Effects of Nitric Oxide and Noradrenergic Function on Skin Electric Resistance of Acupoints and Meridians

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ABSTRACT

Objectives: The objectives of this study were to determine the effects of L-arginine–derived nitric oxide (NO) synthesis and noradrenergic function on skin electrical resistance of acupoints and meridians.

Design: Experiments were performed on male Sprague-Dawley rats anesthetized with sodium pentobarbital. Low skin-resistance points (LSRP; BL 56, PC 6, CV 17), non-LSRP positions (along the meridians), and non-LSRP, non-meridian control positions (adjacent to but not along the meridians) were determined on the skin surface by measurements of the skin stimulus-evoked electrical currents. The effects of L-arginine–derived NO synthesis and noradrenergic function on the currents, representing skin electrical resistance, were examined in the LSRP, non-LSRP, and non-meridian control points.

Results: The skin stimulus–evoked electrical currents at BL 56 ($36.4 \pm 1.4 \ \mu A$), PC 6 (35.4 ± 1.2), and CV 17 (33.1 ± 1.4) were significantly higher than those in non-LSRP and non-meridian control positions ($p < 0.01$, $n = 7$). The currents were consistently increased after repeated stimulation along the skin as a function of time. Intravenous injections of L-arginine (3 mg/kg, 10 mg/kg, and 30 mg/kg) and 3-morpholinyl-sydnoneimine (SIN-1; $1 \ \mu g/kg$, $3 \ \mu g/kg$, and $10 \ \mu g/kg$) produced dose-dependent increases in the currents ($p < 0.05$, $n = 5$–6), but currents were not altered by injections of D-arginine (3 mg/kg, 10 mg/kg, and 30 mg/kg). Stimulus-evoked increases in currents were blocked by intravenous injections of either N^G-propyl-L-arginine (NPLA, 3 mg/kg), N-nitro-L-arginine methyl ester (L-NAME, 10 mg/kg), or guanethidine (3 mg/kg), a noradrenergic blockade.

Conclusions: This is the first evidence showing that L-arginine–derived NO synthesis and noradrenergic transmission modify the skin electric conductance of LSRP. L-Arginine–derived NO synthesis appears to mediate noradrenergic function on skin sympathetic nerve activation, which contributes to low resistance characteristics of acupoints and meridians.

INTRODUCTION

Acupuncture meridian theory (channels and collaterals, *jingluo*) is an important component system that has been described in Traditional Chinese Medicine (TCM) for thousands of years. This system is the central theory of many unconventional medical systems and has drawn the attention of many investigators around the world.[1–3] Meridian theory deals with physiologic regulation and pathologic changes in the human body[4,5] and it guides the diagnosis and treatment of TCM in many aspects, especially in relation to acupuncture.

Previous studies from several research groups have confirmed that most acupuncture points in both humans and animals correspond to high electrical conductance and low skin resistance points (LSRP) on the body surface along the meridians.[3,6–9] It is well-documented that skin electrical resistance depends upon the activity of the sympathetic nervous systems and that stimulation of sympathetic pathways lowers the skin-resistance levels.[10,11] Morphologic studies

have shown that hair follicles and nervous components are enhanced in the meridians/acupoints, which represent areas of potentially high neuronal activity.[7,12]

It has been demonstrated that nitric oxide (NO) is perhaps one of the most important messenger molecules, much like a neurotransmitter with a widespread signaling mechanism and function.[13–15] NO stimulates norepinephrine (NE) release from the central and peripheral nervous systems, which increases sympathetic nerve activity.[16–19] Our recent studies found that NO contents and neuronal NO synthase (nNOS) expression are consistently higher in the skin acupoints/meridians associated with low electric resistance.[20]

The purpose of the present study was to determine the effects of L-arginine–derived NO synthesis and noradrenergic function on the low electric resistance of acupoints/meridians. The study examined whether the low electric resistance in acupoints/meridians is modified by treatment with either L-arginine, 3-morpholinyl-sydnoneimine (SIN-1, an exogenous NO donor), N^G-propyl-L-arginine (NPLA, a selective inhibitor of neuronal NO synthesis), or L-NAME (a nonselective inhibitor of NO synthesis), or by treatment with guanethidine to achieve noradrenergic blockade.

METHODS

Animal preparation

All experiments were performed using adult (5–6 months), male Sprague-Dawley rats. The protocol was approved by the Harbor University of California Los Angeles Animal Use Committee, and was conducted in accordance with American Association for the Acreditation of Laboratory Animal Care and National Institutes of Health guidelines. The animals were maintained on a 12-hour light–dark cycle in temperature- and humidity-controlled rooms. Food and water were available ad libitum.

Location and measurement of LSRP

LSRP on the skin surface of BL 56, PC 6, and CV 17 were tested in each group of rats. The specific regions were chosen in the experiments based on the following rationales: (1) The points can be easily identified on the body; (2) the points have enough distance away from non-LSRP along the meridian and non-LSRP, non-meridian control points; and (3) areas represent meridians located on the leg, arm, or trunk. Locations of acupoints/meridians were detected by measurements of LSRP corresponding to the acupoints of animals and human described in the Chinese classical topography.[1,9] Each acupoint location was identified and currents were measured. The meridian lines were marked by connecting the LSRP, and the 2–3-mm width of meridian regions containing LSRP were identified.[1] Control points were non-LSRP, non-meridian areas located adjacent to each corresponding meridian line.[21]

Measurements of skin electrical current

BL 56, PC 6, and CV 17 were located and skin electric currents were measured using a Dermatron electrodiagnostic device (Pitterling Electronics, Munich, Germany). To locate the points, electrodes were attached to the left fore or hind paw of each animal while the Dermatron stimulator/locator (3 mm in diameter) was gently placed on the skin area being tested with equal and optimal pressure. The Dermatron LED panel illuminates and a resistance scale displays the skin's current. Acupoint currents were measured with conductance thresholds expressed in current (μA) to the nearest 1 μA. Once the exact center of BL 56, PC 6, or CV 17 point was located, the acupoint stimulator produced a gentle rotational movement and the current at each point was recorded. This process was repeated three times, and the mean current was determined for each point.

The measurements were also confirmed by using another Acupuncture Meridian Locator (type WQ6F30, Dong Hua Electronic Instrument Factory, Beijing, China) on the skin regions. This instrument has been used to locate exactly all the 12 meridians of 1–mm width in coincidence with the ancient acupuncture meridian charts.[1] Pulse current (40 Hz) amplified to 4.0 was applied to the skin surface using a stainless steel electrode 1 mm in diameter. A single stimulus consisted of four to five applications within a 2–3-second period on the point.

Protocol

LSRP on the skin surface along the meridians were tested in each rat and the meridian lines were marked following previously described methods.[1,3,7,8] The room temperature was maintained at 26–27°C. The rats were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally) and shaved. Femoral venous cannulae were implanted for systemic delivery of anesthesia and compounds. The skin electrical currents were measured and recorded at 0, 30, 60, 90, 120, 150, 180, and 210 minutes.

The rats were randomly divided into seven groups ($n =$ 5–7/group): (1) control group (saline); (2) L-arginine (3 mg/kg, 10 mg/kg, and 30 mg/kg)–treated group; (3) SIN-1 (1.0 μg/kg, 3.0 μg/kg, and 10 μg/kg)–treated group; (4) D-arginine (3 mg/kg, 10 mg/kg, and 30 mg/kg)–treated group; (5) NPLA (3 mg/kg)–treated group; (6) L-NAME (10 mg/kg)–treated group; and (7) guanethidine (3 mg/kg)–treated group. The compounds or the same volume of saline were intravenously injected into rats in each group. For rats in the L-arginine-, SIN-1–, and D-arginine–treated groups, injections were administered with a 10-minute interval between doses, and currents were measured and recorded before and after each injection. For rats in the NPLA-, L-NAME–, and guanethidine-treated groups, currents were measured and recorded before and at 30, 60, 90, 120, and 150 minutes after the injections.

Chemicals

Drugs and chemicals used in these experiments were L-arginine (Sigma Chemical, St. Louis, MO), D-arginine (Sigma), NPLA (Calbiochem, LaTolla, CA), L-NAME (Sigma), guanethidine (Sigma), and SIN-1 (Tocris, Ellisville, MO).

Statistical analysis

Results are expressed as mean ± standard error of the mean (SEM). Five to seven rats were used for each defined group. A mixed design analysis of variance (ANOVA) and post hoc tests were used to analyze significant differences, with p values <0.05 considered to be significant.

RESULTS

Skin electrical resistance responses to repeated measurement/stimulation of acupoints

Figure 1 shows the skin electrical currents of BL 56, PC 6, and CV 17 compared to their non-LSRP and non-meridian controls after 210 minutes of repeated stimulation/measurements. Baseline values were obtained immediately after anesthesia administration and before treatment (time = 0 min). The mean baseline current (μA) for BL 56 was 36.4 ± 1.4 (mean ± SEM), which was significantly higher than the non-LSRP located along the BL meridian (30.9 ± 1.4, $p < 0.05$) and for the non-LSRP, non-meridian control point adjacent to the BL meridian (28.2 ± 1.3, $P < 0.05$). Currents in BL 56, PC 6, and CV 17 points were consistently increased in response to repeated measurements in a time-dependant fashion during 0, 30, 60, and 90 minutes. During 210 minutes of repeated stimulation/measurements, current increase became blunted at 90–120 minutes and did not continually increase after 120 minutes (Fig. 1). Similar changes in currents were also observed in their non-LSRP and non-meridian controls after repeated measurements. A difference was revealed between skin currents over time after repeated electric stimulation ($F_{6,126} = 7.69$, $P < 0.05$), between BL 56 and non-LSRP ($F_{1,84} = 7.88$, $p < 0.05$), and BL 56 and non-meridian points ($F_{1,84} = 14.00$, $p < 0.05$) over time (Fig. 1, top panel).

The mean baseline current for PC 6 was 35.4 ± 1.2, which was significantly higher than the non-LSRP along the PC meridian (30.2 ± 1.2, $p < 0.05$) as well as the non-LSRP, non-meridian control point adjacent to the PC meridian (28.1 ± 1.2, $p < 0.05$). Two-way ANOVA revealed significant differences of the skin currents in PC 6 over time after repeated electric stimulation ($F_{6,126} = 9.06$, $p < 0.01$) as well as between the PC 6 and non-LSRP ($F_{1,84} = 8.24$, $p < 0.05$) and PC 6 and non-meridian points ($F_{1,84} = 19.00$, $p < 0.05$) over time (Fig. 1, middle panel).

The mean baseline current (μA) for CV 17 (33.1 ± 1.4) was significantly higher than the non-LSRP along the CV meridian (26.9 ± 1.3, $p < 0.05$) and the non-LSRP control
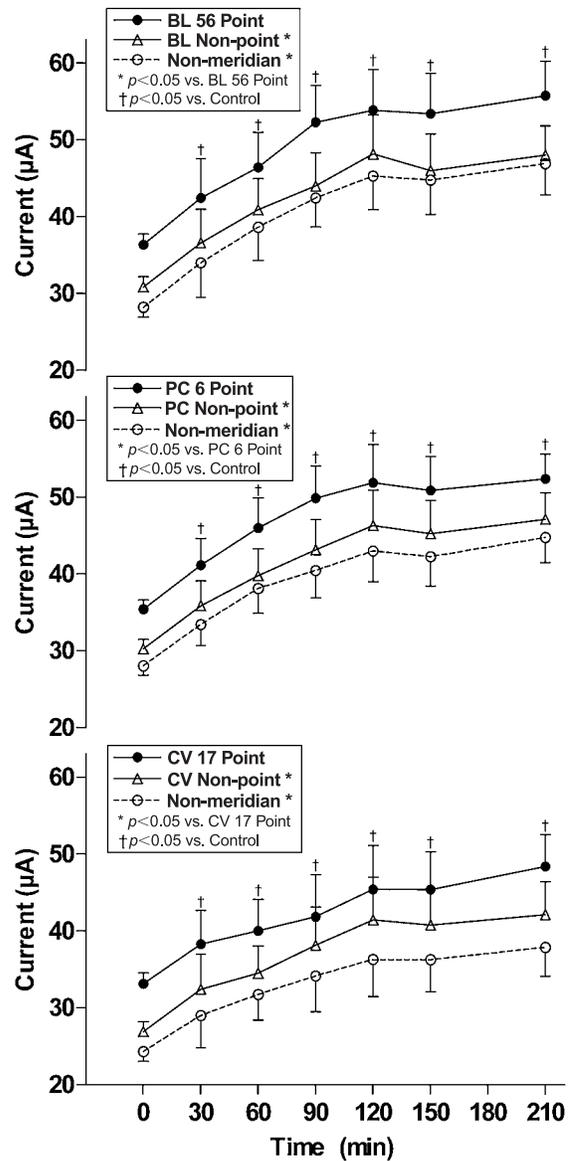

FIG. 1. Time-course histogram of skin electric currents (μA) induced by repeated electrical stimulation in BL 56, PC 6, and CV 17 points compared to non–low skin resistance points (LSRP) and non-meridian positions. Measurements were conducted 30 minutes each for 210 minutes in rats anesthetized with sodium pentobarbital. Currents in BL 56, PC 6, and CV 17 points were consistently increased in response to repeated measurements in a time-dependent fashion. Currents were also increased in a time-dependent manner for non-points and non-meridians after repeated measurements. BL, Bladder meridian; PC, Pericardium meridian; CV, Conception Vessel meridian; non-point: non-LSRP positions along meridians; Non-meridian, non-meridian control point adjacent to meridians. Lines represent mean value and vertical lines represent SEM ($n = 7$). *$p < 0.05$, by analysis of variance, compared with points. †$p < 0.05$ compared to baseline control (0 min).

point (24.3 ± 1.3, $p < 0.05$). There were significant differences of the skin currents in CV 17 over time after repeated electric stimulation ($F_{6,126} = 4.44$, $p < 0.01$), as well as between the CV 17 and non-LSRP ($F_{1,84} = 4.79$, $p < 0.05$),

and CV 17 and non-meridian point ($F_{1,84} = 15.89$, $p < 0.05$) over time (Fig. 1, bottom panel).

Effects of L-arginine and an NO donor on skin electrical resistance of acupoints/meridians

Figure 2 shows the dose-dependent increases in the stimulus-evoked currents of BL 56, PC 6, and CV 17 by intravenous injection of L-arginine (3 mg/kg, 10 mg/kg, and 30 mg/kg) with their non-LSRP along the meridians and non-meridian control points adjacent to the meridians. A significant increase in the dose-dependant currents was revealed in L-arginine–treated rats in BL 56, PC 6, and CV 17 (Fig. 2, right panel, $F_{4,69} = 26.40$, $F_{4,69} = 13.75$, $F_{4,69} = 21.52$, $p < 0.01$, respectively), but currents were not altered by injections of D-arginine (Fig. 2, left panel).

Figure 3 shows the dose-dependent increases in the stimulus-evoked currents of BL 56, PC 6 and CV 17 by intravenous injection of SIN-1 (1 μg/kg, 3 μg/kg, and 10 μg/kg), with their non-LSRP along the meridians and non-meridian control points adjacent to the meridians. SIN-1 treatment resulted in significant increases in currents compared to those in nontreated rats in BL 56, PC 6, and CV 17 within the same period of time ($F_{4,78} = 29.68$, $F_{4,78} = 21.74$, $F_{4,78} = 16.69$, $p < 0.01$).
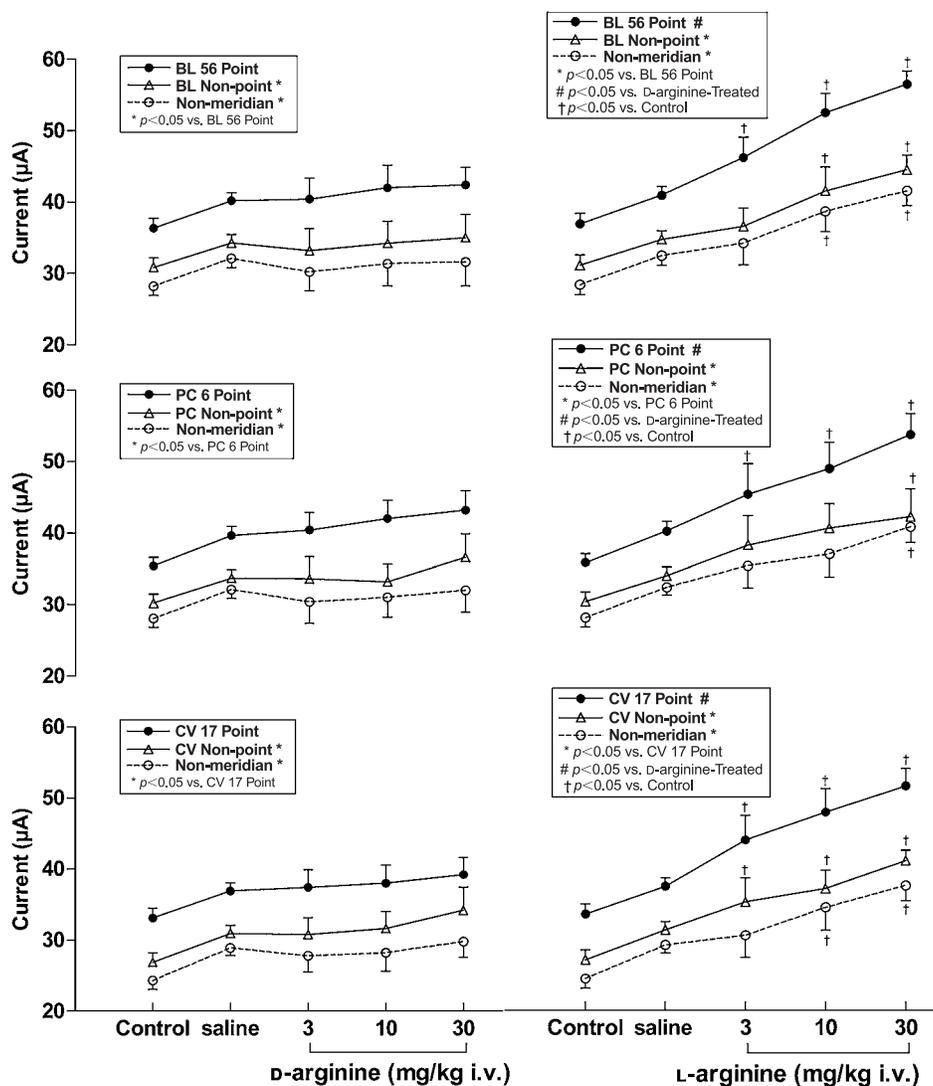

FIG. 2. Dose-dependent increases in skin currents (μA) induced by repeated electrical stimulation after intravenous (i.v.) injections of L-arginine in BL 56, PC 6, and CV 17 compared to non–low skin resistance points (LSRP) and non-meridian positions in rats (right panels). Currents of points, non-LSRP, and non-meridian controls were not altered by injections of D-arginine (left panels). Other details (on studies, statistical analyses, and abbreviations) are as in Figure 1.
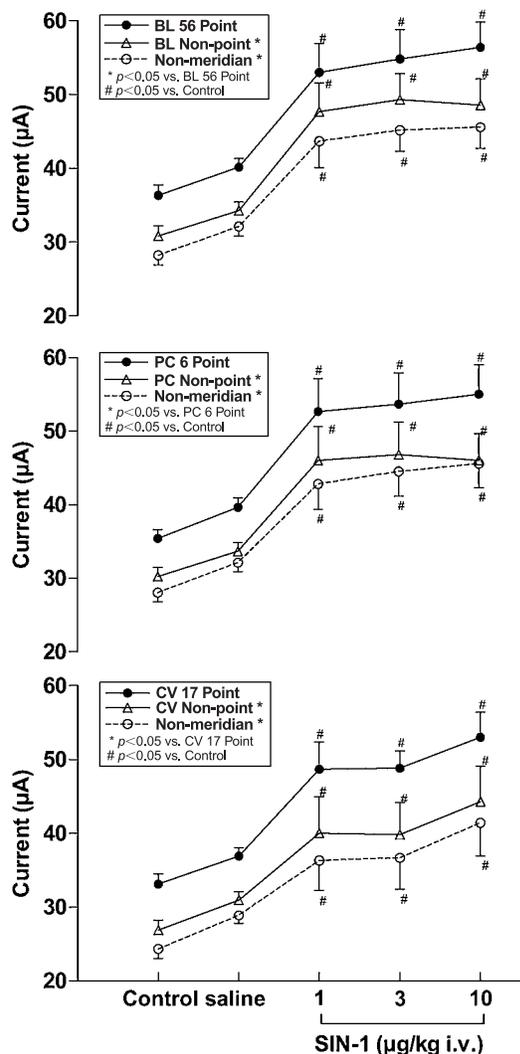
FIG. 3. Dose-dependent increases in skin currents (μA) induced by repeated electrical stimulation after intravenous (i.v.) injections of SIN-1 in BL 56, PC 6, and CV 17 compared to non–low skin resistance points (LSRP) and non-meridian positions in rats. SIN-1, 3-morpholinylsydnoneimine. Lines represent the mean values; vertical lines represent SEM ($n = 5$–7). *$p < 0.05$ by analysis of variance (ANOVA) compared to points. #$p < 0.05$ compared to baseline control (0 min). Two-way ANOVA revealed that significant increases in currents were produced in SIN-1–treated rats in BL 56, PC 6, and CV 17 ($F_{4,78} = 29.68$, $F_{4,78} = 21.74$, $F_{4,78} = 16.69$, $p < 0.01$, respectively). Other details (on studies, statistical analyses, and abbreviations) are as in Figure 1.

Effects of NPLA, L-NAME, and guanethidine on skin electrical resistance of acupoints/meridians

Figures 4 and 5 illustrate the changes in skin electrical current in response to repeated stimulation/measurement after intravenous injections of either saline vs. NPLA (3 mg/kg, Fig. 4, left panel), L-NAME (10 mg/kg, Fig. 4, right panel), or guanethidine (3 mg/kg, Fig. 5). The repeated stimulations/measurements-induced increases in time–response

curves for BL 56 currents were attenuated by intravenous injections of either NPLA (Fig. 4 left top panel, $F_{1,60} = 3.45$, $p = 0.06$), L-NAME (Fig. 4, right top panel, $F_{1,60} = 7.44$, $p < 0.05$), or guanethidine (Fig. 5, top panel, $F_{1,60} = 3.42$, $p = 0.07$). Similar attenuation effects were found for the currents of PC 6 as a result of intravenous injections of either NPLA (Fig. 4, left middle panel, $F_{1,60} = 7.03$, $p < 0.05$) or guanethidine (Fig. 5, middle panel, $F_{1,60} = 3.47$, $p = 0.07$), but L-NAME did not produce a statistically significant inhibition (Fig. 4, right middle panel, $F_{1,67} = 0.41$, $p = 0.52$). The time–response curves for CV 17 currents induced by repeated measurements/stimulations also appeared to be attenuated by NPLA or L-NAME, although the decreases fell short of statistical significance (Fig. 4, left bottom panel, $F_{1,60} = 0.09$, $p = 0.77$; Fig. 4, right bottom panel, $F_{1,60} = 1.70$, $p = 0.19$). Guanethidine attenuated stimulations/ measurements-induced increases in time–response curves for CV 17 currents (Fig. 5, bottom panel, $F_{1,60} = 3.38$, $p = 0.07$, respectively). The time–response curves for current increases of non-LSRP points and non-meridian control points induced by repeated measurements/stimulations were also significantly or marginally significantly shifted to the right compared to values in animals with saline treatments (Fig. 5).

DISCUSSION

We examined the electrical resistance of LSRP, non-LSRP along the meridian as well as non-LSRP, non-meridian control points induced by repeated measurements/stimulations on the skin surface in rats. The effects of L-arginine–derived NO synthesis and noradrenergic function on the skin electrical currents, representing skin electrical resistance, were also observed in the LSRP, non-LSRP, and non-meridian control points. The main results and new findings of these studies are: (1) the skin electrical currents in responses to electric stimulation are significantly higher in BL 56, PC 6, and CV 17 than those in non-LSRP, and non-meridian control points; (2) the currents are consistently enhanced following repeated measurements/stimulations along the skin in a time-dependent manner; (3) intravenous injections of L-arginine and SIN-1 produced dose-dependent increases in the currents, but the currents were not altered by intravenous injections of D-arginine; and (4) the increases in currents induced by repeated measurements/stimulations were blocked by intravenous injections of either NPLA or L-NAME, inhibitors of NO synthesis, or by guanethidine, a noradrenergic blocker. This is the first evidence showing that L-arginine–derived NO synthesis and noradrenergic transmission modify the skin electric conductance of LSRP. The results suggest that L-arginine–derived NO synthesis and noradrenergic function mediate skin sympathetic nerve activation, which contributes to low resistance characteristics of acupoints and meridians.
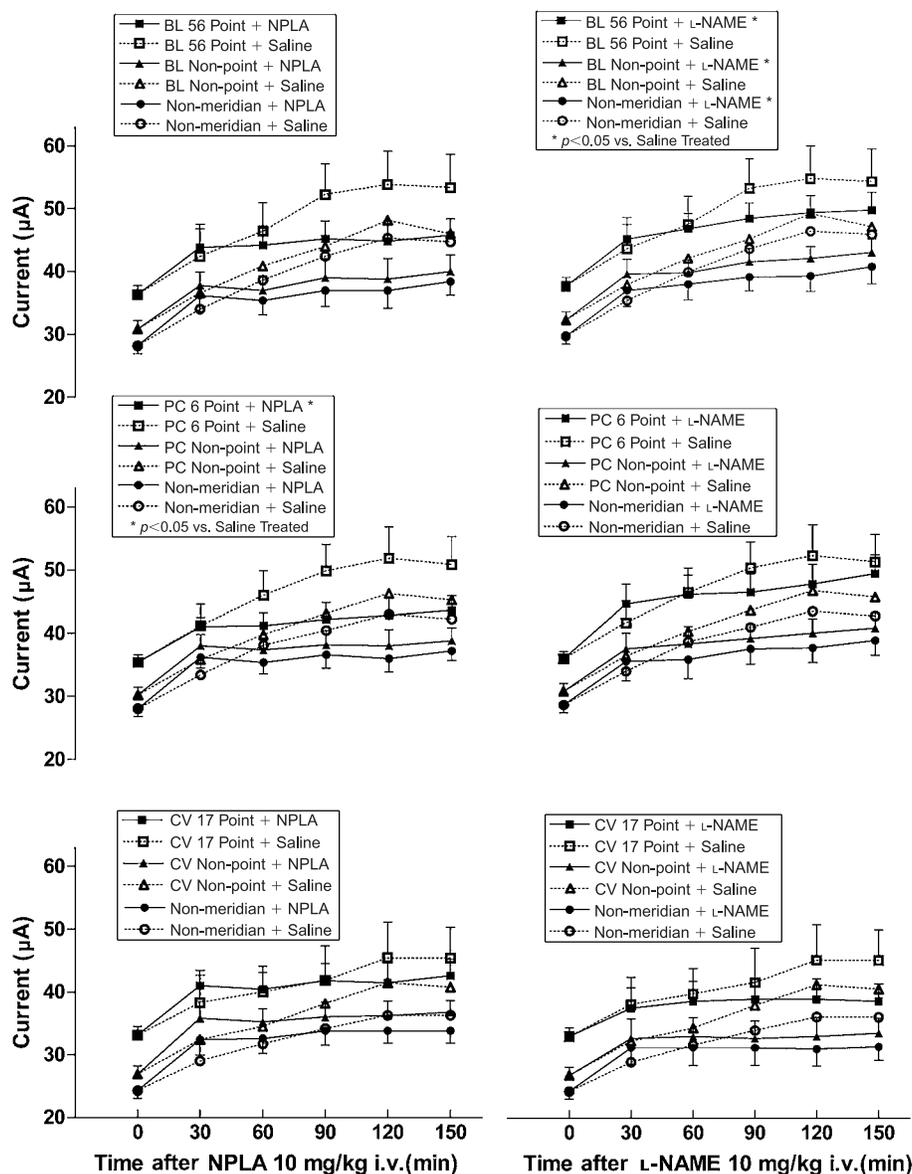
FIG. 4. Time–responses curves for increases in currents induced by repeated measurements/stimulations after intravenous (i.v.) injections of saline, N^G-propyl-L-arginine NPLA (left panels) or N-nitro-L-arginine methyl ester (L-NAME) (right panels) in BL 56, PC 6, CV 17, non–low skin resistance points (LSRP), and non-meridian positions. Lines represent mean values; vertical lines represent standard error of the mean ($n = 5$–7). *$p < 0.05$, compared to saline-treated rats. Other details (on studies, statistical analyses, and abbreviations) are as in Figure 1.

Several studies have shown that acupuncture points possess characteristics of low electrical resistance and high electrical currents in both humans and animals.[3,6–9] Other studies have demonstrated that this characteristic is not only present at the acupuncture point but also along the lines (about 1.0 mm in width) of the meridians that are described in the traditional acupuncture charts.[1,9] It has been suggested that low impedance acupuncture points on the skin may reflect the variation in anatomic concentration of nerve fibers beneath the skin and may represent areas of potentially high neuronal activity.[7] Investigators noted that, at the light microscopic level, the numbers of nerve bundles, nerve fibers, and nerve endings were higher in the skin under the low impedance line than those in their adjacent control areas in both patients and rats.[1,21] The results of the present study show that LSRP are detected by their low electrical resistance characteristics in the BL 56, PC 6, and CV 17 point in rats. These locations closely correspond to the acupoints of animals described in the Chinese classical topography, which were evolved from comparative anatomy based on technical development in classical human topography.[1,9] The currents in responses to electric stimulation–induced by the locator were significantly higher in BL 56, PC 6, and CV 17 acupoints than those in non-LSRP and non-meridian control points.
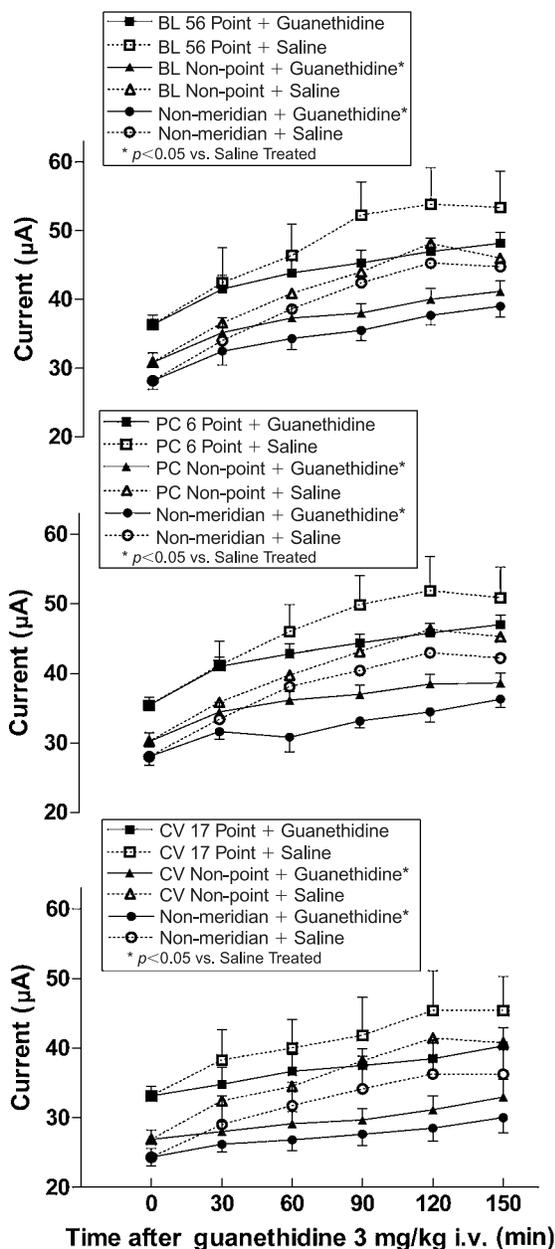
FIG. 5. Time–responses curves for increases in currents induced by repeated measurements/stimulations after intravenous (i.v.) injections of guanethidine in BL 56, PC 6, CV 17, non–low skin resistance points (LSRP), and non-meridian positions. Lines represent the mean values; vertical lines represent SEM (n = 5–7). *p < 0.05 compared to saline-treated group. Other details (on studies, statistical analyses, and abbreviations) are as in Figure 1.

Our results are consistent with previous studies reported that acupoints/meridians possess high electric currents and further demonstrate that the skin electrical currents are consistently enhanced after repeated stimulation along the skin. It has also been demonstrated that applying mechanical knocking on the body surface induces high percussion sound, which is present over the lines of the meridians.[1,22] The char-

acteristics of LPSC and high percussion sound (dual direction transduction, advancement at a slower rate, and blockade by local application of the pressure) further suggest the responses mediated by meridian systems. The present results support the previous studies, which reported that meridian function was activated by mechanical stimulation, and suggest that skin electrical currents along acupoints/meridians can be enhanced by repeated electrical stimulations.

Recently it has been reported that the epidermis and the outer root sheath possess both nNOS immunoreactivity and NADPH diaphorase reactivity.[23] Dermal microdialysis has demonstrated that NO levels and other chemical messengers in human skin increase during the inflammatory weal and flare response.[24,25] Our previous studies have shown that increased NO content in the meridians/acupoints is associated with an enhanced nNOS but not eNOS, indicating that elevated NO in the acupoints/meridians is involved in neuronal NO-ergic systems.[20] The present results suggest that the low electric resistance of acupoints/meridians in rats is enhanced by treatment with an exogenous NO donor and blocked by the treatment with a selective inhibitor of neuronal NO synthesis. The data also show that L-arginine produces increases in the currents induced by repeated stimulation but the currents were not altered by D-arginine. These data support previous findings that characteristics of low electrical resistance of acupoints/meridians accompany an enhanced nNOS-NO and that NO is chemically important in the function of acupoints/meridians.[20] The present results further suggest that L-arginine–derived NO synthesis is involved in the stimulus-evoked increases in electrical currents (conductance) of acupoints/meridians.

Considering the potential role of NO in the biophysical characteristics of skin acupoints/meridians, many studies have reported that NO serves as a messenger in the neurons, much like a neurotransmitter with a widespread signaling mechanism and function.[13–15] Previous work has demonstrated that nitroglycerin, an NO donor, increases the release and synthesis of NE in the central and peripheral nervous systems, suggesting that NO produces noradrenergic activation in neurons.[16,17] It has been demonstrated that NO donors stimulate the release of NE from neurons both *in vivo* and *in vitro*.[18,19] Additionally, previous work has shown that the skin resistance levels are decreased by stimulation of sympathetic pathways either locally or systemically.[10] Interruption or retardation of the flow of impulses over sympathetic pathways to a given area of skin causes marked elevation of resistance in that area either by pharmacologic blockade, local anesthetic, peripheral nerve lesions, or severance of pre- or post-ganglionic pathways.[10,11,26] It is well established that the actual value of skin electrical resistance depends upon the activity of the sympathetic nervous system and blockade of sympathetic function enhances the skin resistance.[10,11,26] The present data demonstrate that the increases in the currents induced by repeated stimulation in the acupoints/meridians were blocked by intravenous injec-

tions of guanethidine, blocking noradrenergic function. The results suggest that noradrenergic transmission serves as a messenger for sympathetic nerve activation in the dermal neurons, which contribute to their low electrical resistance characteristics. Enhanced NO in the acupoints/meridians may evoke the release of NE in sympathetic nerve terminals, which plays an important role in response to skin electroconductance and reduces skin resistance.

Acupuncture points and meridians have been discovered to have high electrical conductance which is related to the high density of the gap junction.[2,27] Recent advances in the morphogenetic singularity theory suggest that acupuncture points originate from the organizing centers in morphogenesis.[28] It has been demonstrated that NO is a potent modulator of gap junctional coupling in endothelial cells[29] and that the NO donors reduce the inhibitory junction potentials, thus increasing conductance.[30] NO-induced vasodilation through both cGMP-dependent and independent pathways relies on gap junctional communication.[31] Moreover, acupuncture points and meridians have been discovered to have high electric conductance, which is related to high-density of gap junction.[2,27] Our findings are also consistent with results which indicate that an increase of NO leads to a decrease in electrical resistance in the acupoints/meridians and suggest that NO may enhance gap junction communication, which increases meridian conductance. These studies can not exclude direct effects of NO on release of noradrenergic transmission in the acupoints/meridians. A more sophisticated approach would be required to address this issue. Despite these limitations, our results from NO and noradrenergic function studies consistently suggest a sympathetic nerve effect of L-arginine–derived NO in the acupoints/meridians.

In summary, skin electrical currents are significantly higher in BL 56, PC 6, and CV 17 than those in non-LSRP and non-meridian control points. The currents in response to electrical stimulation are consistently enhanced after repeated measurements/stimulations. The increases in currents induced by repeated stimulations were enhanced by intravenous injections of L-arginine or an exogenous NO donor and blocked by inhibitors of NO synthesis and guanethidine, blocking noradrenergic function. These data provide evidence that L-arginine–derived NO synthesis and noradrenergic transmission modify skin electric conductance, which contributes to low-resistance characteristics of acupoints and meridians.

ACKNOWLEDGMENTS

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