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A fully implanted drug delivery system for peripheral nerve blocks in behaving animals

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ABSTRACT

Inhibiting peripheral nerve function can be useful for many studies of the nervous system or motor control. Accomplishing this in a temporary fashion in animal models by using peripheral nerve blocks permits studies of the immediate effects of the loss, and/or any resulting short-term changes and adaptations in behavior or motor control, while avoiding the complications commonly associated with permanent lesions, such as sores or self-mutilation. We have developed a method of quickly and repeatedly inducing temporary, controlled motor deficits in *rhesus macaque* monkeys via a chronically implanted drug delivery system. This assembly consists of a nerve cuff and a subdermal injection dome, and has proved effective for delivering local anesthetics directly to peripheral nerves for many months. Using this assembly for median and ulnar nerve blocks routinely resulted in over 80% losses in hand and wrist strength for *rhesus* monkeys. The assembly was also effective for inducing ambulatory motor deficits in rabbits through blocks of the sciatic nerve. Interestingly, while standard anesthetics were sufficient for the rabbit nerve blocks, the inclusion of epinephrine was essential for achieving significant motor blockade in the monkeys.

1. Introduction

Temporarily disrupting the function of peripheral nerves to prevent normal sensory and/or motor function is useful for studies of neurophysiology, behavior, motor control, and, more recently, neural interfaces. Our group has used this method to develop a cortically controlled functional electrical stimulation (FES) system to restore hand function during paralysis (Pohlmeyer et al., 2007). Unlike a nerve transection or other chronic method of inducing paralysis, a temporary pharmacological block allows repeated comparisons between the normal and blocked state. Furthermore, long-lasting deafferentation or paralysis can also lead to long-term complications in the animals' health. These risks are greatly reduced by a temporary block.

A peripheral nerve block is typically done by a percutaneous injection of local anesthetic directly to the nerve at an area in which it is relatively superficial or otherwise accessible. The nerve can be located by stimulating electrically through a needle as it is inserted. The stimulation is reduced in intensity as the needle approaches the nerve until the current strength and magnitude of the physical response indicates close proximity. Ideally the needle will not actually touch the nerve, in order to avoid making an intraneural injection (Capdevila et al., 2004; Raj, 1991; Selander et al., 1977; Sung, 2004). It is important for the subject to remain still during this procedure, as even small movements can prevent proper injections. This can be particularly difficult with an awake animal. It is possible to use a general anesthetic for restraint, but the anesthesia can then confound the effects of the desired experiment.

Given the difficulties involved in performing reliable peripheral nerve blocks (PNBs) in animals, we developed a method that uses a fully implantable drug delivery assembly. This assembly consists of a chronically implanted nerve cuff connected to a subdermal injection dome. A similar nerve cuff was used to deliver a controlled anesthetic dosage to selectively block the gamma input to muscle spindles during locomotion in the cat (Hoffer and Loeb, 1983). In that system, however, the proximal end of the cannula was brought out through the skin. We chose to use subdermal injection domes so that the entire assembly could be implanted to reduce the risk of infection, and the likelihood of damage when the animal is in its home cage. Other nerve cuff applications have included studies involving nerve recording, stimulation, or the application of growth factors, anesthetics or other drugs to nerves (Andreasen and Struijk,

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2003; Grill and Mortimer, 1998; Haugland et al., 1999; Hoffer and Kallesoe, 2000; Kroin et al., 1986; McDonald and Zochodne, 2003; Strange and Hoffer, 1999; Tarler and Mortimer, 2004). The extensive use of nerve cuffs has made information regarding appropriate cuff sizing and materials readily available, and has provided ample evidence that they can be safely used over long periods (Cuoco and Durand, 2000; Grill and Mortimer, 2000; Larsen et al., 1998; Stein et al., 1977).

Macaque monkeys have frequently been used in studies of spinal nerve blocks (Denson et al., 1981; Denson et al., 1984) and tests of the toxicity of regional anesthetics (Munson et al., 1977; Munson et al., 1975; Rosen et al., 1983), which suggested that standard regional anesthetics, such as lidocaine and bupivacaine, would also be effective for PNBs. Recently, work by (Moritz et al., 2008) that focused on brain-machine interfaces used peripheral nerve blocks using either chloroprocaine or lidocaine (with epinephrine) delivered either through a catheter inserted into the epineurium or in some cases, with nerve cuffs and a percutaneous catheter similar to that used previously in cats (Hoffer and Loeb, 1983).

2. Materials and methods

2.1. Nerve cuff assembly

The drug delivery assembly described here consisted of a Silastic cuff that was placed around the nerve and connected to a subdermal injection dome via a short cannula. Anesthetics injected into the dome were thus delivered directly to the nerve. Since all the components were located beneath the skin, the chance of infection was greatly reduced.

2.1.1. Rabbit nerve cuffs

The basic design of the rabbit cuffs consisted of a Silastic tube (slit open lengthwise to permit placement around a nerve) that incorporated three stimulating wires, and was attached to a cannula as shown in Fig. 1A. The wires were sewn into the proximal end of the cuff, the cuff's exterior at that location being insulated with Silastic adhesive (Silbione MED ADH 4300 RTV) to prevent current spread to the surrounding tissue (Hoffer and Loeb, 1983; Stein et al., 1977). These wires were used to evoke muscle twitches to test the effectiveness of the nerve block.

The cannulae and cuffs were all made from laboratory grade Dow Corning tubing. The cuffs themselves were typically 0.132″ ID; 0.183″ OD, although slightly different diameters were occasionally used depending on the size of the sciatic nerve in each animal. Using only a single type of tubing (0.040″ ID; 0.085″ OD), to connect the cuff directly to the injection dome limited the flexibility of the assembly. Thus, the cuff was joined to the injection dome using a short piece of thin, flexible tubing (0.020″ ID; 0.037″ OD), attached to the thicker tubing, as shown in Fig. 1A. Several different methods of attaching the cannulae to the cuffs were explored, but none appeared to be superior to the others. In most cases, the cannula was simply attached to the middle of the cuff by slitting about 5 mm of the distal end of the cannula lengthwise, inserting the split ends of the cannula through a slit in the wall of the cuff, and suturing them to the inside of the cuff with 4–0 Neurolon. The cannula was cemented in place with more Silastic adhesive.

2.1.2. Monkey nerve cuffs

For the monkey cuffs, the cannula was connected to a small rectangular sheet of Silastic (thickness: 0.007″) at a 90° angle in the same manner as the attachment to the cuff described above. The Silastic sheet was then wrapped around the nerve at the time of surgery (Fig. 1D and E). This approach was used to provide a more flexible, custom-fitted cuff design to address concerns about joint motion and limited implant space at the elbow. Since the effectiveness of the nerve block in the monkeys was established using behavioral tasks, no stimulating wires were needed.

2.1.3. Subdermal injection domes

Mentor injection domes (350-DOMPK) were used for the injections. Since two or more domes were implanted in the arm of the monkeys, the smaller "micro" domes were used (Fig. 1B shows a pair of domes after implantation), while for the rabbits the larger standard size was adequate. The fill volumes of the combined dome and cannula were approximately 0.5 ml for the rabbit assemblies,

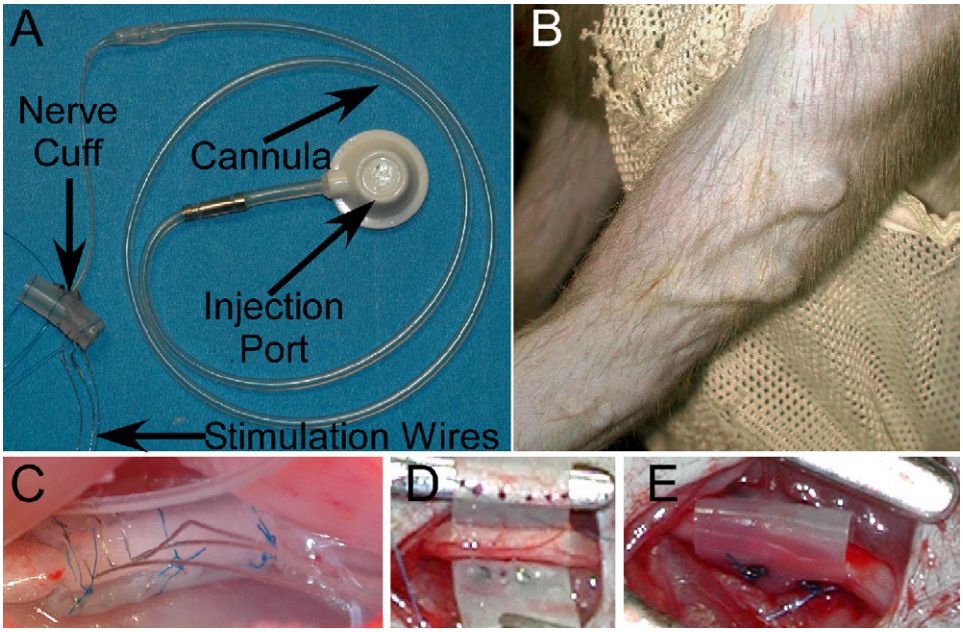

Fig. 1. (A) Nerve cuff, cannula, and injection port used in rabbit experiments. (B) The appearance of the injection dome beneath the skin in the upper arm of monkey M2. (C) A nerve cuff around the rabbit sciatic nerve. The three stimulating wires are visible in the foreground. (D–E) show the implantation of a cuff around the ulnar nerve in M2 before (D) and after (E) the silastic has been shaped into a tube around the nerve.