although anticholinergics, botulinum toxin and neuromodulation have been available for NDO, the specific treatment targeting DSD is scarce. Recent studies demonstrated that upregulation of neurotrophic factors such as BDNF are involved in SCI-induced DSD and inefficient voiding, due to activation of mechanosensitive Aδ-fiber afferent pathways rather than C-fiber afferents whose hyperexcitability contribute to NDO. Thus, anti-neurotrophic factor therapies, Aδ-fiber afferent targeting therapies using subpopulation-specific viral vectors and/or mechanosensitive channel blockers targeting acid-sensing ion channels (ASIC) or Piezo channels could be new modalities for the treatment of inefficient voiding due to DSD after SCI.