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EDITORIAL

New pharmacological approaches against chronic bowel and bladder problems in paralytics

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Abstract

Spinal cord injury (SCI) leads generally to an irreversible loss of sensory functions and voluntary motor control below injury level. Cures that could repair SCI and/or restore voluntary walking have not been yet developed nor commercialized. Beyond the well-known loss of walking capabilities, most SCI patients experience also a plethora of motor problems and health concerns including specific bladder and bowel dysfunctions. Indeed, chronic constipation and urinary retention, two significant life-threatening complications, are typically found in patients suffering of traumatic (*e.g.*, falls or car accidents) or non-traumatic SCI (*e.g.*, multiple sclerosis, spinal tumors). Secondary health concerns associated with these dysfunctions include hemorrhoids, abdominal distention, altered visceral sensitivity, hydronephrosis, kidney failure, urinary tract infections, sepsis and, in some cases, cardiac arrest. Consequently, individuals with chronic SCI are forced to regularly seek emergency and critical care treatments when some of these conditions occur or become intolerable. Increasing evidence supports the existence of a novel experimental approach that may be capable of preventing the occurrence or severity of bladder and bowel problems. Indeed, recent findings in animal models of SCI have revealed that, despite paraplegia or tetraplegia, it remains possible to elicit episodes of micturition and defecation by acting pharmacologically or electrically upon specialized lumbosacral neuronal networks, namely the spinal or sacral micturition center (SMC) and lumbosacral defecation center (LDC). Daily activation of SMC and LDC neurons could potentially become, new classes of minimally invasive treatments (*i.e.*, if orally active) against these dysfunctions and their many life-threatening complications.

Key words: Prevention of intensive care problems; Quality of care; Temporary recovery of vital functions; Micturition; Defecation; Spinal networks; Central pattern generators

Core tip: This editorial is one of the first to describe

clearly the existence of an urgent medical need for new pharmacological products aimed at providing non-invasive solutions for those suffering chronically of constipation and urinary retention or detrusor-sphincter dyssynergia. Products combining several already known and safe active ingredients for new or synergistic effects acting upon specific central networks of neurons that normally control these functions are of particular interest.

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INTRODUCTION

Spinal cord injury (SCI) either traumatically (*e.g.*, falls, car or sport accidents) or non-traumatically induced (*e.g.*, multiple sclerosis, angioma, *etc.*) generally leads to an irreversible loss of sensory functions and voluntary motor control below injury level. In the United States and Canada, 1.3 million people (approximately 20-25 million worldwide) currently live with a traumatic SCI[1,2] which is a 5-fold increase (*i.e.*, attributed to improvements in acute emergency care) compared with prevalence values assessed previously. As such, SCI has thus progressively become the 2nd most important neurological problem in North America after Alzheimer's disease (*i.e.*, approximately 5 million patients)[2,3]. No therapy can repair SCI *per se*, cure paralysis or even significantly prevent related chronic complications, dysfunctions, multiple debilitating diseases and life-threatening problems (*i.e.*, cardiovascular problems, osteoporosis, muscular atrophy, anemia, spasticity, urinary tract infections, bed sores, pneumonia, sepsis, bladder and bowel problems, *etc.*)[4]. Only symptomatic drugs and biologics are currently used to minimize consequences (*e.g.*, aspirin for pain, antibiotics for infections, *etc.*)[5].

Urination, also called micturition or voiding, is the process of disposing urine from the urinary bladder through the urethra to the outside of the body. When urinary retention (UR) occurs, the bladder remains full which may cause complete anuria that is a medical emergency as the bladder distend (stretch) to enormous sizes. If the bladder distends enough it may become painful and tear. The increase in bladder pressure can also prevent urine entering from the ureters or even cause urine to back up and get into the kidneys, causing hydronephrosis, pyonephrosis, and kidney failure. It has been associated also with urinary tract infections, sepsis and cardiac arrest[6,7]. In chronic cases, UR may cause bladder stones, atrophy of the detrusor muscle, diverticula in the bladder wall and related infections. In cervical injured patients, bladder problems also impact autonomic responses that are affected by SCI, *e.g.*, a full bladder leads to autonomic dysreflexia, hypertension, severe headaches, stroke or cardiovascular failure.

Bowel problems such as diarrhea, fecal incontinence, irritable bowel syndrome (IBS) or constipation typically occur when the gastrointestinal (GI) tract does not work properly. More specifically, constipation is characterized clinically as difficult or infrequent (*i.e.*, < 3 times/wk) passage of stools[8]. In the general population, constipation is often caused by diet problems (*e.g.*, low fiber), lack of exercise, dairy products, stress, pregnancy, medicines such as laxatives, antacids, antidepressants, iron, pain killers or by structural abnormalities (*e.g.*, colon polyps, cancer, diverticula, anal problems, *etc.*)[9,10]. Related-secondary complications include fissures, fecal impaction, ulceration, abdominal distension, hemorrhoids, bleeding, pain and, occasionally, septic shock and death[11]. Chronic constipation is experienced overall by 60 M North Americans[10].

PATHOPHYSIOLOGY OF BLADDER AND BOWEL DYSFUNCTIONS IN PATIENTS WITH SCI

Normally, the process of urination (also called micturition) involves coordination between the central, autonomic and somatic nervous systems that is under voluntary control (brain). Specifically, muscles involved in micturition (*i.e.*, those activating bladder, urethra and pelvic floor) are essentially controlled by coordinated inputs from spinal or sacral micturition center (SMC) neurons[12]. Brain structures (*e.g.*, pontine micturition center) provide additional inputs mediated by SMC for facilitation or inhibition[13-15]. In brief, as the bladder fills, sensory receptors in the bladder wall trigger the micturition motor behaviour - a coordinated contraction of the detrusor and relaxation of the urethral and periurethral muscles[13]. When control over urination is abnormal, urinary incontinence generally occurs. However, for incompletely understood reasons, in patients with SCI and other related pathologies, the opposite problem occurs - that is UR and detrusor-sphincter dyssynergia that lead to improper capacity to empty bladder content is expressed in absence of descending brain inputs.

The gastrointestinal system is a 20 foot-long system comprising the stomach and intestine (bowel) that essentially releases hormones (*e.g.*, gastrin, secretin, melatonin, ghrelin, *etc.*) for local regulation of digestion, absorption and elimination[16]. However, to achieve that, it critically depends also on food transit (> 24 h/meal) that is ensured by rhythmic muscle contractions, *i.e.*, peristalsis, defined as cyclic rostrocaudal series of coordinated contractions and relaxations of GI smooth muscles mediated locally by two main sensorimotor reflexes using acetylcholine, noradrenaline, substance P, adenosine triphosphate, *etc.*[17-19]. In clear contrast with

causes and mechanisms underlying constipation in the general population, bowel problems after SCI (typically chronic constipation, *i.e.*, more than 12 wk/year) is specifically attributed to a dysfunctional control by the CNS of peristalsis and colorectal motility[20-24]. Defecation requires interactions between the somatic, autonomic and central nervous systems. Specifically, supraspinal networks (*e.g.*, pontine defecation center) that send inputs to lumbosacral defecation center (LDC) neurons and corresponding motoneurons (Onuf's nucleus) for control of autonomic and somatic systems (smooth muscles, sphincters) involved in colorectal motility and defecation[16,23,25,26]. Consequently, a failure of supraspinal inputs to modulate LDC neurons (*e.g.*, due SCI) may lead to reduced colorectal motility and increased constipatory problems[16,23,25].

CURRENTLY USED APPROACHES ARE UNACCEPTABLE OR UNSAFE

As of now, there are five (5) main approaches or tools used to control bladder problems after SCI[27-30]: (1) bladder drainage with chronic indwelling catheters or intermittent catheters but frequent hospitalizations, urinary tract infections, bladder and kidney damage and sepsis can be induced when chronically used; (2) drugs (sedatives, anticholinergic, alpha-adrenergic, cholinergic) with peripheral actions on the contraction of bladder muscles or relaxation of sphincters but constipation, dry mouth, blurred vision can also be induced; (3) electrostimulation of sacral anterior roots but it also impairs sexual function and is generally not considered as user-friendly; (4) diapers or condom sheaths can also be used although generally poorly accepted by patient mainly for self-esteem reasons; or (5) *Botox* injection (in bladder, *e.g.*, detrusor muscle) is sometime recommended but only for those specifically experiencing related mild incontinence rather than UR. In other words, UR remains considered as a poorly addressed medical need.

Regarding chronic constipation, SCI patients are currently bound to use nonspecific approaches to reduce the severity of this debilitating problem: (1) stool softeners and laxatives (*e.g.*, Fleet, Senokot, Metamucil, Dulcolax, Colace, Diocto, Exlax); (2) digital rectal stimulation or sacral root stimulation of reflexes; (3) digital evacuation by professionals; or (4) surgery (*e.g.*, ileostomy)[17,31-35]. Although some of the above-mentioned approaches may be suitable for occasional constipation, they are generally not recommended for repeated use. Indeed, when chronically used, they are associated with significantly reduced efficacy and increased side effects such as bloating, cramps, nausea, fever, vomiting, breathing trouble, fainting, flatulence, dependency, diarrhea, electrolyte imbalance, rectal bleeding, pain, nerve lesion, intestinal paralysis, IBS, renal failure, hernia, seizure, arrhythmia, and sepsis[35-39]. Therefore, chronic constipation after SCI or related disorders is still considered as a poorly addressed medical need that would benefit from novel, innovative and potent medicines[39].

EVIDENCE OF A NOVEL NON-INVASIVE AND SAFER APPROACH

Given the problematic described above, it is imperative that scientists attempt rapidly to identify user-friendly, safe and well-tolerated treatments that could specifically and selectively prevent and reduce SCI-related chronic constipation, UR/detrusor sphincter dyssynergia and related health concerns. In fact, some researchers have recently begun to obtain promising results towards that goal. Indeed, a few laboratories in France, Japan, United States, China and Canada have been exploring the feasibility and potential of modulating either SMC neurons or LDC neurons for acute induction of on-demand episodes of micturition or defecation after SCI.

In a rat model of paraplegia (spinal transection at thoracic level T10), Chinese and Americans found that serotonergic agonists of the 5-HT7 subclass, administered intravenously (*iv*) can augment voiding reflex efficacy suggesting SMC-facilitating actions (also called external urethral sphincter central pattern generator by some researchers) given the well-known expression of 5-HT7 receptors in that sacral area of the spinal cord[40]. This mechanism of action is also supported by similar effects obtained following intrathecal administration of 5-HT agonists[41]. Other receptors may be involved since activation (*iv* administration) of the 5-HT1A receptors in these conditions also induced similar effects[42].

A few years prior to those pharmacological studies, a promising role for specific sacral networks in micturition had been clearly shown by Americans who after stimulation at or immediately dorsal to the dorsal gray commissure at S(1) level observed strong (at least 20 mmHg) bladder contractions as well as strong (at least 40 mmHg) external urethral sphincter relaxation, resulting in bladder voiding in cats either intact or spinal cord-injured at the thoracic level[43].

In parallel, my own laboratory in Canada has undertaken extensive drug screening studies aimed at identifying brain permeable drugs that could powerfully elicit, within minutes, some episodes of voiding in chronic paraplegic mice. A few families of ligands including 5-HT1A, 5-HT2 and 5-HT1A/7 agonists were found to elicit within 30 min some significant micturition effects. However, among all tests performed, it was a drug combination composed of buspirone (5-HT1A agonist) and 8-OH-DPAT (5-HT1A/7 agonist) that ended up producing the best micturition-inducing effects upon subcutaneous (*sc*) administration[44]. Comparable effects were found also upon oral gavage suggesting that an orally active tablet comprising both active ingredients could become the first ever SMC-activating drug treatment against bladder dysfunction and related-secondary complications in patients with SCI and

comparable neurological disorders[45].

A comparable approach has been explored in recent years to determine the role of electrical stimulation or pharmacological ligands in LDC-mediated potent reflex defecation[46]. Japanese found that ghrelin receptor agonists such as capromorelin or CP464709 administered *sc* or *iv* (lumbosacral level) can increase fecal pellet production in SCI rats[47,48]. Indirectly, electrical stimulation of the pudendal nerve or of sacral roots can also trigger reflex defecation presumably by afferent-induced activation of LDC neurons given that comparable effects were found with intraspinal stimulation at S2 level[49-51].

As performed for micturition-inducing effects, we also conducted drug screening studies aimed at identify brain permeable drugs capable, within minutes, of inducing episodes of defecation in chronic paraplegic mice. Although, a few families of ligands were found to elicit some defecatory effects, it is a drug combination composed of buspirone (5-HT1A agonist) and neostigmine at low doses (cholinesterase inhibitor) that displayed the best defecation-inducing effects upon *sc* administration[52]. Again, comparable effects were found following oral gavage suggesting that an orally active tablet comprising both active ingredients could become the first ever LDC-activating drug treatment against chronic constipation and related-secondary complications in patients with SCI and comparable neurological disorders[53].

Since both technologies identified in our laboratory are already being developed, under contractual agreement, by a pharmaceutical company called Nordic Life Science Pipeline, it may be reasonably to expect that at least one of these therapies may be granted approval for commercialization in Canada, United States and Europe by 2022[54].

CONCLUSION

SCI is an increasing problem worldwide. It has recently become the second most important neurological problem after Alzheimer's disease. Beyond paralysis and loss of locomotion, several dysfunctions and life-threatening secondary complications associated with bladder and bower problems are often experienced by patients with SCI. Unfortunately, no safe or acceptable treatments have been found to control the occurrence or severity of these significant health concerns which, in turn, forces patients to seek emergency and critical care treatment on a regular basis. Pharmacological or electrical modulation of spinal command centers involved in controlling micturition and defecation behaviors may eventually constitute rather selective, specific and hence safe treatments against chronic constipation and UR after SCI.

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