

Mechanisms of Action of Sacral Neuromodulation for Fecal Incontinence

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Abstract

Fecal incontinence is a devastating condition that may lead to the complete isolation of the individual in severe cases. Sacral neuromodulation has become one of the most important options for treatment of those cases. Although its indications are expanding, the mechanisms of actions are not fully understood. This study aimed to review the main articles regarding sacral neuromodulation mechanisms of action, dividing them into two main categories: direct and central mechanisms.

Keywords: Sacral Neuromodulation; Fecal Incontinence

Introduction

Fecal incontinence is a disabling condition with great impact in social and physical functions. The prevalence reported in United Kingdom is of up to 10%, around 17% in United States and approaches 50% in nursing homes [1-3]. Although frequently associated with birth injuries and aging, the pathophysiology is a complex myriad of pelvic floor disorders, anorectal sensation, colorectal motility and sphincter integrity.

Initial management of these patients usually includes conservative measures such as dietary changes, anti-diarrheal medications, biofeedback and supportive devices [4]. Because of the low success rates of these approaches surgical intervention is often considered, ranging from bulking agents, sphincter procedures (e.g. direct repair, artificial sphincter and dynamic graciloplasty) and ultimately a stoma [5,6].

In the past three decades a great development has been seen in the field of neuromodulation, which consists of low-voltage stimulation to direct or indirect sacral spinal nerves [7,8]. It was first described for the treatment of urinary incontinence as a bridge between conservative treatment and surgical intervention, but great improvement was also noted both for fecal incontinence and constipation [9,10]. It is believed that it can modify neuromuscular aspects that involve defecation, with the remarkable benefits of both being reversible and dose-dependent. Matzel was the first to propose and standardize its application specifically directed to fecal incontinence [7].

Although the mechanisms of action are still not completely understood, the comprehension of such mechanisms is of utmost importance for patient selection and improvement of outcome. The aim of this work is to review the evidence on the mechanisms of sacral neuromodulation (SNM) for fecal incontinence.

Methods

It was reviewed articles investigating mechanisms of action for SNM in fecal incontinence. It was searched the Medline (PubMed, Ovid) and The Cochrane Library databases using the terms: "sacral neuromodulation", "sacral nerve stimulation", "fecal incontinence", "faecal

incontinence” and “mechanism of action. Publications up to January 2019 were included, both human and experimental studies, and the references of the included articles were searched for appropriate additional works. Studies that evaluated SNM for urinary incontinence, congenital abnormalities and spinal cord injuries were excluded.

Results

A total of 38 studies were found proposing mechanisms of sacral neuromodulation for continence disorders. These can be divided into two main categories: direct effects, those that affect the rectum and the sphincter complex, and central effects, those influencing anorectal reflexes and the colonic motility.

Direct mechanisms

In the first study proposing SNM for fecal incontinence, Matzel, *et al.* [7] postulated that the direct stimulation into the sacral nerve roots implicated on improvement of both rest and squeeze pressures and a long-term effect of increase in voluntary sphincter function, presumably due to change from fast twitch fatigable muscle fibers (type II) into slow twitch fatigue-resistant fiber (type I). Other works have also described a statistically significant rise in both rest and squeeze pressures [11-18], although some only shown an increase of the anal squeeze pressure [8,19-27] or no impact of direct manometric findings [28-31]. A systematic review by Mirbagheri, *et al.* [32], including 37 studies, found a trend toward improvement in both maximum rest and squeeze pressures with a median difference of the mean of 5.9 and 14.8 mmHg, respectively. However, there was no correlation between manometric findings and clinical presentation.

It is also believed that SNM alters the rectal physiology, markedly on sensitivity, volume and compliance. Vaizey, *et al.* [25] recorded rectal wall contractility 24 h after neuromodulation showing an increase in the maximum tolerated volume and initial sensation. The previous mentioned systematic review described an improvement in rectal sensitivity, with a decrease of thresholds for sensation for urge and maximum tolerated volume, although no difference was seen on compliance [32].

Although the adaptation of sacral reflex arcs is the most accepted mechanism for these manometric findings [25,32,33], more complex changes in rectal physiology are seen. For example, Kenefick, *et al.* [34] demonstrated an immediate rise in rectal blood flow measured by rectal laser Doppler flowmetry after SNM.

Mechanism	Author	Evidence
Increase in anal pressure	Kenefick, <i>et al.</i> [12]; Ganio, <i>et al.</i> [14]; Rosen, <i>et al.</i> [16]; Altomare, <i>et al.</i> [17]; Ratto, <i>et al.</i> [18] Matzel, <i>et al.</i> [8]; Ripetti, <i>et al.</i> [23]; Vaizey, <i>et al.</i> [25]; Jarrett, <i>et al.</i> [26]; Chan, <i>et al.</i> [27] Sheldon, <i>et al.</i> [28]; Harris, <i>et al.</i> [29]; Malouf, <i>et al.</i> [30]; Uludag, <i>et al.</i> [33] Mirbagheri, <i>et al.</i> [32]	Increase in anal rest and squeeze pressure Increase in anal squeeze pressure only No manometric difference Systematic review – increase in both maximum rest and squeeze pressure.
Increase in rectal sensitivity, volume and compliance	Vaizey, <i>et al.</i> [25] Mirbagheri, <i>et al.</i> [32]	Increase in maximum tolerated volume and initial sensation Systematic review – improvement of rectal sensitivity and maximum tolerated volume; no change in rectal compliance
Increase in rectal blood flow	Kenefick, <i>et al.</i> [34]	Rise in median rectal blood flow

Table 1: Summary of the evidence of direct mechanisms for SNM in fecal incontinence.

Central mechanisms

The stimulation of sacral nerve roots also results in afferent effects in the central nervous system. A number of studies have evaluated the neurophysiological consequences in the cortical presentation of the anal sphincter pathway. Both Sheldon, *et al.* [28] and Harris, *et al.* [29], in clinical studies with different designs involving transcranial magnetic stimulation with 10 and 8 patients respectively, studied the changes in the anal sphincter motor cortex with conflicting results. In the former study, it was seen a reduction in the cortical representation of the anal sphincter, but the latter showed an excitability effect on the same area, possibly due to synaptic neuronal plasticity.

Another observation on clinical scenario was obtained from PET and MRI imaging in a work from Lundby, *et al.* [35], with 8 patients, which showed an increase in regional cerebral blood flow in the frontal cortex after 30-minute sacral stimulation. Interestingly, after 2 weeks of SNM, it was observed a shift of the area with increased flow to the dorsal part of the caudate nucleus, area involved in learning and reward processing, although no correlation with clinical improvement has been demonstrated [35].

Experimental studies have also investigated the impact of SNM on the central nervous system. Griffin, *et al.* showed an increase in the expression of a molecular marker of neuronal plasticity in sensory areas of the cerebral cortex of rats after SNM [36]. A number of animal studies have shown other findings such as increased evoked potentials over the sensory cortex, decrease in rectal hypersensitivity and increase in the threshold to bear colonic distention [37-39].

The afferent stimulus is believed to play a role in modulating colorectal motility after SNM. Uludag, *et al.* [40] have demonstrated a decrease in bowel movements after SNM, but with no differences in manometric findings and colonic transit time. Even though Michelsen, *et al.* [41] also concluded that SNM reduces the frequency of defecation and does not alter the gastrointestinal transit time, their work with colorectal scintigraphy demonstrated an increase in retrograde transport from the descending colon (from a median score of 0 to 2 percent, $p = 0,039$). Finally, a double-blind randomized crossover trial by Patton, *et al.* [42] using high-resolution fiber-optic catheter positioned throughout the colon demonstrated a significant increase in the frequency of retrograde colonic propagating sequences after SNM compared to sham stimulation ($p = 0.014$), with no impact on antegrade colonic movements.

Mechanism	Author	Evidence
Changes in the cortical representation of the anal sphincter	Sheldon, <i>et al.</i> [28]. Harris, <i>et al.</i> [29]	Reduction of the area of the anal sphincter motor cortex Cortical excitability and neuronal plasticity in the anal sphincter motor cortex
Increase cerebral blood flow	Lundby, <i>et al.</i> [35]	Rise in cerebral blood flow after SNM, first in the frontal area e then at the caudate nucleus
Neuronal plasticity	Ishigooka, <i>et al.</i> [38]; Griffin, <i>et al.</i> [36].	Increase expression of molecular markers of neuronal plasticity in rats
Reduced colorectal motility	Uludag, <i>et al.</i> [40]; Michelsen, <i>et al.</i> [41]. Michelsen, <i>et al.</i> [41]; Patton, <i>et al.</i> [42]	Reduced bowel movements Increase in retrograde transport in the colon

Table 2: Summary of the evidence of central mechanisms for SNM in fecal incontinence.

Discussion and Conclusion

Although SNM has been extensively used in fecal incontinence management, its mechanism is not clear yet. The pathophysiology of fecal incontinence does not only comprise of anal sphincter dysfunction, but also more complex factors such as rectal sensation and colorectal motility [43].

Most studies on this topic have investigated the impact of SNM on anal sphincter function through manometric findings and resulted in conflicting results. A systematic review, with data from 37 studies, have concluded that SNM increases both rest and squeeze pressures with a mean difference of the mean of 5.9 and 14.8 mmHg, respectively [32]. However, it is noteworthy that most of the included studies account with a small sample size, ranging from 2 to 32 patients, and with a large methodological heterogeneity of techniques and measurements.

Other than measurements of anal sphincter pressures, the impact on rectal compliance, sensitivity and volume is also a matter of debate. The same previous mentioned review included 7 works evaluating these parameters, ranging from 11 to 23 patients, and showed an improvement in sensitivity and volume, with no significant change in compliance [32]. These findings corroborate the fact that SNM does not only alter the anal sphincter but also modulates sacral reflex arcs that composes the complex mechanism of defecation [25,33].

The stimulation of sacral nerve roots both generates efferent effects, but also afferent stimulus, which are believed to play a significant role in the central nervous system and colonic motility. The works on this topic are mainly experimental or with a small sample size. In rats, SNM has shown to induce neuronal plasticity and excitability in the anal sphincter cortex [36,38]. In the clinical setting, there was conflicting evidence on SNM either exciting or inhibiting the cortical representation of anal sphincter, but another functional work revealed an increase in focal cerebral blood flow measured with PET and MRI [28,29,35]. Although is not clear the impact on cortical excitability, SNM seems to result in changes in central nervous system pathways and excitability.

Other than that, SNM appears to alter colonic motility, specially increasing retrograde transport. Two studies have suggested this finding using different methods, one with colonic scintigraphy and the other by colonic manometry [41,42]. Interestingly, another work showed that although SNM reduces the number of bowel movements, it was not seen an impact on the colonic transit time [40]. These and the central previous mentioned mechanisms may explain the benefit of SNM even in patients with anorectal malformations and even sphincter defects, as demonstrated by Melenhorst., *et al.* [44], which showed a significant reduction of incontinence episodes in patients with sphincter defects up to 33% of circumference.

Finally, despite the remarkable benefits of SNM in the treatment of fecal incontinence, it is not yet clearly understood the mechanisms of action. Current evidence suggest that this treatment modality play a significant role in modulating not only anorectal function, but also influencing on colonic motility and even in central nervous system pathways and cortical representation. Further research is needed to enlighten the way that SNM impact gastrointestinal physiology.

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