ELSEVIER

Autonomic Neuroscience: Basic and Clinical 122 (2005) 69 – 76

AUTONOMIC NEUROSCIENCE: Basic & Clinical

www.elsevier.com/locate/autneu

Spinal cord stimulation attenuates visceromotor reflexes in a rat model of post-inflammatory colonic hypersensitivity

Beverley Greenwood-Van Meerveld [a,b,*], Anthony C. Johnson [a], Robert D. Foreman [b], Bengt Linderoth [b,c]

[a] *Oklahoma Center for Neuroscience, Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma, United States*
[b] *Department of Physiology, Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma, United States*
[c] *Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden*

Received 28 February 2005; received in revised form 4 August 2005; accepted 6 August 2005

Abstract

Spinal cord stimulation (SCS) has been found to relieve neuropathic and ischemic pain clinically and to attenuate a nociceptive reflex in an animal model of acute colonic hypersensitivity. The goal of the present study was to determine the effect of SCS in a rat model of post-inflammatory colonic hypersensitivity. Acute inflammation was induced in rats by a single enema of trinitrobenzenesulfonic acid (TNBS) (50 mg/kg, 0.5 ml, 25% EtOH). Control rats received a single saline enema. A visceromotor behavioral response (VMR), induced by innocuous colorectal distention (30 mm Hg, 10 min) was used to quantify the level of colonic sensitivity on day 3 and 30 post-enema. Prior to VMR testing, under general anesthesia, an electrode (cathode) was placed epidurally on the dorsal surface of the spinal cord at L1 with a paravertebral anode plate. Three to 7 days after implantation of the SCS electrode, the effect of SCS (50 Hz, 0.2 ms, amplitude 90% of motor threshold for 30 min) on colonic sensitivity was determined. On day 30, rats that had received a single TNBS enema were hypersensitive to innocuous colonic distention when compared to rats that received a saline enema (VMR/10 min: TNBS: 17.2±0.8 vs. Saline: 9.6±1.1, $p<0.01$). Spinal cord stimulation significantly reduced the VMR in the TNBS-enema group to a value that resembled the saline-enema group (VMR/10 min: TNBS: 11.2±1.2 vs. Saline: 10.0±1.0). This study provides the first evidence that SCS might be a potential therapeutic for the treatment of abdominal pain observed in patients with post-inflammatory irritable bowel syndrome.

Keywords: Irritable bowel syndrome; Spinal cord stimulation; Pain; Visceromotor response; Post-inflammatory visceral hyperalgesia

1. Introduction

Chronic visceral pain of gastrointestinal origin is poorly understood and lacks an effective therapy. Abdominal pain and discomfort is the major complaint in patients with irritable bowel syndrome (IBS). Abnormal (or heightened) visceral sensory perception has been proposed to account for many of the symptoms of IBS. Evidence in support of this concept consists of the observation that gastrointestinal distention in patients with IBS evokes pain at lower distention pressures compared to asymptomatic control subjects (Ritchie, 1973; Whitehead et al., 1990; Lembo et al., 1996). Interestingly, significant subsets of patients that recover from an acute infectious gastroenteritis also exhibit IBS symptomatology (Chaudhary and Truelove, 1962; Bergin et al., 1993; Collins et al., 1999). Moreover, in patients with inflammatory bowel disease (IBD), remission and recovery from gastrointestinal inflammation is associated with IBS-like symptoms (Isgar et al., 1983).

A model for quantifying the level of visceral sensation in rats by measuring visceromotor behavioral responses (VMR) induced by colorectal distention has been developed (Ness and Gebhart, 1988). This model has been modified by using trinitrobenzenesulfonic acid to produce a post-

* Corresponding author. V.A. Medical Center, Research Administration Rm. 151, 921 N.E. 13th St., Oklahoma City, OK 73014, United States. Tel.: +1 405 270 0501x3547; fax: +1 405 290 1719.
E-mail address: Beverley-Greenwood@ouhsc.edu (B. Greenwood-Van Meerveld).

1566-0702/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.autneu.2005.08.002

inflammatory visceral hypersensitivity in rats. This hypersensitivity resembles that observed in patients with IBS who have recovered from an acute colonic inflammation (Gibson and Greenwood-Van Meerveld, 2000). Studies have shown that in response to sensitization, innocuous colorectal distention evokes a VMR, which resembles that induced by nociceptive stimuli in non-sensitized rats (Greenwood-Van Meerveld et al., 2002). These findings strongly suggest that alterations in neuronal activity within the spinal cord may be involved in processing information from the colon, and that induced abnormalities in spinal neuronal processing may lead to the development of visceral hypersensitivity.

Electrical stimulation of the dorsal columns of the spinal cord (spinal cord stimulation; SCS) has been employed for more than 30 years to treat chronic severe pain (Meyerson and Linderoth, 2000). The cardinal indication for using this treatment is neuropathic pain, which is often due to nerve root or peripheral nerve lesions; but also, nociceptive pain, as seen for example in an ischemic limb, has responded well to SCS (Meyerson and Linderoth, 2000; Linderoth et al. (in press)). The mechanism by which SCS provides pain relief is poorly understood but may involve both spinal and supraspinal neural circuits (Linderoth and Foreman, 1999; Linderoth and Meyerson, 2002). The mechanisms of pain relief for neurogenic and ischemic pain by SCS are probably fundamentally different for neurogenic and ischemic pain (Linderoth and Foreman, 1999). In neurogenic pain the pain-perpetuating neural mechanisms seem to be counteracted more directly (Linderoth and Meyerson, 2002) while in ischemic pain the effects of SCS on tissue ischemia itself are considered to be the phenomenon leading to a secondary relief of the pain. Since SCS has been demonstrated in animal models of neuropathic pain, to suppress neuronal hyperexcitability in the spinal cord (Yakhnitsa et al., 1999), it might be possible that similar effects could be exerted on pathological neuronal processing induced by colorectal distension of a hypersensitive colon. Additional effects on ischemic pain, complex regional pain syndromes and on elevated viscerosomatic reflex activity may be obtained by the effects of SCS on sympathetic activity (Linderoth et al., 1994; Linderoth and Foreman, 1999; Tanaka et al., 2003) or via recently demonstrated antidromic mechanisms (Croom et al., 1998; Linderoth and Foreman, 1999; Tanaka et al., 2003).

The purpose of the present study was to determine if SCS affected viscerosomatic reflexes in animals with a hypersensitive colon. Effects of SCS on visceral functions have earlier been reported, e.g. effects on bladder hypersensitivity in MS cases (Tallis et al., 1983) and single reports on intestinal function (Kemler et al., 2001). In an earlier animal study that examined the effects of SCS on enhanced viscerosomatic reflexes in a model of acute colonic hypersensitivity, we observed a potent inhibitory effect of SCS on abdominal spasms resulting from colorectal distensions (Greenwood-Van Meerveld et al., 2003). Based on this report, one single patient with IBS was implanted with a SCS system (Krames and Mousad, 2004). The effect on episodes of diarrhea, pain, etc. was remarkable. Since few effective therapies exist for IBS, this case study induced hope for a new therapeutic strategy. However, the scientific basis for a larger human study is still weak and the first animal study was performed using a model of acute colonic hypersensitivity. Therefore, in the current study we examined whether SCS can modulate viscerosomatic reflexes in a rodent model of the post-inflammatory colonic hypersensitivity performed at a stage where the colonic histology should again appear normal. It is important to note that compared to rat models in which colonic hypersensitivity is observed during active colitis (Ness and Gebhart, 2001), it is our model of post-inflammatory colonic hypersensitivity which more closely mimics the pathophysiological conditions observed in patients with post-infective IBS.

2. Materials and methods

2.1. Animals

Experiments were performed on male Sprague Dawley rats (Charles Rivers, Wilmington, MA), housed under controlled conditions (21 °C, 0600–1800 hours light/dark cycle) with availability to standard rat chow and water ad libitum. Upon arrival, each rat was double-housed for 7 days and acclimated to the animal facility. To reduce the stress associated with experimentation, each rat underwent a second 7-day period of habituation to the experimental environment. During this acclimatization period, between the hours of 10:00 AM and noon, each day rats were brought into the laboratory environment, weighed, and handled for at least 5–10 min by the investigator. Prior to the experiment, the animal was fasted 12–18 h with free access to water. Upon completion of experimentation rats were euthanized via an overdose of isoflurane. The protocol was approved by the Oklahoma City Veterans Affairs Medical Center Animal Care Sub-Committee in accordance with the provisions of the U.S. Animal Welfare Act (1966 and amendments), and as described in the Guide for Care and Use of Laboratory Animals, ILAR Commission on Life Sciences (AAALAC-International Guidelines) (ILAR 1996).

2.2. Induction of colonic inflammation

After the acclimation period, rats were fasted overnight (12–18 h) with free access to water. The rats were then brought to the laboratory and briefly anesthetized with isoflurane (1.5–3%). While sedated, the rats received an enema (8.0 cm from anus, flexible tubing ID 3.0 mm) of either trinitrobenzenesulfonic acid (TNBS) (50 mg/kg, 0.5 ml, 25% EtOH) or saline. To minimize loss of the liquid enema, the rats' hindquarters were elevated until they regained consciousness. The rats were then returned to their