Editorial focus

Title: Stimulating bioelectronic medicine discovery for urological disorders

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Will this era of disruptive technologies bring new opportunities for treating urological- and kidney-related disorders? This seems likely if recent major government and private investments in bioelectronic medicines are any indicator.

Interest in bioelectronic medicine has grown rapidly following a series of public-private initiatives which signaled the intention of GlaxoSmithKline to develop “electroceuticals” that could transform the use of biological stimulation devices as therapeutics (2). Further significant investments in this emerging field were then made by US government agencies (13). One source has been the Defense Advanced Research Projects Agency (DARPA), but possibly more relevant to urological and kidney-related disorders is the NIH Common Fund program Stimulating Peripheral Activity to Relieve Conditions (SPARC), which is specifically targeting bioelectronic medicine research to organ dysfunction. The NIDDK is one of four Institutes working in partnership with the NIH Office of the Director on this program (https://commonfund.nih.gov/sparc).

Is bioelectronic medicine new technology or old technology with a new name? Electrical stimulation of the nervous system had been used in urology since the 1970s (3), when pioneering work produced the first experimental “neuroprotheses” designed to recover voiding and storage function in patients with spinal cord injuries. Neuromodulation or neurostimulation techniques are now well established as an effective therapeutic technology for treating urological dysfunction, and devices approved by FDA are available (5).

However, given the rapid evolution of consumer technologies and strategic positioning of technology companies to disrupt the health sector, it is easy to see how electrical stimulation therapeutics could also be rapidly transformed—for example, by introducing more selective modes of stimulation, miniaturization, closed-loop control, and more effective programming (5, 7). It is also expected that bioelectronic medicines will not be confined to electrical stimulation as technology will also advance magnetic, optical and other modes of stimulation. For this reason, the therapeutic targets of bioelectronics medicines will be far more extensive and diverse than those previously targeted by electrical neurostimulation techniques (8).

A major perceived benefit of bioelectronic medicine is the possibility of treating disorders where small molecule drugs and economic model of pharmaceutical companies have provided few solutions. Detrusor underactivity (DU) and Underactive Bladder (UAB) are related urological disorders that are representative examples of clinical conditions of this type where effective pharmacotherapy is unavailable. A working definition of DU is provided by the International Continence Society (ICS) as “a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span”, but it has limitations and a complex relationship with the broader symptom complex of UAB that have been repeatedly discussed and reviewed by experts in the literature (4).

As is typical of many urological, kidney-related and other organ based disorders, DU and UAB have complex multi-model pathophysiology that is difficult to diagnose and mostly poorly understood, which also frequently involves direct or indirect contributions from other diverse disorders. This includes other urological disorders such as bladder outflow obstruction (BOO) as well as neurogenic disorders, diabetes and other metabolic conditions and ageing (1).

A challenge to the development of bioelectronics medicines will be the availability of clinical relevant animal models that predict efficacy in humans. Animal models have traditionally been a foundation but also
a limitation for drug discovery, and it is possible that this will also be true for electroceuticals as well. In this context, it is significant that Gonzalez and Grill (2017) (11) have added a new model based on obese-prone rats to the pool of animal models of DU/OA available for research on electrostimulation techniques (3). Obese-prone/obese-resistant rats have been used extensively to study diet-induced obesity (10) but not urological disorders. In this new study, obese-prone rats developed urinary retention and impaired detrusor contractility as shown by urodynamic evidence of increased volume threshold, decreased peak micturition pressure, and decreased voiding. The urological parameters affected in different animal models of obesity and type 1 and 2 diabetes has been recently reviewed (6). The urological dysfunction in obese-prones was similar to detrusor underactivity-like symptoms reported in Zucker diabetic fatty rats (a type 2 diabetes model). In GK rats (a type 2 diabetes model in non-obese rats), however, there are conflicting reports of both bladder overactivity and underactivity could be explained by an underlying relationship with age and duration of the chronic condition (6). This complexity of urological outcomes extends to other animal models of obesity and type 1 and 2 diabetes, and is consistent with DU/OAB comprising only a fraction of the urological complications of obesity and diabetes (UCOD) that have been identified in humans (6). The obese-prone rat model requires more extensive characterization to determine if the underlying pathophysiology contributing to symptoms of DUA are in any way homologous to human DU/OAB, but in the meantime, this first report demonstrates that it can be a useful assay for studying electrical stimulation techniques. Increasing the diversity of animal models available will provide opportunities to compare and further explore the relationship between DU/OA symptoms and underlying pathophysiology specific to each model.

One of the priorities at this early stage of developing bioelectronic medicines is to understand the physical organization or “connectome” of the nervous system networks that interface with organ systems (2). In this regard, the genitourinary system has one of the most complex connectomes of any visceral organ system, as it comprises somatomotor, sympathetic and parasympathetic autonomic (visceromotor) components that interface with sacral and lumbar spinal cord, which in turn interface with circuitry in the brainstem and higher brain areas(9, 12). Previous work has provided a basic understanding of the regional or macroscopic connectivity of these major components of nervous system controlling genitourinary function. Consistent with previous studies using alternate animal models, the first systematic investigation of electrical stimulation at different sites in the obese-prone rat model suggested different efficacy with stimulation of motor branch of the pudendal nerve causing greater improvements in urodynamic parameters than either stimulation of the sensory branch of the pudendal nerve or pelvic nerve (11). Existing clinical neurostimulation/neuromodulation techniques (3, 5) target relatively few of the multiple points in the neural network that interface with the urinary tract and kidneys (Fig. 1). Some of the alternate sites have been studied extensively but not yet resulted in successful translation with confirmation by clinical trials. However, this history of research and successful translation of electrical devices (3, 5, 7) suggests that treatment of urological and kidney-related disorders could benefit significantly from the rational design of bioelectronic medicines that improve targeting or specificity of neurostimulation/neuromodulation techniques. Parallel development of relevant animal models of the complex disorders that cause urological complications will contribute significantly to the successful translation of bioelectronic medicines in this context.
References


Legend

**Figure 1.** Basic organization of the autonomic visceromotor (sympathetic: dark blue; parasympathetic: red), sensory (green) and somatomotor (light blue) neurons in the lumbar and sacral spinal outflow that contribute to neuronal networks that interface with organs of the lower urinary tract and external urinary sphincter. Targeting bioelectronic medicines to the points shown in the legend on the right will affect distinct combinations and classes of these neurons in both peripheral and spinal cord networks. In obese-prone rats (11), stimulation of the pelvic nerve will mostly target axons of sensory afferent and spinal autonomic preganglionic neurons, whereas stimulation of the motor and sensory branches of the pudendal nerve will more selectively target axons of somatomotor and sensory neurons, respectively. Future bioelectronic medicines could address the limitations of existing neurostimulation/neuromodulation techniques, which only have a very limited capability for selective stimulation of specific classes of axons in mixed nerves.