Brain Research Bulletin 121 (2016) 169–177

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Systemic administration of vitamins C and E attenuates nociception induced by chronic constriction injury of the sciatic nerve in rats

Ana Paula K. Riffel*, Jéssica A. de Souza, Maria do Carmo Q. Santos, Andréa Horst, Taína Scheid, Carolina Kolberg, Adriane Belló-Klein, Wania A. Partata

Departamento de Fisiologia, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

ARTICLE INFO

Article history:
Received 2 December 2015
Received in revised form 18 January 2016
Accepted 3 February 2016
Available online 6 February 2016

Keywords:
Mechanical threshold
Thermal threshold
Sciatic functional index
Antioxidant
Lipid peroxidation
Oxidative stress

ABSTRACT

Antioxidants have been tested to treat neuropathic pain, and α-Tocopherol (vitamin E—vit. E) and ascorbic acid (vitamin C—vit. C) are potent antioxidants. We assessed the effect of intraperitoneal administration of vit. C (30 mg/kg/day) and vit. E (15 mg/kg/day), given alone or in combination, on the mechanical and thermal thresholds and the sciatic functional index (SFI) in rats with chronic constriction injury (CCI) of the sciatic nerve. We also determined the lipid hydroperoxides and total antioxidant capacity (TAC) in the injured sciatic nerve. Further, we assessed the effects of oral administration of vit. C + vit. E (vit. C + E) and of a combination of vit. C + E and gabapentin (100 mg/kg/day, i.p.) on the mechanical and thermal thresholds of CCI rats. The vitamins, whether administered orally or i.p., attenuated the reductions in the mechanical and thermal thresholds induced by CCI. The antinociceptive effect was greater with a combination of vit. C + E than with each vitamin given alone. The SFI was also improved in vitamin-treated CCI rats. Co-administration of vit. C + E and gabapentin induced a greater antinociceptive effect than gabapentin alone. No significant change occurred in TAC and lipid hydroperoxide levels, but TAC increased (45%) while lipid hydroperoxides decreased (38%) in the sciatic nerve from vit. C + E-treated CCI rats. Thus, treatment with a combination of vit. C + E was more effective to treat CCI-induced neuropathic pain than vitamins alone, and the antinociceptive effect was greater with co-administration of vit. C + E and gabapentin than with gabapentin alone.

1. Introduction

The role of reactive oxygen species (ROS) has been emphasized in the generation of neuropathic pain (Treede et al., 2008; Guedes et al., 2006), pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al., 2008). Based on these findings, some dietary antioxidants have been tested for their clinical efficacy in treating neuropathic pain because they tend to be safe and well tolerated (Areti et al., 2014). α-Tocopherol (vitamin E—vit. E) and ascorbic acid (vitamin C—vit. C) are potent antioxidants with high biological activity (Warzyniak et al., 2013) and widely accepted by the general public (Traber and Stevens, 2011). Vit. E is a potent lipophilic chain-breaking antioxidant, found in biological membranes (Bruno et al., 2006), and also acts on inflammatory mediators (Garelnabi et al., 2012; Wu et al., 2001) and signalling molecules involved in nociception (Naziroğlu and Özgül, 2013; Hedge et al., 2012). α-Tocopherol is its most active isomer, and is rapidly depleted in the body, requiring regeneration through other antioxidants present in the water-soluble portion of the cell, such as ascorbate (Halliwell, 2006). The latter is the monovalent anion of vit. C (L-ascorbic acid), an effective water-soluble antioxidant (Rice, 2000) and an essential cofactor in numerous enzymatic reactions (Takanaga et al., 2004). There is evidence that vit. C has an antinociceptive effect (Okubo et al., 2012; Schencking et al., 2010).

A previous study showed that the systemic administration of a combination of vit. C + vit. E inhibited the early behavioral responses to formalin injection and neuropathic pain behavior after peripheral-nerve injury (Lu et al., 2011). This study used spared nerve injury as a neuropathic pain model. One of the most commonly employed animal models of neuropathic pain is the chronic constriction injury (CCI), which simulates the symptoms of chronic nerve compression that correspond to causalgia or complex regional pain syndrome in patients (Jaggi et al., 2011; Klusáková and Dubový, 2009). According to Jaggi et al. (2011), each animal model has been created with specific methodology, and the results tend to vary widely with slight changes in methodology to induce

* Corresponding author at: Departamento de Fisiologia, Instituto de Ciências Básicas da Saúde, UFRGS, Rua Sarmento Leite, 500, 90050-170 Porto Alegre, RS, Brazil.
E-mail address: anapkr@gmail.com (A.P.K. Riffel).

http://dx.doi.org/10.1016/j.brainresbull.2016.02.004
0361-9230/

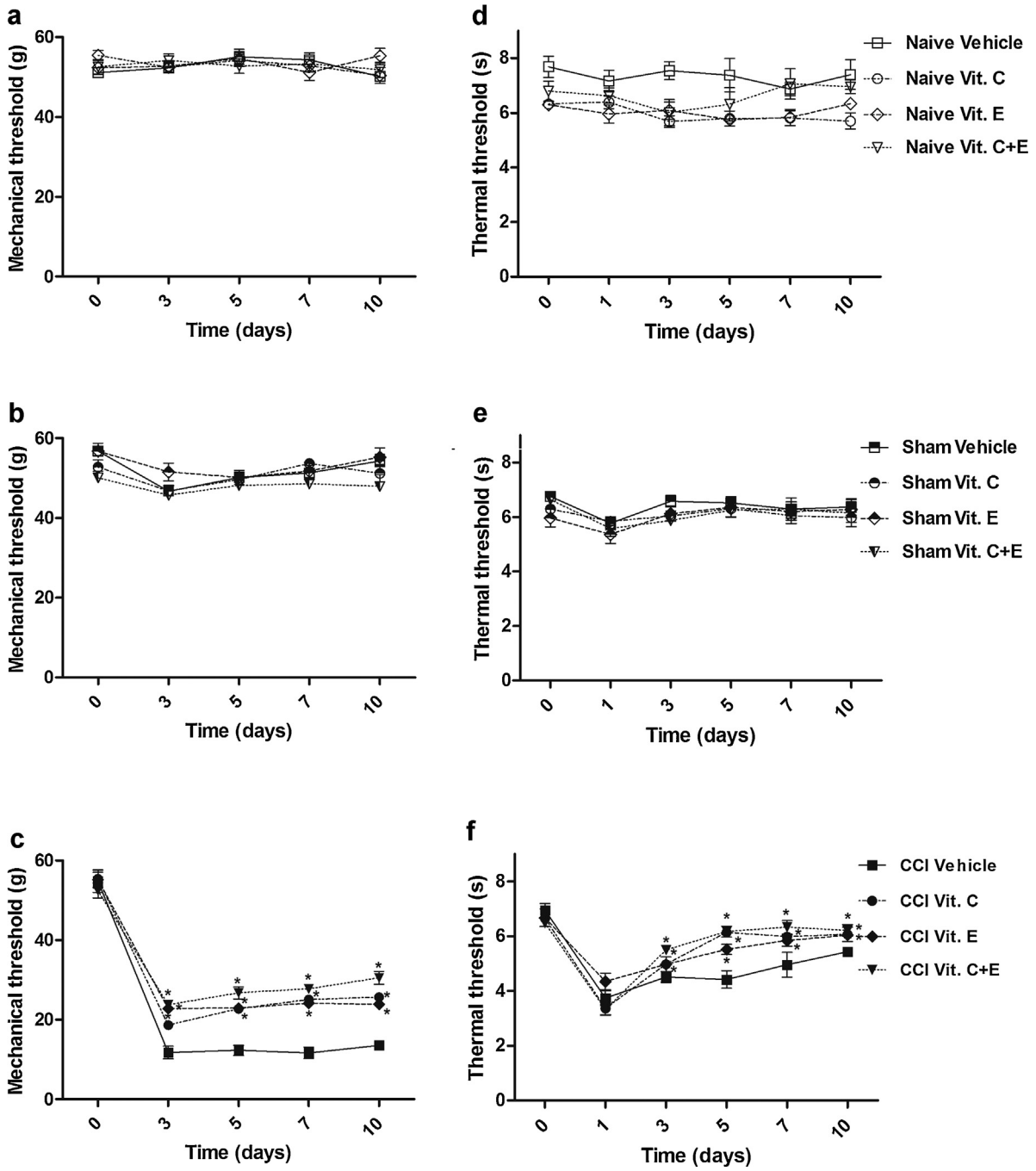

Fig. 1. Assessment of mechanical (a, b, c) and thermal (d, e, f) thresholds in rats with CCI of the sciatic nerve, which received vehicle, vit. C (30 mg/kg/day), vit. E (15 mg/kg/day) or a combination of these vitamins (vit. C + E), intraperitoneally (i.p.), for 10 days. Data represent mean ± SEM. * Indicates significant difference compared to pre-nerve lesion values (repeated-measures ANOVA followed by Tukey post-hoc test, n = 6, $P < 0.05$). Naive vehicle, saline-treated naive rats; Naive vit. C, vit. C-treated naive rats; Naive vit. E, vit. E-treated naive rats; Naive vit. C + E, vit. C + E-treated naive rats; Sham vehicle, saline-treated sham rats; Sham vit. C, vit. C-treated sham rats; Sham vit. E, vit. E-treated sham rats; Sham vit. C + E, vit. C + E-treated sham rats; CCI vehicle, saline-treated CCI rats; CCI vit. C, vit. C-treated CCI rats; CCI vit. E, vit. E-treated CCI rats; CCI vit. C + E, vit. C + E-treated CCI rats. The days after surgery are represented on the *x*-axis.

pain; therefore, it is essential that data from different pain models be reported and interpreted in the context of the specific pain model. Thus, our study assessed the effect of intraperitoneal (i.p.) administration of vit. C (30 mg/kg/day), vit. E (15 mg/kg/day) and vit. C + vit. E (vit. C + E), in the same doses, given for 3 and 10 days, on the mechanical and thermal thresholds of rats submitted to CCI of the sciatic nerve. In addition, we analyzed the sciatic functional index (SFI), as a proof of functional recovery post-nerve lesion, as well as the lipid hydroperoxides and the total antioxidant capacity (TAC) in the injured sciatic nerve.

We also assessed the effects of oral administration of vit. C + E and co-administration of vit. C + E with gabapentin (100 mg/kg/day, i.p.) on the mechanical and thermal thresholds, using the same treatment time periods described above. Co-administration was used because the co-administration of ascorbic acid and other analgesic drugs (morphine and tramadol) provide a better antinociceptive effect than individual drugs (Zeraati et al., 2014). Gabapentin was used because it is often used as an analgesic to control neuropathic pain (Hamidi et al., 2014; Magrinelli et al., 2013). Our study also evaluated the effect of the administration