Editorial

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INVESTIGATIVE AND CLINICAL UROLOGY
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Regenerative pharmacology in urology

Regenerative pharmacology has been defined as "the application of pharmacological sciences to accelerate, optimize, and characterize (either *in vitro* or *in vivo*) the development, maturation, and function of bioengineered and regenerating tissues" [1,2]. It is a general term and can be thought of as the utilization of a particular growth factor, chemokine, or antibody against disease-relevant factors, to stimulate or block a specific response in a tissue or organ. The ultimate goal of regenerative pharmacology is to *cure* disease through restoration of tissue/organ function, a strategy distinct from standard pharmacotherapy; which is often limited to the amelioration of symptoms.

Regenerative pharmacology approaches have been used within several fields of regenerative medicine, both preclinically and clinically [3]. Molecules produced by mesenchymal stem cells regulate many biological functions including cell growth, replication, differentiation, signaling, apoptosis, adhesion and angiogenesis, may be used therapeutically [4]. Such molecules have been reported to be effective in regenerating e.g., the pelvic floor [4], and may stimulate the mobilization of native cells to the sites of disease/injury [3]. These cell products include a myriad of molecules including chemokines, growth factors (vascular endothelial growth factor [VEGF], fibroblast growth factor, transforming growth factor-alpha), interleukins (IL-1, IL8) and hormones. These molecules are involved in important paracrine and receptor-mediated processes associated with tissue regeneration. Identifying the involvement of some of these molecules in disease development and *using them as therapeutic agonists or antagonists* illustrate principles of regenerative pharmacology. Recent applications of regenerative pharmacology in urology include e.g., use of the chemokine, C-X-C motif chemokine 12 (CXCL12), in nonhuman primates to restore urethral sphincter deficiency [3], antibodies to nerve growth factor (NGF) and antibodies to neurite outgrowth inhibitor (Nogo-A) as treatments for interstitial cystitis [5] and neurogenic lower urinary tract dysfunction [6], respectively.

C-X-C MOTIF CHEMOKINE 12

Chemokines and chemokine receptors regulate multiple processes such as morphogenesis, angiogenesis, and immune responses and are considered potential targets for drug development. Several studies have explored the effects of the chemokine CXCL12 (sometimes called stromal derived factor-1; SDF-1), on cell trafficking and homing of progenitor cells to sites of injury through a receptor (CXCR4/CXCR7) mechanism and enhancing cell survival once at the injury site. Cells from injured organs highly express CXCL12, which causes an increase of local CXCL12 levels and peripheral and bone marrow progenitor cells follow the chemical gradient to the organ [3]. In a nonhuman primate model of chronic intrinsic urinary sphincter deficiency, local injection of CXCL12 had better effect than injected skeletal muscle precursor cells in restoring sphincter structure and function [7]. This raises interesting possibilities of CXCL12 therapy (alone or in combination with cells or other growth factors) for cohorts of patients resistant to cell therapy. CXCL12 does not work alone and is known that the expression of VEGF often coincides with activation of CXCL12. Both pathways contribute to mobilization of endothelial cells and vasculogenesis response to hypoxia and injury. Whereas the CXCL12/CXCR4 axis activates the progenitor cell cascade and its trophic support of tissue growth, VEGF amplifies the skeletal muscle paracrine cascade capable of directly promoting muscle cell survival independent of CXCL12. A theoretical pathway by which CXCL12 and VEGF interact to produce tissue regeneration in the urinary tissue is that CXCL12 works primarily to stimulate cell mobilization to the site of injury. Although CXCL12 has some vasculogenesis properties, it is thought that VEGF is needed to provide lasting vasculogenesis and neurogenesis; both of which support tissue growth. There are numerous applications where CXCL12 and VEGF are used as regenerative pharmacologic tools on a variety of tissues and which highlight the importance of understanding interactive

pathways in tissue regeneration.

NERVE GROWTH FACTOR

Bladder pain syndrome/interstitial cystitis (BPS/IC) is one of the most common chronic disorders of the urinary bladder. The pathophysiology is unknown, but several studies have shown that there is an increased level of NGF in the bladder of BPS/IC patients. NGF is a neurotrophin which is essential for the differentiation and survival of sensory and sympathetic neurons during development. In adults, it has been suggested that NGF, through the sensitization of nociceptive neurons, is important in the generation and potentiation of pain following tissue injury and inflammation. Inhibition of NGF signalling has been shown to reduce pain-like behavioural responses in a number of animal models of visceral pain. Tanezumab is a humanized anti-NGF monoclonal antibody that binds with high affinity and specificity to NGF, preventing it from interacting with receptors on nociceptive neurons. In a randomized, double-blind, placebo controlled phase 2 study, Evans et al. [5] investigated tanezumab as a treatment for interstitial cystitis pain. A total of 34 patients received tanezumab and 30 received placebo. Patients with interstitial cystitis received a single intravenous dose of 200-μg/kg tanezumab or placebo. A significantly higher proportion of patients on tanezumab responded as improved in the global response assessment and tanezumab also significantly reduced urgency episode frequency vs placebo. The authors concluded that tanezumab had shown preliminary efficacy in the treatment of pain associated with interstitial cystitis. Even if the side effects in this study were modest, results from other studies revealing that tanezumab could produce serious adverse effects have stopped further development. Never the less, identifying a target and using antibodies to counteract its actions illustrates that the approach may open new possibilities of treatment.

NEURITE OUTGROWTH INHIBITOR

Pharmacological treatment of neurogenic bladder dysfunction has been limited and only modestly successful in reducing the symptoms of neurogenic detrusor overactivity, and curative treatments are not available. Neurite outgrowth inhibitor or Nogo, also known as Reticulon-4, is a protein that has been identified as an inhibitor of neurite outgrowth in the central nervous system. One of the 3 isoforms, Nogo-A, and its receptors NgR1 and S1PR2, have been extensively studied [8], and it has been shown that Nogo-A destabilises the cytoskeleton via the rho/rho-associated protein kinase (ROCK) pathway. This causes growth cone collapse and inhibition of neuronal growth and plasticity by down-regulation of growth-associated genes. Suppression or neutralisation of Nogo-A or its receptor NgR1 leads to an increase in sprouting, axonal regeneration and neuronal plasticity. Regenerative and compensatory sprouting as well as long distance regeneration of fibres in many parts of the spinal cord and brain can be enhanced and thereby to greater functional recovery after different types of central nervous system (CNS) injuries and [8]. Relevant for micturition control, these processes probably lead to new connections and functional circuits, for example from the pontine micturition centre to the sacral micturition neurons, directly or via long proprio-spinal interneurons. In addition, anti–Nogo-A antibodies could induce plasticity in the circuits the pontine and sacral micturition centres causing reorganisation [6]. To elucidate the mechanisms of action and the potential of anti–Nogo-A antibody therapy for treating neurogenic lower urinary tract dysfunction, animal studies with detailed urodynamic measurements in different neuronal disease models are currently ongoing [6]. Clinical studies are in progress and will show if anti-Nogo-A antibody treatment has the potential to improve our management of neurogenic lower urinary tract dysfunction associated with e.g., spinal cord injury, stroke and multiple sclerosis.

FUTURE PERSPECTIVES

There are a multitude of molecules of interest for urological application, including the chemokine CXCL12, antibodies against NGF, and the inhibitor of neurite outgrowth in the CNS, Nogo-A, and clinical testing of these factors may lead to the introduction of treatments of various urological disorders. Thus, application of regenerative pharmacology principles has the potential to identify treatment paradigms that will optimize, and possibly replace the cell-based and tissue engineering-based approaches to tissue repair and replacement in urology.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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