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Nicotine facilitates reinnervation of phenol-injured perivascular adrenergic nerves in the rat mesenteric resistance artery

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ABSTRACT

Nicotine has been shown to have neuroprotective and neurotrophic actions in the central nervous system. To elucidate the peripheral neurotrophic effects of nicotine, we determined whether nicotine affected the reinnervation of mesenteric perivascular nerves following a topical phenol treatment. A topical phenol treatment was applied to the superior mesenteric artery proximal to the abdominal aorta in Wistar rats. We examined the immunohistochemistry of the distal small arteries 7 days after the treatment. The topical phenol treatment markedly reduced the density of tyrosine hydroxylase (TH)-LI and calcitonin gene-related peptide (CGRP)-LI fibers in these arteries. The administration of nicotine at a dose of 3 mg/kg/day (1.5 mg/kg/injection, twice a day), but not once a day or its continuous infusion using a mini-pump significantly increased the density of TH-LI nerves without affecting CGRP-LI nerves. A pretreatment with nicotinic acetylcholine receptor antagonists hexamethonium, mecamylamine, and methyllycaconitine, but not dextrometorphan, canceled the TH-LI nerve reinnervation induced by nicotine. Nicotine significantly increased NGF levels in the superior cervical ganglia (SCG) and mesenteric arteries, but not in the dorsal root ganglia, and also up-regulated the expression of NGF receptors (TrkA) in the SCG, which were canceled by hexamethonium. These results suggested that nicotine exhibited neurotrophic effects that facilitated the reinnervation of adrenergic TH-LI nerves by activating α7 nicotinic acetylcholine receptor and NGF in the SCG.

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1. Introduction

Perivascular adrenergic nerves innervate most blood vessels and play an important role in maintaining vascular tone via the transmitter norepinephrine, co-transmitter neuropeptide Y (NPY), and ATP (Lindsay and Harmar, 1989; Lundberg, 1996). Mesenteric arteries, which comprise the largest vascular bed in the body and affect systemic blood pressure, are densely innervated by not only sympathetic adrenergic nerves, but also non-adrenergic non-cholinergic nerves (NANC) (Kawasaki et al., 1988). We previously reported that rat mesenteric arteries were densely innervated by NANC calcitonin gene-related peptide (CGRP)-containing nerves

Abbreviations: BSA, bovine serum albumin; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglia; LI, like immunoreactivity; NANC, non-adrenergic non-cholinergic nerves; NGF, nerve growth factor; nNOS, neuronal nitric oxide synthase; NPY, neuropeptide Y; PBS, phosphate-buffered saline; SCG, superior cervical ganglia; SDS, sodium dodecyl sulfate; TH, tyrosine hydroxylase; TrkA, tyrosine receptor kinase A

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(CGRPergic nerves) (Kawasaki et al., 1988), adrenomedullin-containing nerves (Hobara et al., 2004), and neuronal nitric oxide synthase (nNOS)-containing nerves (nitrergic nerves) (Hatanaka et al., 2006). These studies proposed that NANC CGRPergic and nitrergic nerves along with sympathetic adrenergic nerves contributed to the neurogenic regulation of vascular tone (Kawasaki et al., 1990; Hatanaka et al., 2006).

We previously demonstrated that the in vivo topical application of phenol markedly reduced the innervation of CGRPergic nerves and neuropeptide Y (NPY)-containing sympathetic adrenergic nerves in rat mesenteric resistance arteries, and also that nerve growth factor (NGF) facilitated the reinnervation of both types of nerves injured by phenol (Hobara et al., 2006). Furthermore, previous studies reported that adrenomedullin (a vasodilator peptide), angiotensin II (a vasoconstrictor peptide), and hepatic growth factor exhibited the ability to facilitate the reinnervation of mesenteric perivascular nerves injured by the topical treatment with phenol (Hobara et al., 2007a, 2007b, 2008), which has been used to block peripheral nerve activity (Wang and Bukoski, 1999). These studies also revealed that the facilitatory effects of angiotensin II via the stimulation of angiotensin II type 2 receptors and hepatic growth factor on the reinnervation of mesenteric perivascular nerves were selective to CGRPergic nerves (Hobara et al., 2007b, 2008), implying that in vivo phenol-induced perivascular nerve lesions are useful for searching for substances with neurotrophic actions.

Nicotine, an agonist for nicotinic acetylcholine receptors, has been shown to have neuroprotective (Akaike et al., 1994) and neurotrophic (Terry and Clarke, 1994; Martinez-Rodriquez et al., 2003; Formaggio et al., 2010) actions in the central nervous system. However, it currently remains unknown whether nicotine has neurotrophic effects in the peripheral nervous system. We previously reported that nicotine stimulated the $\alpha3\beta4$ subtype of nicotinic acetylcholine receptors on perivascular adrenergic nerves and caused vasodilation via CGRPergic nerves (Eguchi et al., 2007; Kawasaki et al., 2011), suggesting that nicotine interacts with the perivascular nervous system.

The present study was designed to investigate whether nicotine had neurotrophic activities on the reinnervation of mesenteric perivascular nerves after in vivo denervation using a topical treatment with phenol. To investigate the effects of nicotine and its possible mechanisms, the density of perivascular nerve innervation in the rat mesenteric resistance artery following perivascular nerve damage with a phenol treatment and the involvement of nicotinic acetylcholine receptor, nerve growth factor (NGF), and its high affinity receptor (tyrosine receptor kinase A; TrkA) were examined.

2. Materials and methods

2.1. Experimental animals

Eight-week-old Wistar rats (purchased from Shimizu Experimental Animals, Shizuoka) were used in this study. Animals were given food and water ad libitum. They were housed in the Animal Research Center of Okayama University at a controlled ambient temperature of 22 °C with 50 ± 10% relative humidity and a 12-h light/12-h dark cycle (lights on at 8:00 AM). This study was carried out to minimize the number of animals used and suffering, and was performed in accordance with the Guidelines for Animal Experiments at Okayama University Advanced Science Research Center, Japanese Government Animal Protection and Management Law (No. 115) and Japanese Government Notification on Feeding and Safekeeping of Animals (No. 6).

2.2. Surgical procedures

The in vivo denervation of perivascular nerves in the mesenteric arteries of these rats was performed as described previously (Hobara et al., 2006). Briefly, an abdominal midline incision was made under anesthesia with sodium pentobarbital (50 mg/kg, intraperitoneally), and the superior mesenteric artery proximal to bifurcation from the abdominal aorta was carefully exposed and topically swabbed with 10% phenol solution (in 90% alcohol-saline) using a cotton bud. After swabbing, an antibiotic (penicillin G; Sigma-Aldrich Japan, Tokyo) was infused around the surgical area and the incision was then closed. To examine the influence of the operation, sham-operated rats underwent the same surgical procedures with swabbing with a vehicle (saline or 90% alcohol without including phenol) instead of the phenol solution. After the operation, animals were transferred into individual cages in a temperature-controlled room and received intramuscular injections of penicillin G (3.1 mg/kg) for 3 consecutive days. After the phenol treatment and sham operation, animals were killed by deep anesthesia for use in the experiments described below on Day 7.

2.3. Administration of nicotine and nicotinic acetylcholine receptor antagonists

Nicotine at 1 and 3 mg/kg was administered by a subcutaneous injection once a day (1 and 3 mg/kg/injection), twice a day (0.5 and 1.5 mg/kg/injection), or by a continuous injection through a mini-osmotic pump (model 1007D, Alzet; Alza, Palp Alto, CA, USA) containing nicotine for a period of 7 days. A mini-pump was implanted into the dorsal subcutaneous area immediately after the phenol-swabbing surgery and nicotine was administered s.c. at a rate of 1 mg/kg/day or 3 mg/kg/day. Nicotine at concentrations of 83.3 mg/mL for 1 mg/kg/day or 250 mg/mL for 3 mg/kg/day was dissolved in sterile saline and injected into the osmotic mini-pump.

In the series of experiments using nicotinic acetylcholine receptor antagonists, mecamylamine (1.5 mg/kg/injection, total 3 mg/kg/day; central and peripheral nicotinic acetylcholine receptor antagonist), hexamethonium (5 mg/kg/injection, total 10 mg/kg/day; peripheral nicotinic acetylcholine receptor antagonist) (Baranowska et al., 2008), methyllycaconitine (2 mg/kg/injection, total 4 mg/kg/day; selective $\alpha7$ nicotinic acetylcholine receptor antagonist) (Turek et al., 1995), or dextromethorphan (2.5 and 5 mg/kg/injection, total 5 and 10 mg/kg/day; $\alpha3\beta4$ nicotinic acetylcholine receptor antagonist) (Damaj et al., 2005) was subcutaneously injected twice a day for 7 days 15 min before the treatment with nicotine (1.5 mg/kg/injection).

2.4. Immunohistochemical study

Animals treated with topical phenol and saline, nicotine (1.5 mg/kg/injection, twice a day, for 7 days), or nicotine plus each nicotinic acetylcholine receptor antagonist were anesthetized with a large dose of pentobarbital-Na. The superior mesenteric artery was cannulated with polyethylene tubing and Zamboni solution (2% paraformaldehyde and 15% picric acid in 0.15 M phosphate buffer) was then infused. The mesenteric artery was removed together with the intestine, as described previously (Hobara et al., 2005, 2006). The third branch of the mesenteric artery proximal to the intestine was removed and immersion-fixed in Zamboni solution for 48 h. After fixation, the artery was repeatedly rinsed in phosphate-buffered saline (PBS), immersed in PBS containing 0.5% TritonX-100 overnight, and incubated with PBS containing normal goat serum (1:100) for 60 min. The tissue was then incubated with rabbit polyclonal anti-TH antiserum (1:300) (Phoenix Pharmaceuticals Inc., Belmont, CA, USA) or rabbit polyclonal anti-CGRP (Biogenesis Ltd., Poole, UK) antiserum (1:300) for 72 h at 4 °C. After being incubated, the artery was washed in PBS and the sites of the antigen-antibody reaction were revealed by incubating

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