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BRAIN RESEARCH

Research Report

Roles of peripheral terminals of transient receptor potential vanilloid-1 containing sensory fibers in spinal cord stimulation-induced peripheral vasodilation

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ABSTRACT

Background: Spinal cord stimulation (SCS) is used to relieve ischemic pain and improve peripheral blood flow in selected patients with peripheral arterial diseases. Our previous studies show that antidromic activation of transient receptor potential vanilloid-1 (TRPV1) containing sensory fibers importantly contributes to SCS-induced vasodilation. Objectives: To determine whether peripheral terminals of TRPV1 containing sensory fibers produces vasodilation that depends upon the release of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) during SCS. Methods: A unipolar ball electrode was placed on the left dorsal column at lumbar spinal cord segments 2–3 in sodium pentobarbital anesthetized, paralyzed and ventilated rats. Cutaneous blood flow from left and right hindpaws was recorded with laser Doppler flow perfusion monitors. SCS was applied through a ball electrode at 30%, 60%, 90% and 300% of motor threshold. Resiniferatoxin (RTX; 2 μg/ml, 100 μl), an ultra potent analog of capsaicin, was injected locally into the left hindpaw to functionally inactivate TRPV-1 containing sensory terminals. In another set of experiments, $CGRP_{8-37}$, an antagonist of the CGRP-1 receptor, was injected at 0.06, 0.12 or 0.6 mg/100 μl into the left hindpaw to block CGRP responses; N-omega-nitro-L-arginine methyl ester (L-NAME), a nonselective nitric-oxide synthase (NOS) inhibitor, was injected at 0.02 or 0.2 mg/100 μl into the left hindpaw to block nitric oxide synthesis; (4S)-N-(4-Amino-5[aminoethyl] aminopentyl)-N′-nitroguanidine, TFA, a neuronal NOS inhibitor, was injected at 0.02 or 0.1 mg/100 μl into the left hindpaw to block neuronal nitric oxide synthesis. Results: SCS at all intensities produced vasodilation in the left hindpaw, but not in the right. RTX administration attenuated SCS-induced vasodilation at all intensities in the left hindpaw ($P < 0.05$, $n = 7$) compared with responses before RTX. $CGRP_{8-37}$ administration attenuated SCS-induced vasodilation in the left hindpaw in a dose dependent manner (linear regression, $P < 0.05$) compared with responses before $CGRP_{8-37}$. In addition, L-NAME at a high dose, but not (4S)-N-(4-Amino-5[aminoethyl]aminopentyl)-N′-nitroguanidine, TFA, decreased SCS-induced vasodilation ($P < 0.05$, $n = 5$). Conclusion: While TRPV1, CGRP and NO

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are known to be localized in the same nerve terminals, our data indicate that SCS-induced vasodilation depends on CGRP release, but not NO release. NO, released from endothelial cells, may be associated with vascular smooth muscle relaxation and peripheral blood flow increase in response to SCS.

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1. Introduction

Spinal cord stimulation (SCS) was used for the first time to treat patients with pain in 1967 (Shealy et al., 1967). Cook was the first to observe that SCS increased blood flow to lower limbs in patients (Cook et al., 1976). SCS is an excellent alternative therapy for treating patients with peripheral arterial disease (PAD) including occlusive and vasospastic conditions, particularly when the diseases are unsuitable for the conventional revascularization treatments. The promising benefits of SCS include improvement of blood flow in the microcirculation, relief of ischemic pain and reduction of amputation rate (Linderoth and Foreman, 1999; Erdek and Staats, 2003). Furthermore, SCS is minimally invasive and has few serious complications. Approximately 70% of patients experience benefits with SCS, although it is considered as the last resort to treat inoperable patients with PAD (Cameron, 2004). Annually more than 14,000 SCS implantations are performed worldwide (Linderoth and Foreman, 2006). A recent report also suggests that transcutaneous oxygen measurement is a predictor for treatment success of SCS (Petrakis and Sciacca, 2000). Benefits of SCS on ischemia in the limbs and feet are largely dependent on the increase of blood flow during SCS. Two theories are proposed to explain SCS-induced vasodilation. One theory is that SCS decreases sympathetic outflow, which subsequently reduces vascular constriction and produces peripheral vasodilation (Linderoth et al., 1991a,b, 1994). Another theory is that SCS produces the release of vasodilators from the sensory terminals into the vascular tissue via activation of sensory fibers (Croom et al., 1997a). The antidromic and sympathetic theories are complementary. The balance of the dual mechanisms is associated with the sympathetic activity level, SCS intensity and individual patients, or animal strains in the experimental studies (Tanaka et al., 2003b). Previous studies have indicated that depression of sympathetic activity (Linderoth and Foreman, 2006) may account for a part of the effect, but that antidromic activation of sensory fibers and subsequent release of vasodilators accounts for a major portion of the SCS effect (Croom et al., 1996, 1997a,b, 1998; Tanaka et al., 2001, 2003a,b, 2004). A recent study has shown that SCS-induced vasodilation is predominantly mediated via transient receptor potential vanilloid-1 (TRPV1) containing sensory fibers (Wu et al., 2006). TRPV1 and vasodilators including calcitonin gene related peptide (CGRP) and possibly nitric oxide (NO) are co-localized in the peripheral terminals of TRPV1 containing sensory fibers (Kopp et al., 2001; Collins et al., 2002; Eguchi et al., 2004; Wang et al., 2006). Activation of TRPV1 and subsequent depolarization of terminals by SCS are very likely to release these vasodilators and to produce vasodilation.

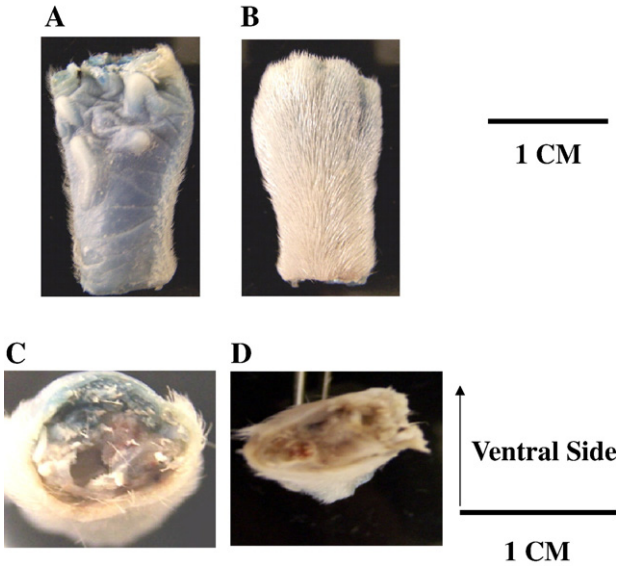

Fig. 1 – Local injection of 100 μl solution of 2% skyblue dye into left paw. (A) Ventral side of the middle of the left paw. (B) Dorsal side of the middle of the left paw. (C) Cross-section of the middle of the left paw. (D) Cross-section near the left ankle.

The aim of the present study was to determine whether peripheral terminals of TRPV1 containing sensory fibers produce vasodilation that depends on the release of CGRP and NO during SCS. We determined whether: (1) local hindpaw injection of resiniferatoxin (RTX), an ultrapotent TRPV1 agonist for desensitizing TRPV1 containing terminals (Pan et al., 2003; Zahner et al., 2003; Wu et al., 2006, 2007), influences SCS-induced vasodilation; (2) local hindpaw injection of $CGRP_{8-37}$, an antagonist of CGRP-1 receptor, affects SCS-induced vasodilation; (3) local hindpaw injection of (4*S*)-*N*-(4-Amino-5[aminoethyl]aminopentyl)-*N*′-nitroguanidine, TFA, a neuronal NOS (nNOS) inhibitor, alters the effects of SCS on peripheral blood flow; and (4) local hindpaw injection of *N*-omega-nitro-L-arginine methyl ester (L-NAME), a nonselective nitric-oxide synthase (NOS) inhibitor, influences SCS-induced vasodilation. The experiments were performed in anesthetized, paralyzed and artificially ventilated rats. Our previous studies have confirmed that more than 95% of effects of SCS on vasodilation are via antidromic activation of sensory fibers in this experimental setup and protocol (Tanaka et al., 2003b).

The results showed that local hindpaw injection of RTX abolished SCS-induced vasodilation. The hindpaw injection of $CGRP_{8-37}$ at the middle and high dose also largely decreased the vasodilation produced by SCS. In addition, L-NAME at a high dose, but not (4*S*)-*N*-(4-Amino-5[aminoethyl]aminopentyl)-*N*′-nitroguanidine, TFA, reduced SCS-induced vasodilation. Our data indicate that SCS-induced vasodilation largely depends on CGRP release from the terminals of TRPV1 containing sensory fibers. NO, possibly released from endothelial cells, but not from nerve endings is also necessary in SCS-induced vasodilation.

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