Conduction block of mammalian myelinated nerve by local cooling to 15–30°C after a brief heating

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J Neurophysiol 115: 1436–1445, 2016. First published January 6, 2016; doi:10.1152/jn.00954.2015.—This study aimed at understanding thermal effects on nerve conduction and developing new methods to produce a reversible thermal block of axonal conduction in mammalian myelinated nerves. In 13 cats under α-chloralose anesthesia, conduction block of pudendal nerves (n = 20) by cooling (5–30°C) or heating (42–54°C) a small segment (9 mm) of the nerve was monitored by the urethral striated muscle contractions and increases in intraurethral pressure induced by intermittent (5 s on and 20 s off) electrical stimulation (50 Hz, 0.2 ms) of the nerve. Cold block was observed at 5–15°C while heat block occurred at 50–54°C. A complete cold block up to 10 min was fully reversible, but a complete heat block was only reversible when the heating duration was less than 1.3 ± 0.1 min. A brief (<1 min) reversible complete heat block at 50–54°C or 15 min of nonblock mild heating at 46–48°C significantly increased the cold block temperature to 15–30°C. The effect of heating on cold block fully reversed within ~40 min. This study discovered a novel method to block mammalian myelinated nerves at 15–30°C, providing the possibility to develop an implantable device to block axonal conduction and treat many chronic disorders. The effect of heating on cold block is of considerable interest because it raises many basic scientific questions that may help reveal the mechanisms underlying cold or heat block of axonal conduction.

Materials and Methods

All protocols regarding the use of animals in this study were approved by the Animal Care and Use Committee at the University of Pittsburgh. Experimental setup. A total of 13 cats (6 female and 7 male, 3.0–4.2 kg; Liberty Research, Waverly, NY) were used in this study. The animals were anesthetized by isoflurane (2–5% in oxygen) during surgery and maintained with α-chloralose anesthesia (65 mg/kg iv and supplementation as needed) during data collection. A pulse oximeter (9847 V; NONIN Medical, Plymouth, MN) was attached on the tongue to monitor the heart rate and blood oxygen level. A tracheotomy was performed and a tube was inserted to maintain the airway open. A catheter was inserted into right carotid artery to monitor systemic blood pressure. Another catheter was inserted into the left cephalic vein for saline and drug administration. Through an abdominal incision, the ureters were isolated, cut, and drained externally. A catheter was inserted into the urethra via a small incision in the proximal urethra. The catheter was connected to a pump (SP200i; World Precision Instruments, Sarasota, FL) and a pressure transducer (BLPR; World Precision Instruments) via a three-way stopcock (30600-25; Cole-Parmer, Chicago, IL) to slowly (1 ml/min) perfuse the urethra and measure the urethral pressure increase caused by neurally evoked contractions of external urethral sphincter (EUS) striated muscle (Fig. 1). All incisions were closed by sutures at the end of surgery. The animals were euthanized under deep anesthesia at the end of the experiments by intravenous injection of potassium chloride.

The pudendal nerves containing the motor axons innervating the EUS were exposed via 3- to 4-cm incisions between the tail and sciatic notch and cut bilaterally with the distal end tied with a suture (Fig. 1). The right or left pudendal nerve was studied individually. One of the pudendal nerves was passed through a small (9 mm long) coil (2-mm inner coil diameter) of copper tubing (no. 8117; K&S Precision Metals, Chicago, IL) (Fig. 1). One end of the copper tubing (outside diameter: 1.57 mm and inside diameter: 0.36 mm) was connected to a syringe via a plastic tube for manually infusing different temperature water to locally cool or heat the nerve segment in the coil. The temperature inside the coil was monitored by a thermocouple.
with the sensor tip positioned in the center of coil (Fig. 1). The coil fit closely around the nerve and the thermocouple, so that the thermocouple tip was in contact with both the nerve and the coil. The thermocouple was connected either to a commercially available thermometer (model 4482; Control, Friendswood, TX) or to a thermocouple amplifier (OMNI-AMP-IV-23-115; Omega Engineering, Stamford, CT) that was connected to a computer for displaying the temperature (±0.1°C resolution). The mean temperature was maintained within ±1°C of the targeted temperature by manually adjusting the infusion rate. A bipolar stainless steel hook electrode was placed on the nerve proximal to the copper coil (Fig. 1) to test whether local temperature change inside the coil could block the urethral contraction responses induced by repeated short trains of stimulation (1–10 V, 50 Hz, 0.2 ms, 5 s on and 20 s off) generated by a stimulator (S88; Grass Technologies, West Warwick, RI). Stimulation intensities sufficient to generate >40 cmH₂O increases in urethral pressure were used during the experiments. The nerve, coil, and electrodes were all immersed in the warm saline pool formed by retracting the skin flaps using sutures. The saline pool temperature (35–37°C) was monitored by another thermometer (model 4482; Control) and maintained during the experiment by a heating lamp and by adding warm saline as needed.

**Experimental protocol.** In the first group of nine cats, the nerve was first briefly (40–60 s duration) cooled sequentially to temperatures of 30, 25, 20, 15, 10, and 5°C in −5°C steps. Then, the nerve was briefly (40–60 s duration) heated sequentially to temperatures of 42, 44, 46, 48, 50, 52, and 54°C in +2°C steps. Between these brief cooling/heating periods, enough time (50–150 s) was given for the EUS contraction amplitude to fully recover. Once a reversible complete heat block was observed (usually at 50–54°C), the temperature was not further increased. Instead, the brief cooling protocol was repeated to examine the changes in cold block temperatures, and the duration of change was then monitored by repeatedly (50–to 150-s interval) and briefly (40–60 s) cooling the nerve until the cold block temperature returned to control level, which was confirmed by repeating the brief cooling protocol. The duration of cold block at an increased temperature is defined as the time when the mean pressure of the smallest urethral contraction during a cold block was maintained at <25% of control (see Fig. 6A). At the end of this group of experiments, different heating durations (0.6–3.8 min) were tested at the reversible block temperature (50–54°C) to determine the heating duration for a nonreversible block. A complete block was defined as an EUS contraction amplitude <5% of control contractions. A reversible block was defined as recovery of the EUS contraction amplitude to >90% of control within 5 min after termination of heating/cooling, while nonreversible block was defined as failure of the contractions to recover to 90% of control within 5 min after termination of heating/cooling.

In the second group of four cats, the repeated cooling protocol as described above was performed initially to determine the cold block temperature. Then, the nerve was heated three times for a period of 5 min to 46 or 48°C, which are temperatures just below the heat block temperature (50–54°C). After each heating, the cold block temperature was measured by the repeated cooling protocol. The cat numbers and left/right pudendal nerves used in different tests are listed in Table 1.

**Data analysis.** To measure the temperature effects on nerve conduction, the mean amplitude of the smallest urethral contraction induced by short trains of pudendal nerve stimulation during each brief cooling/heating was normalized to the mean amplitude of two to three urethral contractions just before the cooling/heating. The results obtained from nerves in different animals under the same experimental conditions were averaged and reported/plotted as mean ± SE. Statistical significance (P < 0.05) was detected by t-test (see Fig. 4B) or ANOVA followed by Dunnett multiple comparison (one-way, see Figs. 6B and 7B) or Bonferroni multiple comparison (two-way, see Figs. 5B and 6C).
RESULTS

Conduction block of the pudendal nerve by local cooling or heating. Short trains (5 s on and 20 s off) of pudendal nerve stimulation (50 Hz, 0.2 ms, 1–10 V) induced short duration EUS contractions that generated relatively consistent urethral pressure increases of amplitude $H_{11022}^{40}$ cmH$_2$O (Figs. 2A and 3A). Manual perfusion of cold water (0–10°C) through the copper coil quickly (5–10 s) reduced the temperature recorded by the thermocouple inside the coil to 5–30°C that was maintained for 40–60 s (marked by the black bar under the pressure trace in Fig. 2A). Once the perfusion was stopped, the temperature quickly (10–30 s) returned to a temperature close to the saline pool temperature (35–37°C). Similarly, brief heating the nerve (Fig. 3A) was achieved by manual perfusion of hot water (50–60°C) through the copper coil.

When the temperature was gradually decreased by local cooling, a partial conduction block of the pudendal nerve occurred starting at 15°C (Fig. 2, A and B). In the 20 tested nerves, a complete block was achieved at 15°C in 2 nerves, at 10°C in 6 nerves, and at 5°C in a total of 14 nerves with a partial block in the remaining 6 nerves. Figure 2B shows the average results. The urethral contraction responses fully recovered once the cold temperature was returned to a temperature close to the warm saline pool temperature (Fig. 2A), indicating that the brief (40–60 s) cold block was completely reversible. Long-lasting (4.5–10 min) complete cold block was tested in three nerves, showing a similar reversibility (Fig. 2C).

When the temperature was gradually increased by local heating, a partial block of nerve conduction occurred starting at 50°C (Fig. 3, A and B). In the 14 tested nerves, a complete block was achieved at 50°C in 2 nerves, at 52°C in 6 nerves, and at 54°C in 6 nerves. Figure 3B shows the average results. Although heat block of short duration ($<1.17$ min) was fully reversible (Figs. 3A and 4A), a longer duration (2.23 min) produced a partial nonreversible block or a complete loss of urethral contractions (Fig. 4A). On average, reversible heat block was achieved with a heating duration of $1.3 \pm 0.1$ min while nonreversible (partial or complete) heat block occurred with a heating duration of $2.7 \pm 0.2$ min (Fig. 4B). The nonreversible heat block (Fig. 4A) was monitored for 5–45 min (average 17 ± 4 min) in 12 nerves with no recovery of urethral contractions.

Local heating shifted cold block temperature to 15–30°C. Reversible complete heat block increased the temperature for cold block. Before any heating, a partial cold block usually occurred at 15°C with a complete cold block at 5°C (Fig. 5A). However, after a brief (55 s) reversible complete heat block at 54°C the cold block occurred on the same nerve with a partial block starting from 25°C and a complete block at 20°C (Fig. 5A). On average a brief (40–60 s) reversible complete heat block at 50–54°C shifted the cold block response curve to a temperature $\sim10°C$ higher than the control curve (Fig. 5B).

Table 1. Animals and nerves used to collect data for different figures

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R and L, right and left pudendal nerve. X marks a check for data.
cooler cooling the nerve to <15°C for 1–10 min (Fig. 2) or by a brief (<1 min) local heating to >50°C (Fig. 3). However, the cold block temperature could be increased to 15–30°C after a reversible complete heat block at 50–54°C (Fig. 5) or after repeated nonblock heating at 46–48°C (Fig. 7). The increased temperature for cold block fully recovered with time (Fig. 6). The interaction between heating and cooling on nerve conduction is the most important observation in this study that raises many basic scientific questions about the influence of temperature on nerve conduction or block and potentially is also important for developing an implantable thermal block device to treat many chronic disorders.

It is well known that extreme cold (<15°C) or heat (>46°C) can block conduction in mammalian myelinated nerves (Klumpp and Zimmermann 1980; Paintal 1965; Stecker and Baylor 2009). However, long-duration application of these extremely low or high temperatures can result in nerve injury (Jia and Pollock 1999; Vujaskovic et al. 1994). Nonreversible nerve block was produced in cats by locally heating the tibial nerve to 46.5°C for 110 min or to 51°C for 10 min (Klumpp and Zimmermann 1980). Although conduction block was not observed in cat tibial nerves at temperatures <46°C (Klumpp and Zimmermann 1980), it was reported in dogs that locally heating the sciatic nerve at 45°C for 60 min caused a decrease in nerve conduction velocity and hindlimb dragging for 3–11 min (Vujaskovic et al. 1994). Nerve injury was also reported in rats when the sciatic nerve was cooled to 5°C for 120 min (Jia and Pollock 1999). Therefore, it is obvious that these extremely low or high temperatures are not safe for a long duration application. However, our results showed that a very different approach can be used to achieve nerve conduction block by locally changing the nerve temperature. It only requires pretreatment with a brief (<1 min) fully reversible heat block at 50–54°C (Fig. 5) or ~15 min of nonblock heating at 46–48°C (Fig. 7) followed by a mild cooling to 15–30°C to block the nerve conduction. The effect of heating pretreatment on cold block persists for ~40 min (Fig. 6). The 15–30°C temperature is probably safe for mammalian myelinated nerves. The heating durations used in this study are also probably safe because they produced fully reversible nerve block (Fig. 5) or had no effect on nerve conduction (Fig. 7). In addition, these heating durations are only ~10% of the durations required to produce a nonreversible nerve block (Klumpp and Zimmermann 1980). However, the safety for repeated application of the short duration heating will still need to be determined.

The cumulative effect of repeated heating on the threshold for cold block is likely dependent on the frequency of application. For clinical applications requiring very frequent applications, the effect of nonblock heating at 46–48°C could be additive and reach an unsafe level. Therefore, it is possible that temperatures <46°C might be used chronically to maintain the effect of nonblock heating on cold block. Previous studies in rats and dogs showed that locally heating the sciatic nerve at 43–44°C for 30–60 min was safe and only produced reversible ultrastructural and electrophysiological changes on the nerve (Hoogeveen et al. 1993; Vujaskovic et al. 1994). Therefore, it is reasonable to propose a new method to block mammalian myelinated nerves by alternately applying local heating and cooling between 45°C and 15°C after the cold block temperature threshold has been increased by the method used in this

DISCUSSION

This study in cats showed that a mammalian myelinated nerve (pudendal nerve) can be reversibly blocked by locally

Fig. 2. Cold block of the urethral pressure response induced by pudendal nerve stimulation (PNS). A: urethral pressure trace showing a complete nerve block at 5°C (cat 9/5 left nerve). The square wave under the trace indicates the duration of each short train (5 s) of PNS (50 Hz, 0.2 ms, 3.2 V). The black bar under the trace indicates the duration of cooling by the copper coil. The bottom tracing shows a continuous recording of temperature between the copper coil and the nerve. B: average urethral pressure responses at different temperatures (n = 20 nerves). The mean pressure of the last response during each cooling period was normalized to the response just before the cooling. C: cold block is fully reversible even after long-lasting (5 min) complete block (cat 4/right nerve).
study. Certainly, a substantial amount of investigation is needed in the future to confirm or refute these proposals.

Currently other methods are used in clinical applications for nerve conduction block. Injection of local anesthetics has been used for many years to produce brief nerve block because it is difficult to deliver these drugs chronically. Recently, high-frequency (kHz) electrical stimulation generated by implantable stimulators is being used clinically to chronically block the vagus nerve for obesity treatment (Sarr et al. 2012) or to block the spinal roots for treatments of chronic pain (Ceullar et al. 2013; van Buyten et al. 2013). High-frequency stimulation has also been proposed to block the pudendal nerve to restore

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Fig. 3. Heat block of the urethral pressure response induced by PNS. A: urethral pressure trace showing a complete nerve block at 52°C (cat 8, left nerve). The square wave under the trace indicates the duration of each short train (5 s) of PNS (50 Hz, 0.2 ms, 1.0 V). The black bar under the trace indicates the duration of heating by the copper coil. The bottom tracing shows a continuous recording of temperature between the copper coil and the nerve. B: average urethral pressure responses at different temperatures (n = 14 nerves). The mean pressure of the last response during each heating period was normalized to the response just before the heating.

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Fig. 4. Reversibility of heat block is dependent on heating duration. A: at 54°C nerve block is reversible after 1.17 min heating, but it is nonreversible after 2.33 min heating (cat 9, left nerve). The black bar under the trace indicates the duration of heating by the copper coil. The bottom tracing shows a continuous recording of temperature between the copper coil and the nerve. B: summarized results (n = 12 nerves). Heating temperature = 50–54°C. *Significant difference (P < 0.0001, paired t-test).
lower urinary tract function after spinal cord injury (Gaunt and Prochazka 2009; Tai et al. 2004). However, high-frequency stimulation will always generate an initial nerve firing before it can block nerve conduction (Tai et al. 2004). The initial nerve firing is problematic for many clinical applications such as suppressing pain, because initial painful sensation could be induced before nerve block occurs. The thermal block method proposed in this study provides a reversible nerve block without generating an initial response. Furthermore, current thermoelectric Peltier technology (Ackermann et al. 2010; Aronov and Fee 2011; Rothman and Yang 2003) also makes it possible to design and develop an implantable device to produce a local temperature change between 15 and 50°C. Heating/cooling a peripheral nerve using Peltier technology (Ackermann et al. 2010) requires very different electrode geometry to wrap around the nerve than the electrodes used for heating/cooling brain tissue (Aronov and Fee 2011; Rothman and Yang 2003). However, this challenge can be met by either enclosing the nerve with two Peltier devices or by covering the nerve with a highly thermal conductive metal on a Peltier device. Therefore, if a thermal block technology based on this study can be proven in the future to be safe and effective in human subjects, it could potentially be used for many clinical applications to treat chronic disorders such as obesity, pain, heart failure, and voiding dysfunction after spinal cord injury (Ceullar et al. 2013; Floras 2009; Gaunt and Prochazka 2009; Sarr et al. 2012; Tai et al. 2004; van Buyten et al. 2013; Waataja et al. 2011). It is worth noting that this study only investigated the block of motor nerves. For potential clinical applications to block sensations such as pain, additional studies should be performed to investigate the preheating effects on cold block in small myelinated Aδ or unmyelinated C fiber afferents.

The mechanisms underlying cold or heat block are currently unclear. However, it is well known that temperature determines the kinetics of sodium and potassium channel activity (Frankenhaeuser and Huxley 1964; Hodgkin and Huxley 1952). Therefore, it is possible that extreme cold or hot temperatures can produce significant changes in ion channel kinetics to cause conduction block. However, a recent study in rats (Baylor and Stecker 2009) showed that the reduction in conduction velocity by cooling the sciatic nerve was not affected by a concentration-dependent drug-induced blockade of sodium or potassium channel, implying that the low temperature effect on conduction velocity may be related to changes in the passive properties of the myelinated axon. It has been suggested that low temperature thickens the axon membranes to of sciatric nerve, resulting in stiffness of the acyl chains and strain in the protein channels that alters the sodium channel function, and thereby reduces conduction velocity (Luzzati et al. 1999). On the other hand, the low temperature effect on the amplitude of
the action potential is sensitive to a concentration-dependent drug-induced blockade of sodium channels (Baylor and Stecker 2009). Therefore, both the ion channel kinetics and the passive properties of myelinated axons might play a role in cold block of myelinated nerve.

It is easy to understand how prolonged heat block can cause nerve damage, because it is known that excessive heating can cause edema, blood vessel occlusion, severe endothelial cell damage, and demyelination (Hoogeveen et al. 1993). However, little is known about the mechanisms underlying reversible heat block. Based on what happens in cold block, it is possible that both the ion channel kinetics and the passive properties of myelinated axons could also play a role in reversible heat block. Furthermore, it is known that axonal membrane capacitance significantly increases at the heat block temperature (Leuchtag 1995). This locally increased capacitance can cause redistribution of charges along the axon and produce a local depolarization that may block axonal conduction.

In this study we discovered that a brief or mild heating could increase the cold block temperature (Figs. 5 and 7). This effect of heating on cold block can last for many minutes and is fully reversible (Fig. 6). Since ion channel kinetics change instantly with changes in temperature (Frankenhaeuser and Huxley 1964; Hodgkin and Huxley 1952), they are less likely to contribute to the prolonged heating effect on cold block. However, it is possible that a brief or mild heating can cause a change in the passive properties of myelinated axons, which is fully reversible with time. More studies are warranted to further understand the mechanisms of axonal block induced by temperature change and the interactions between cold and hot temperatures in the conduction or block of myelinated axon.

The results in this study agree well with previous studies. Cold block of sciatic nerve conduction was reported previously to occur at 5–15°C in cats (Paintal 1965). Cold block of pudendal nerve conduction was also observed at 2–10°C in dogs (Schumacher et al. 1999). In this study the temperature was lowered quickly (within 5–10 s) and then maintained for only 40–60 s. A previous study of rat sciatic nerve used a much slower cooling protocol by lowering the temperature at a rate of $\frac{1}{100}$°C/min (Stecker and Baylor 2009), which corresponds to a duration of $\frac{1}{20}$ min for each temperature ($\pm 1°C$) tested in our study. Even with such a slow temperature change a temperature $<16°C$ was still required to block the conduction of sciatic nerve in rats, indicating that the cooling protocol used in our study is accurate enough to determine the cold block response curve (Fig. 2B). It is worth noting that cold block

Fig. 6. After a brief reversible heat block the increased temperature for cold block recovers with time. A: after a brief heat block at 54°C, the cold block at 20°C was gradually lost with time and eventually became ineffective to block nerve conduction. However, cold block at 15°C could be achieved for a longer period than 20°C. The second trace continues from the first trace in the same animal (cat #9/ left nerve). The black bar under the trace indicates the duration of heating/cooling by the copper coil. The bottom tracing shows a continuous recording of temperature between the copper coil and the nerve. B: durations of cold block were different for different increased cold block temperatures. *Significantly ($P < 0.05$) different from 10°C data (one-way ANOVA); $n=7$ nerves. C: cold block temperature curve fully recovered with time after a brief reversible heat block. Reversible heat block at 50–54°C was applied for 40–60 s; $n = 9$ nerves.
occurs in a wider temperature range (5–15°C) than heat block (50–54°C), which may indicate very different mechanisms for cold and heat block. In addition, it is known that cold block temperature is not related to nerve conduction velocity (Paintal 1965). Therefore, the gradual block as the temperature becomes lower (Fig. 2) is more likely due to the temperature gradient in the nerve generated by the copper coil rather than due to blocking axons of different diameters. However, stimulation intensity was not increased briefly during a complete block to examine the effect of activating axons of different diameters. Therefore, how the block temperature changes with stimulation intensity still needs to be investigated in future experiments.

A previous study in cats reported that a temperature >46°C was required for a heat block of myelinated axons (Klump
and Zimmermann 1980). This temperature for heat block that is slightly lower than the threshold blocking temperature in our study (Fig. 3) could reflect different experimental methods. The length of the heated nerve was 15 mm in the previous study (Klumpp and Zimmermann 1980) but was only 9 mm in our study. In addition, a recent study in rats showed that the sciatic nerve could be blocked by increasing local temperature about 9°C from room temperature using very focused (<0.1 mm) infrared laser (Duke et al. 2013). The effect of heating or cooling different lengths of nerve needs to be investigated. Many other questions will also need to be answered in future studies. For example, will cooling also affect the heat block temperature? What is the duration for different heating temperatures to maximally increase cold block temperature? Can the duration of the increased sensitivity to cold block be prolonged with additional intermittent mild heating at 42–44°C? These questions are important for understanding the mechanisms underlying cold/heat block and for translating the thermal block technology into clinical applications.

In summary, the prolonged effect of a brief period of heating on the threshold temperature for producing cold block of axonal conduction is an important observation that may lead to new insights into the physiological properties of myelinated axons and to the development of new clinical methods to treat neurogenic dysfunctions using thermal-induced changes in axonal conduction.

REFERENCES


GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


