Preemptive Spinal Cord Stimulation Reduces Ischemia in an Animal Model of Vasospasm

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ABSTRACT
SPINAL CORD STIMULATION (SCS) has been increasingly used in the treatment of ischemia caused by obliteratorive diseases in the extremities and in the cardiac circulation. The most promising effects have been obtained when physicians suspect that a major vasospastic component underlies the ischemic symptoms (e.g., as in Raynaud's disease). Despite the clinical success of this treatment method, little is known about the mechanisms underlying the pain relief it produces and its anti-ischemic effects. Most earlier experimental studies have used normal animals or animals with cerebral vasospasm induced by injection of autologal blood into the cerebrospinal fluid space. In the present study, we applied SCS in a rat model via implanted electrodes to study the effect of preemptive stimulation on the ischemia caused by vasospasm in a neurovascular flap in the groin; the vasospasm was induced by mechanical pressure applied to the feeding artery. In rats treated with SCS, delivered with parameters similar to those used clinically, the percentage of flaps recovering normal microcirculation after the spasm was significantly higher than in the untreated control group (100 and 28%, respectively; P < 0.05), and the maximal blood flow after the ischemic episode was significantly higher in the SCS group than in the control group (127 and 51 arbitrary units, respectively; P < 0.05). The percentage of animals regaining the premanipulation circulation after the
provocation of a second spasm was also greater in the SCS-treated group than in the control animals (50 and 14%, respectively; P < 0.05). Pilot studies showed that this protective effect was specific to SCS given before spasm induction, an observation corroborated by clinical experiences. Different hypothetical mechanisms based on these observations are discussed. Presently, available data favor a depression of sympathetically maintained vasoconstriction by SCS as an important factor, but some observations also point to the importance of a local release of vasoactive substances (e.g., the calcitonin gene-related peptide). The animal model used in the present study may supply a convenient system for future studies of the mechanisms behind the SCS-enhanced resolution of vasospasm after different types of provocations.

Electrical spinal cord stimulation (SCS) is currently used in many centers to treat ischemic pain and ischemia in peripheral vascular disease. The most promising results in peripheral ischemia have been obtained when a vasospastic component is dominant (6,19,24). SCS has also proved efficient in reducing pain in patients with cardiac arteriosclerosis, as well as in patients with angina who have angiographically normal vessels (Syndrome X) (1). Furthermore, studies on animal models have demonstrated that high cervical SCS may reduce the vasospasm and restore the cerebral blood flow in experimental subarachnoidal hemorrhage (21,26). The knowledge concerning the mechanisms behind these beneficial effects has been fragmentary, but recent experimental studies indicate that suppression of sympathetic activity (14–16,25) and the release of vasoactive substances (3,20) may be important for the effect.

The causes of vasospasm are multiple (22); however, besides the endogenous factors, physical stress (especially stretching) to the vessels, both in plastic microsurgery and vascular neurosurgery, seems to be an important provoking agent. Experiments on isolated vessels in rats, with and without previous SCS, point to local changes in the vascular walls as a possible basis for the vasodilatory effects of stimulation (5).

Many animal studies aimed at exploring the mechanisms behind the microcirculatory changes induced by SCS have been performed on normal animals without ischemia (13) or on models of subarachnoid hemorrhage. However, in the studies of the responsiveness of local ischemia to various chemicals and to transcutaneous electric nerve stimulation (TENS), animal models with ischemic flaps have been used (10). Furthermore, trials with TENS on patients who had undergone microsurgical procedures involving free
neurovascular flaps with a risk of ischemia demonstrated that the microcirculation in the flaps remained significantly better with electrical stimulation than without (12,18).

In the present study, we applied SCS via implanted electrodes in a rat model of local vasospasm induced by the mechanical stimulation of the vessel supplying an island flap in the groin. This island flap model was described earlier by Gheradini et al. (4). Pilot studies on single animals indicated that SCS was much more effective if applied before the spasm induction rather than after flap ischemia was evident. Therefore, we decided to test whether preemptive SCS would prevent or decrease both the vasospasm and the subsequent flap ischemia evoked by the physical manipulation of the feeding vessel.

MATERIALS AND METHODS

Animals

Thirteen male Sprague-Dawley rats (body weight, 250-300 g) were housed in standard conditions (at a temperature of 20-22°C, in a light-cycled environment). They had free access to food and water. The procedures of this study were examined and approved by the Regional Ethical Committee for Animal Research.

Surgery

The experimental protocol consisted of two surgical procedures, with a rest period of 3 to 5 days between the operations. For the first session (the implantation of the electrode system), surgical anesthesia was induced by 3% halothane in a mixture of 50% oxygen and 50% air delivered by an open-circuit nose mask system at 1.5 l/min. Body temperature was maintained at 37.5 ± 0.5°C by an automatic heating device (CMA/150, CMA Microdialysis AB, Stockholm, Sweden).

After a laminectomy was performed at T12, a monopolar system for spinal cord stimulation was implanted. This system had an intraspinal cathode (silver; diameter, 2.0 mm) placed extradurally at vertebral level T11 and an anode (silver; diameter, 6.0 mm) in the subcutaneous tissue over the rib cage. The leads from both electrodes were tunneled subcutaneously to a microcontact sutured to the skin in the neck of the animal. This SCS system has been described in detail elsewhere (17).
After 3 to 5 days of recovery, the rats were anesthetized by intraperitoneal injection of chloral hydrate (0.4 g/kg), and with the rat in the supine position, a groin neurovascular flap based on the epigastric vessels was raised (4). The flap consisted of the skin and the underlying inguinal fat pad. After the vessels were trimmed by using a microscope, the flap was loosely resutured to its anatomic bed by two stitches. This preparation allowed direct observation of the superficial epigastric vessels.

Recording of microcirculation

Microcirculation in the flap (as well as in the corresponding, unoperated area in the contralateral groin) was monitored by a two-channel laser Doppler flowmetric (LDF) system (Periflux 4001 Master; probes PF 408; Perimed AB, Järfälla, Sweden). The LDF meter was set to a bandwidth of 12 kHz and a time constant of 0.03 seconds. Before the skin was cut, microstitches were used to suture two plastic probe holders to the flap and to the control area. This measure effectively minimized movement artifacts in the LDF recording. The preparation was allowed to stabilize for 80 minutes before the first spasm provocation.

Vasospasm induction

Vasospasm was induced by the method introduced by Gherardini et al. (4). The isolated superficial epigastric artery was repetitively compressed to complete closure with two microforceps along a 5-mm length of the exposed vessel for 10 seconds. This procedure was performed by the same experimenter in all sessions. Observation by microscope showed that this maneuver induced spasm, diminishing the diameter of the vessel proper and causing a decrease of microcirculation in its feeding territory as monitored by the LDF system. Two groups of animals were submitted to two spasm periods. In one group (Group A, n = 6), SCS was applied 20 minutes before the first provocation; in the other group (Group B, n = 7) no stimulation was applied via the implanted electrodes, so Group B served as a control group. The experimental protocol is shown in Figure 1.

Spinal cord stimulation

The stimulation parameters used for SCS were tailored to be similar to those used
clinically. SCS was delivered with monophasic pulses (50 Hz; pulse width, 0.2 ms) with two-thirds of the intensity required for a motor response (tonic contraction of the abdominal muscles at the level of the flap), which was tested immediately after the induction of anesthesia (14,17). This intensity activates the large-diameter, low-threshold fibers only and does not recruit the high-threshold, small-diameter fibers subserving nociception, although it is effective in inducing peripheral vasodilation in both the skin and the muscle tissue (13–17). The stimulating current was generated by a Grass standard stimulator via a Grass constant current unit (Grass Instruments, Quincy, MA). The current intensity used for the subsequent SCS varied between 0.6 and 2.2 mA in different animals.

Blood pressure monitoring

Systemic blood pressure was monitored by a catheter introduced into the right carotid artery via a Statham pressure transducer (Statham, Inc., Halo Rey, Puerto Rico). Both LDF and blood pressure data were fed into a Toshiba T3200SXC desktop computer (Toshiba, Japan) with specially designed software (Perisoft Program version 4.41; Perimed AB, Järfälla, Sweden). Program parameters were set to a sampling frequency of 128 samples/s and a smoothing factor of 7. All alterations of microcirculation were expressed in arbitrary perfusion units (PU, 1 PU = 10 mV). The degree of vasospasm-induced flap ischemia, the number of animals regaining the prespasm basal level of microcirculation, and the time to reach the different levels of recovery were recorded as detailed in the Results section. The experimental setup is illustrated in Figure 2.

Statistical analysis

The statistical tests were performed on the raw data but, for simplicity, the data in the Results section indicate the percentage of animals in a group reaching a specified recovery criterion. The log-rank exact test was used to determine whether the time to reach 50 and 100% of prespasm microcirculation was significantly different between the groups. The same test was used for the comparison of times to reach the
maximum flap microcirculation after spasm induction, but the Wilcoxon rank sum test was used to test group differences in the maximal microcirculatory flow reached after a spasm period. Finally, the \( \chi^2 \) test was used to test whether the number of flaps not reaching 50 and 100% recovery was significantly different between the groups (23). In all instances, \( P < 0.05 \) was considered to indicate a significant difference.

RESULTS

Recording of the flap microcirculation

A typical example of the microcirculatory reactions in the flaps to spasm provocation is shown in Figure 3, with one animal from the control group (upper two tracings) and one from the group with preemptive SCS (lower tracings). The control rat demonstrated a profound flap ischemia after the two spasm provocations, and the level of recovery deteriorated between the two spasm periods. The animal who had received SCS before the first spasm period recovered more rapidly and completely.

The data in Table 1 show that the recovery of microcirculation in the group with preemptive SCS was more satisfactory than the recovery in the control group. In the experimental group, a response pattern emerged indicating that SCS, delivered before spasm induction, increased both the number of flaps with complete recovery and the maximal microcirculation after the spasm period (expressed as LDF flux, PU). Also, the capacity for restoration of blood flow in the flaps in the control group was almost eliminated after the second spasm, whereas 50% of the flaps in the SCS group recovered after the second spasm.

Figure 4 shows the percentage of animals in the two groups reaching the 100% (Fig. 4A) and the 50% (Fig. 4B) recovery criteria after different periods of time. Marked and statistically significant differences were found between the two groups (the log-rank exact test, \( P < 0.05 \)). Full recovery of the prespasm circulation was reached within 60 minutes after the first provocation by all the animals receiving preemptive SCS,
whereas only about 25% of the animals in the control group had attained full recovery after this period of time. A 50% recovery was reached rapidly by all the SCS-treated animals (in 11-12 min). At that same time, only about 35% of the control animals had attained 50% recovery.

**Recording of systemic blood pressure**

The recordings of the systemic blood pressure displayed no significant changes during SCS, but during spasm provocation, slight increases were often observed. There were no significant differences between the two groups in this respect (data not shown).

**DISCUSSION**

The results of this study indicate that SCS, applied with current parameters similar to those used in the clinic, may considerably increase the recovery of microcirculation in an ischemic skin flap after mechanically induced vasospasm. Taking into consideration the observations from some pilot experiments in which the SCS was applied in some animals only after the appearance of the deficient microcirculation, as monitored by LDF (Linderoth B, Gherardini G, Ren B, and Lundeberg T, unpublished observations), we think that the stimulation must be delivered before spasm induction to be maximally effective. When the SCS was withheld until the appearance of ischemia, the deficient microcirculation developed about the same as in control animals. This observation also agrees with clinical reports from patients treated by SCS for Raynaud's disease, in whom a much better effect from stimulation was obtained if the SCS was used before the provocation of ischemic pain (e.g., by walking in cold weather) than if the SCS was applied after the pain and the pallor had already appeared.

**Earlier flap studies with electrical stimulation**
Earlier studies on ischemic flaps, both in experimental animals (10) and in patients undergoing plastic surgery (12,18), have demonstrated that ischemia is decreased and flap survival is enhanced by TENS given postoperatively. In contrast to our findings, in the animal studies previously cited (10), TENS given before the flap was raised had little effect on flap survival. However, the TENS intensity used was comparatively high in those studies, so the mode of action may be different from that in our studies. These authors found that their high-intensity TENS could be effective even if applied extrasegmentally to the ischemic area, whereas their low-intensity TENS had to be applied in the proper segment (i.e., at the base of the ischemic flap) to retain its beneficial effect (10).

Possible effector mechanisms

The possible mechanisms for the decreased ischemia and increased flap survival with afferent stimulation of coarse fibers include the release of vasoactive substances like Substance P, the vasoactive intestinal polypeptide, and the calcitonin gene-related peptide (CGRP) (7,10). Some observations support a role for the CGRP; this substance has a much higher vasodilatory potency than the others mentioned above, and it does not evoke fluid extravasation and edema. Furthermore, vasodilation induced by Substance P depends on an intact endothelium whereas some of the CGRP’s capacity for vasodilation seems to persist even after the endothelium is severely damaged, a situation often encountered in peripheral vascular disease (7).

Both in animal experiments (11) and in clinical studies (8), treatment with the CGRP markedly increased the survival of circulatory compromised skin flaps. In the clinical study (8), intravenous administration of the CGRP was even more effective than the treatment with TENS. Furthermore, a recent study with the flap model used in the present study demonstrated that the topical application of the CGRP onto the feeding artery resulted in a resolution of the vasospasm that was faster and more complete than that seen in the untreated animals (4) (Gheradini G, Lundeborg T, Gazelius B, Brodda-Jansen G, Samuelson U, submitted for publication). The time course for the recovery of the flap circulation after the CGRP application was even faster than that after SCS in the present study. Although it has been hypothesized that the effects of TENS on the microcirculation in these circumstances are caused by a release of the
CGRP (18), to the best of our knowledge, this has not been directly demonstrated yet.

Some researchers have proposed that the effect of SCS in ischemia is caused by a transient depression of sympathetically maintained peripheral vasoconstriction (13,14). Furthermore, the effects of subsequent SCS have been decreased by various measures to eliminate or decrease the sympathetic activity, such as sympathetic block with guanethidine, ganglionic block with hexamethonium, the use of more receptor-specific antagonists, or surgical sympathectomy (14–16). In animal experiments, SCS was found to act mainly on [alpha]1-adrenoreceptor-mediated influence (16). The vasospasm in Raynaud's disease may be caused by an increased sensitivity of the peripheral [alpha]1-adrenergic receptors or by an increase in their density (2), so a depression of [alpha]1-receptor-mediated vasoconstriction may constitute one component, explaining the effects of SCS in Raynaud's disease. Also, experimental flap survival may be increased by the preoperative administration of high doses of antiadrenergic drugs like guanethidine, reserpine, and 6-hydroxydopamine (9). In an ongoing study using the same model as in the present experiments, topical application of noradrenaline (Gelfoam; Upjohn Co., Kalamazoo, MI), soaked in 2% noradrenaline/saline solution, onto the feeding artery induced vasospasm similar to that obtained with mechanical provocation. Preemptive SCS seemed to diminish this type of vasospasm and the resulting flap ischemia (Linderoth B, Gherardini G, Ren B, and Lundeborg T, unpublished observations). Further studies on pharmacologically induced vasospasm are in progress.

CONCLUSIONS

SCS seems to decrease vasospasm and the resulting ischemia in an experimental island flap model in the rat, especially if the treatment is given before the ischemic period. Although the underlying mechanisms are obscure, depression of sympathetic activity and the local release of vasoactive substances may be important. This approach can supply a model for further studies of possible mechanisms behind the microcirculatory effects of SCS in ischemia. The present observations also point to a possible method of treating ischemia in microsurgery when the surgeon suspects that vasospasm underlies the patient's condition.
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Linderoth et al. have performed an interesting set of experiments, and their results indicate that neurovascular flaps based on the epigastric vessels and consisting of skin and associated fat demonstrate enhanced microcirculation when spinal cord stimulation is performed. This appears to be related to a decrease of the spasm in the microcirculation of the affected flaps. Although the authors' studies have not demonstrated a precise mechanism whereby this effect could occur, it appears that the sympathetically mediated tone to the microcirculation is decreased by spinal cord stimulation. Further experiments will be needed to determine whether this effect is mediated by the release of certain specific neurotransmitters.

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The authors have used a rodent skin flap model to assess the effects of spinal cord stimulation in the prevention of ischemia from vasospasm. The investigators have suggested that the alteration of the sympathetic tone or the changes in the local release of the vasoactive compound, the calcitonin gene-related peptide, may underlie the improvement in the flap survival from preemptive spinal cord stimulation.

The importance of this work lies in its relation to the development of methods to alleviate ischemia of the extremities (or of transplanted flaps) in response to different mechanical stimuli. Neither ischemia of the central nervous system nor vasospasm induced by subarachnoid hemorrhage was evaluated in this investigation.

KEY WORDS: Laser Doppler flowmetry; Microcirculation; Rat; Skin flap; Spinal cord stimulation; Vasospasm
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