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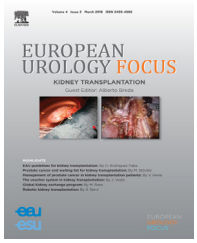

Mini Review – Neuro-urology

Sacral Neuromodulation: Mechanism of Action

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Abstract

Although the mechanism of action of sacral neuromodulation (SNM) is still not fully elucidated, it seems to involve modulation of spinal cord reflexes and brain networks by peripheral afferents according to findings from neurophysiology, electroencephalography, positron emission tomography, and magnetic resonance imaging studies. Moreover, motor effects mediated via efferents on direct stimulation cannot be fully excluded. In this mini-review, we summarize current knowledge on the mechanism of action of SNM.
Patient summary: We reviewed the literature on the mechanism of action of sacral neuromodulation, in which electrical stimulation is applied to the nerves that regulate bladder activity. The mechanism seems to involve modulation of spinal cord reflexes and brain networks by peripheral sensory and possibly motor neurons.

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The mechanism of action of sacral neuromodulation (SNM) has long been an enigma. Although many discoveries still have to be made, much of the veil has already been lifted. Most of the relevant studies investigated patients with overactive bladder syndrome (OAB) and it is thought that SNM inhibits the detrusor muscle without influencing urethral resistance or detrusor contractility during the voiding phase [1]. Modulation of spinal cord reflexes and brain networks by peripheral afferents seems to be involved [2]. This is supported by Sievert and colleagues [3], who reported that early SNM soon after spinal cord injury may prevent neurogenic detrusor overactivity and urinary incontinence, suggesting preservation of nerve plasticity such that C fibers remain silent, detrusor overactivity is avoided, and sympathetic neuron activation in the thoracolumbar cord is suppressed.

In the first study investigating SNM effects on supraspinal centers in humans, Braun and colleagues [4] recorded electroencephalograms in SNM patients and identified reproducible short- and long-latency cortical potentials with a maximum in the sensory cortical area. These were present regardless of whether any stimulation was felt, indicating a supraspinally (sensory) mediated site of modulation. Blok and colleagues [5] used positron emission tomography (PET) to describe how activity in supraspinal centers changes during SNM and found differences in brain activity between acute and chronic stimulation. In the acute phase, changes in areas important for sensorimotor learning were observed (decrease in blood flow in the medial cerebellum and an increase in blood flow in the right postcentral gyrus cortex, right insular cortex, and

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ventromedial orbitofrontal cortex); in the chronic phase, changes in areas important for alertness and awareness were detected (decrease in blood flow in the middle part of the cingulate gyrus, ventromedial orbitofrontal cortex, midbrain, and adjacent midline thalamus, and increase in blood flow in the dorsolateral prefrontal cortex). SNM seems to cause changes in brain activity responsible for detrusor overactivity, bladder filling sensation, urge, and micturition timing [5].

It took more than a decade for other studies to investigate SNM effects on brain activity. In 2017, Weissbart and colleagues [6] and Gill and colleagues [7] used functional magnetic resonance imaging (fMRI) to study changes in brain activity after 6 wk of stimulation and changes in brain activity between stimulation on-off cycles at various stimulus intensities. Weissbart and colleagues [6] noted similar results to Blok and colleagues [5], with several supraspinal areas showing an increase in activity. However, no increase in brain activity could be withheld. In addition, they noted differences between responders and nonresponders: responders had higher activity in the cingulate cortex, inferior frontal gyrus, insula, and thalamus before implantation. These findings suggest that certain patterns of increased brain activity in women with OAB could be associated with therapeutic responses [6]. Gill and colleagues [7] in turn were able to identify differences in brain activity depending on the level of stimulation. Subsensory stimulation deactivated the pons and periaqueductal grey matter, while sensory stimulation deactivated the parietal lobes but activated the insula, and suprasensory stimulation led to widespread activation, including an increase in activity in the somatosensory region. Thus, brain responses to SNM vary with stimulation intensity, which might have therapeutic implications [7]. Lastly, Wenzler and colleagues [8] recorded bladder current perception thresholds (CPTs) to assess the effect of SNM on afferent sensory nerve pathways. They noted measurably higher CPT values after SNM therapy, with maximum changes in myelinated fibers at 250 Hz (Aδ fibers) and 2000 Hz (Aβ fibers), providing further evidence that SNM impacts the sensory function of the bladder.

It was postulated that in patients with nonobstructive urinary retention, SNM inhibits the guarding reflex (the spinal-mediated reflex whereby contraction of the external urethral sphincter results in lowering of intravesical pressure, thereby preventing urinary leakage), so by lowering the sphincter tone, bladder emptying can occur [2]. In women with Fowler's syndrome (primary disorder of external urethral sphincter relaxation: the overactive urethra generates abnormally strong inhibitory afferent signals that block bladder afferent activity at the sacral level and deactivate the periaqueductal grey and higher centers resulting in loss of bladder sensation and voiding dysfunction), it is thought (on the basis of PET and fMRI studies) that SNM aids bladder emptying by blocking inhibition by urethral afferents, leading to restoration of activity associated with brainstem autoregulation and attenuation of cingulate activity [9,10].

We conclude that the mechanism of neuromodulation is not fully understood, but afferents are likely to play a key role in modulating spinal reflexes and brain centers [7,8]. A final argument for this statement is the fact that other neuromodulation techniques (transcutaneous electrical nerve stimulation, transcutaneous/percutaneous tibial nerve stimulation, and pudendal nerve stimulation) seem to show similar effects to SNM although the stimulation occurs at different sites in the body.

However, it is important to note that the neural pathways stimulated that are responsible for activation of afferents leading to modulation of spinal reflexes and brain centers, as well as the methods for achieving adequate afferent stimulation, are all but well understood. Most of the research discussed above is based on the initial studies by Fowler and colleagues [11] and Schurch and colleagues [12], who postulated that the pelvic floor contraction visually observed during implantation of a lead is the result of a spinal reflex response mediated by afferents upon stimulation. However, a very recent study suggests that this view is incorrect and that pelvic floor muscle contractions are due to stimulation of direct efferents [13]. As efficacy rates vary between different neuromodulation techniques (with the highest efficacy rates generally seen for SNM), the involvement of peripheral efferents in pelvic floor motor function cannot be fully excluded.

Conflicts of interest: Stefan De Wachter is a consultant and investigator for Medtronic and Axonics. The remaining authors have nothing to disclose.

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