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EDITORIAL

New avenues for reducing intensive care needs in patients with chronic spinal cord injury

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Abstract

Relatively soon after their accident, patients suffering a spinal cord injury (SCI) begin generally experiencing the development of significant, often life-threatening secondary complications. Many of which are associated with chronic physical inactivity-related immune function problems and increasing susceptibility to infection that repeatedly requires intensive care treatment. Therapies capable of repairing the spinal cord or restoring ambulation would normally prevent many of these problems but, as of now, there is no cure for SCI. Thus, management strategies and antibiotics remain the standard of care although antimicrobial resistance constitutes a significant challenge for patients with chronic SCI facing recurrent infections of the urinary tract and respiratory systems. Identifying alternative therapies capable of safe and potent actions upon these serious health concerns should therefore be considered a priority. This editorial presents some of the novel approaches currently in development for the prevention of specific infections after SCI. Among them, brain-permeable small molecule therapeutics acting centrally on spinal cord circuits that can augment respiratory capabilities or bladder functions. If eventually approved by regulatory authorities, some of these new avenues may potentially become clinically-relevant therapies capable of indirectly preventing the occurrence and/or severity of these life-threatening complications in people with paraplegic or tetraplegic injuries.

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

Core tip: This editorial is one of the first articles to describe clearly the existence of an urgent medical need for new pharmacological products aimed at providing non-invasive solutions for spinal cord injury patients suffering chronically of urinary tract infection or pneumonia. Drugs capable of activating temporarily on demand activity in specific central networks of neurons

that control respiration or micturition are of particular interest.

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INTRODUCTION

Spinal cord injury (SCI) of traumatic origin is generally considered an irreversible condition causing, immediately after trauma, both sensory loss and mobility impairment or complete paralysis[1]. Unfortunately it often leads also, within a few weeks to a few months, to serious chronic complications among which immune problems also knows as central nervous system injury-induced immunodepression (CIDS)[2]. In fact, CIDS is probably one of the main factors contributing subsequently to the development of more specific problems such as urinary tract infections (UTIs), bed sores, pneumonia, sepsis[1]. As of now, biologics (*i.e.*, antibiotics) are generally used to treat these infections[3]. However, antibiotics are associated with the increasing problem of antimicrobial resistance and progressive lack of efficacy against infections[4]. When examined closer, different additional factors may contribute to UTIs and pneumonia specifically after SCI. For instance, descending (*i.e.*, brain and brainstem) control over the sacral spinal cord micturition center is generally lost or impaired after SCI leading to urinary retention (UR) problems[5]. When chronic UR is found, the bladder remains full, although leaking may occur (associated also with bladder sphincter dyssynergia), and overgrowth of bacteria is regularly diagnosed, contributing directly to recurrent UTIs[6]. In the case of pneumonia, specifically for those with tetraplegia (but not only), breathing control problems and reduced coughing capabilities have a direct impact upon mucus accumulation and bacterial overgrowth that leads to pneumonia and, sometimes, respiratory failure[7].

INADEQUACY OF CURRENTLY USED APPROACHES

Medical devices for managing bladder problems are probably the most extensively used means to prevent UTIs. Chronic indwelling catheters or intermittent catheters are typically used for regular bladder drainage and, hence, for reducing incidence of bacterial overgrowth. However, the use of catheters also contributes to UTIs. When chronically performed, these devices are associated with multiple problems including pyuria, pericatheter sepsis, haemorrhage, or bladder and kidney damage[8]. Other alternative approaches are occasionally used such as drugs with peripheral actions on bladder contraction, electrostimulation of sacral anterior roots, diapers or condom sheaths although UR remains largely an unmet medical need that is generally life-threatening[8,9]. For respiratory problems and mucus accumulation, mainly mechanical approaches are normally used, *i.e.,* physical therapy, spontaneous or mechanically assisted coughing, suctioning, and mechanical insufflation-exsufflation[10]. These procedures are rather complex, time-consuming and expensive (*i.e.,* both labor and specialized medical devices)[11].

CENTRALLY-ACTING PHARMACOLOGICAL APPROACHES

There is compelling evidence suggesting that lower incidence of pneumonia or UTIs may be found if, respectively, cardiovascular and pulmonary function or bladder function could be stimulated and improved. To investigate that, some researchers are exploring a novel approach essentially based on central (spinal cord) small molecule therapeutics stimulation of neuronal networks known to normally (*i.e.,* in absence of spinal injuries) control either respiration or micturition.

Proof-of-concept data demonstrating the efficacy of restoring corresponding spinal neuronal activity on voiding reflex have been reported in animal models of SCI. Serotonergic drugs such as 5-HT1A and 5-HT7 agonists were shown indeed, following a single intravenous (*i.v.*) administration, to augment acutely micturition reflex and voiding despite the lack of brain control over that same spinal network in paraplegic rats[12,13]. Central actions upon sacral neuronal networks has been clearly shown by Lecci *et al*[14] following intrathecal administration of similar compounds[14]. My own research group in Canada has built upon these findings to show recently that powerful synergistic effects on reflex voiding may be found by co-administration subcutaneously of 5-HT1A and 5-HT7 receptor agonists in paraplegic mice[15]. Comparable voiding-activating has been shown using direct electrical stimulation of corresponding spinal cord areas in anesthetized chronic paraplegic cats[16].

For breathing problems, the role of another set of neurons has been explored using a comparable approach. It is the crossed phrenic pathway in the spinal cord, also known as CPP, that exhibit significant control of phrenic motoneurons and nerves for diaphragm contraction. It had been found originally by the French researchers Aubier and Pariente, that *i.v.* infusion of aminophylline, an adenosine receptor antagonist, can improve ventilation in dogs *via* stronger diaphragmatic contraction[17]. However, Nantwi *et al*[18] more recently showed that adenosine antagonists aminophylline or theophylline can augment respiration by acting centrally although some additional peripheral actions upon the diaphragm cannot be excluded. Theophylline and aminophylline have both been considered as relatively safe

since approved already by FDA as treatment against chronic obstructive pulmonary disease. Other drugs such as 5-HT1A agonist administered *i.p.* to chronic paraplegic rats have been shown also to stabilize ventilator abnormalities[19]. However, clinical efficacy against respiratory problems and related consequences on mucus accumulation and pneumonia with adenosine antagonists or 5-HT1A agonists remains to be shown.

CONCLUSION

No safe or acceptable treatments have yet been found against the occurrence or severity of significant health concerns such as UTIs and pneumonia in chronic SCI patients. Non-invasive and user-friendly pharmacological acting centrally upon specific spinal command centers involved in controlling micturition and breathing may eventually constitute safe and potent treatments against recurrent infections associated with chronic UR and breathing insufficiency after SCI.

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