EFFECTS OF STEADY MAGNETIC FIELDS ON ACTION POTENTIALS OF SENSORY NEURONS IN VITRO

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ABSTRACT

Exposure to a static field (10 milliTesla) produced by an array of four permanent magnets of alternating polarity (side, facing neuron under study) reduced or blocked action potential (AP) firing by adult mouse dorsal root ganglion neurons in monolayer disassociated cell culture. The effect was reversible with slow recovery of firing over several minutes. Arrays of four magnets of like polarity (all positive or all negative poles; 32-35 milliTesla) also reduced firing, but APs returned within seconds after removal of these arrays. An alternating dipolar array (13.7 milliTesla) had no effect. These findings suggest that the configuration of magnets and gradients within the field may be more important than field strength in determining biological effects. Devices controlling such magnetic fields could be used for the treatment of chronic, medication-resistant pain. ***static magnetic fields, magnetic field gradient, action potentials (AP), cell culture, dorsal root ganglion cells.***

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INTRODUCTION

At this time of heightened public concern about the health impact of magnetic fields[1], there is increasing use of magnetic devices in the practice of clinical medicine. Examples include magnetic resonance imaging of body structures[2]; the use of SQUID (semiconductive quantum interference device) probes to detect magnetic fields produced by cardiac[3,4] and neural[5,7] tissue; the use of pulsed magnetic fields to enhance bone healing[8]; and, the historical use of magnets to treat pain.[9] Yet, understanding of cellular effects of magnetic fields is in its infancy. Theoretical studies have indicated that homogeneous fields of 25-100 Tesla (T: SI unit of magnetic field density) would be required to affect ionic currents of nerve processes.[10,11] Studies of effects of homogeneous fields (up to 10 T) on non-mammalian preparations have yielded mixed results. Some studies reported effects on aspects of neuronal excitability, such as chronaxie, action potential firing and/or response to neurotransmitters.[12-15] Others showed no effects and identified technical flaws in previous studies interpreted as positive.[16-18] Thus, the question of whether magnetic fields alter membrane function remains unresolved.

Adult mammalian sensory neurons can be maintained in vitro and provide a model system in which to test the biological effects of magnetic fields in a controlled environment. Other investigators have recorded from cell bodies of neurons in sensory (dorsal root) ganglia of anesthetized animals. Neurons with stimulus-response characteristics of pain sensitive neurons and fibers with slow conduction velocities, a criterion used clinically to segregate nerve fibers subserving different sensory functions, had long duration action potentials. Mechanosensitive neurons had fast conduction velocities and brief APs.[19-20] In vitro, some sensory neurons responded to pain-producing, substances.[21] Under voltage-clamp conditions using the patch clamp technique, two different sodium currents were observed in dorsal root ganglion neurons.[22,23] We have

identified functional subtypes of neurons in vitro by a combination of AP waveform and firing pattern, chemosensitivity and the type(s) of sodium current generating the AP upstroke.[24] One subtype, the LD neurons, had long-duration (2-5 msec at takeoff potential) APs which fired repetitively during 400 msec intracellularly applied depolarizing current pulses and which were resistant to tetrodotoxin (TTX), a marine toxin known to block fast sodium channels of nerve and muscle. The LID neurons were excited by endogenous (bradykinin, histamine) and exogenous (capsaicin) irritants known to produce pain in man. Properties of LD neurons[24] resembled those of nociceptive neurons in vivo.[19,20] Other neurons (SD) had short duration (0.5-2.0 msec) APs which fired once or a few times during 400 msec depolarizations and were blocked reversibly by TXX. The SD neurons were not excited by irritants. Properties of SD neurons[24] were more like those of mechanoceptive neurons in vivo.[19,20] Pressure application of solution in which sodium was replaced with choline reversibly blocked APs of both LD and SD neurons, i.e. both types of APs were sodium-dependent. Using patch clamp techniques we found some neurons had TTX-resistant sodium current, TTX-sensitive sodium current, or a mixture of the two. By analogy based on effects of TTX, LID neurons APs, and hence those of nociceptive neurons, seem to be generated by the slow, TTX-resistant current. Action potentials of SD, hence mechanoceptive, neurons are generated by the fast TTX-sensitive current typically seen in central neurons and muscle.

In this symposium, we summarize findings which show that inhomogeneous magnetic fields (<20 mT) produced by arrays of permanent magnets reduced AP firing by adult mouse sensory neurons, both LD and SD, in monolayer dissociated cell culture. Preliminary accounts of this work have been published.[25,26]

METHODS

The culture and recording methods were published previously.[24] Briefly, dorsal root ganglia were removed under sterile conditions from adult female mice, boarded and sacrificed by methods approved by the Vanderbilt University Animal Care Committee in accordance with provisions of the DHEW Guide for the Care and Use of Laboratory Animals. The ganglia were minced finely and incubated in Eagle's Minimal Essential Medium (MEM) containing 0.1 mg of crude collagenase and 1 mg trypsin per ml for 45-60 minutes at 37^{o}C. After centrifugation, the pellet was resuspended in culture medium (consisting of 50% (v/v) Eagle's Minimum Essential Medium + 50% Hank's balanced salt solution, supplemented with 1.5 g of dextrose and 0.75 g of $NaHC0_3$ per 500 ml, 5 ml% heat-inactivated horse serum, 5 ml% fetal calf serum, 1 ml% Nu-Serum and 10 ng/ml of nerve growth factor) and triturated to single cells and small clumps. Aliquots of cell suspension were placed in collagen-coated dishes and maintained in an incubator gassed with 90% room air and 10% CO, at 35^{o}C for up to 6 months prior to experimentation. After I week, fluorodeoxyuridine (0.5 m g/ml was added to the medium for 1-2 days to suppress growth of rapidly-dividing, non-neuronal cells. Thereafter, culture medium was changed twice weekly.

Intracellular recording

Standard intracellular electrophysiological recording techniques were used to record from cultures during superfusion (flow rate 0.5-1 ml/min) with phosphate buffer (modified Dulbecco's phosphate-buffered saline; composition millimolar: NaCl 143.4; KCl 4.2; $CaCl_2$ 0.81.0; M-Cl_2 3.0; and glucose 11 in 9.5 mM sodium phosphate buffer at pH 7.40) at 37^{o}C. Use of a bridge amplifier allowed simultaneous measurement of transmembrane voltage and passage of polarizing current through the microelectrodes (>45 megohms, filled with 3 m potassium acetate). Data was stored on video tape after digitization by a modified audio processor. The rising velocities of APs of the different subtypes of dorsal root ganglion neurons (DRGN) studied here depended on external sodium concentration.[24] The maximal rate of rise (V_{max}) of APs was proportional to the peak of the membrane differentiated electronically with respect to time (-dV/dt displayed in figures) and was used as a qualitative assay of sodium currents generating the upstroke of the APs. Lack of effects of magnetic fields on the recording apparatus was indicated by absence of changes in bridge balance and tip potential with the electrode positioned extracellularly near the bottom of the experimental chamber for ten minutes in the magnetic field.

Magnetic arrays

For experiments, stimulus intensity was set just above threshold so that all stimuli elicited APs. After control readings, a neuron was exposed to one or more arrays of up to four permanent, center-charged, neodymium magnets (total of four magnets and/or nonmagnetized blanks) in a plastic case. Initial experiments were performed by positioning the magnetic array above the culture dish with a micromanipulator at a distance of about 1 cm. To avoid displacing the microelectrode, the magnetic array was slightly eccentric. For more quantitative experiments, the arrays were mounted interchangeably on the ocular nosepiece beneath the microscope stage immediately before rotation into position 0.5 cm from the bottom of the culture dish. The

neuron under study was located near the center of the magnetic field. Fields emanating from the surface of the different arrays of magnets facing the neurons under study were measured with a Hall-effect probe positioned in the microscopic field on the bottom of a culture dish and connected to a gaussmeter. Axial components of the fields (mean of ten determinations with the probe placed near the center of the microscopic field, in the same position as neurons were studied electrophysiologically) were 10. 1 mT for four magnets of alternating polarity (Magna Blocä); 13.7 mT for two magnets of alternating polarity; and, 35.1 mT for four magnets of negative polarity. Fields varied as much as 15% in the course of removing and replacing the arrays between measurements. For the recovery periods, the nosepiece was rotated to the original lens position and the array of magnets was removed. During baseline recordings and recovery periods, magnets were kept at least 30 cm from the microscope. Data were excluded if membrane potential changed more that 5 mV, or if the neuron died, signified by loss of AP amplitude and reduction of membrane potential to zero.

Assessment of effects of temperature

Temperature control was accomplished by adjusting the set point of a bipolar controller connected to Peltier devices mounted in contact with an aluminum block surrounding the recording chamber. The thermal probe of a telethermometer was positioned near the edge of the microscopic field containing the impaled neuron under study. For some experiments, temperature was set at 32^{o}C by adjusting the setting of the bipolar controller. After reaching the desired temperature, at least 3 minutes were allowed to ascertain thermal stability before further stimulation. After assessment of AP firing capability at the reduced temperature, the setting of the bipolar controller was returned to the 37^{o}C position to determine reversibility of effects due to temperature change or exposure to magnetic fields at reduced temperature.

FINDINGS

Brief (1.0 msec) depolarizing current pulses applied intracellularly elicited single APs in SD (0.5 to 1.5 msec at the level of the takeoff potential) and LD neurons (2-3 msec duration with a hump on the repolarizing phase). Data were obtained before, during, and after exposure to an array of four magnets of alternating polarity in each of 135 neurons. Figure 1 shows data from an LD neuron. Complete block (all stimuli failed to elicit APs) was achieved within 3-7 min. exposure to the magnetic array in fifty-eight of seventy SD neurons (83%). As APs failed, latency became prolonged and amplitude and V_{max} decreased without changed in resting membrane potential (E_m) Complete recovery (all stimuli elicited APs) occurred in thirty neurons (43%) within 3-12 min. after removal of the magnetic array. Brief steady-state depolarization (10-15 mV) or increased stimulus intensity at the original membrane potential allowed APs to be elicited by all stimuli. Less than 50% of APs were blocked in five neurons (7%), but recovered completely. No change during exposure to the magnetic array was seen in seven neurons (10%). Nine other SD neurons died before recovery could be assessed. Action potential firing was completely blocked in sixty of sixty-five LD neurons (92%). Complete recovery occurred in thirty-one (48%) without changing stimulus intensity. In twenty-six neurons (40%) which did not recover completely, APs could be elicited with increased stimulus intensity or transient depolarization. Action potentials of three neurons (5%) did not recover within fifteen minutes -after complete failure and removal of the magnets. No change occurred in five (8%) neurons. Nine additional LD neurons died before recovery could be assessed.

In four SD and three LD neurons, an array of four positive poles reversibly blocked firing completely. In three SD neurons, APs were blocked completely by four negative poles. In a fourth SD neuron (shown in Figure 2) only 50% of APs were blocked. In two of three LD neurons, about fifty percent of APs were blocked; in the third neuron, APs were completely blocked. Recovery occurred in all these neurons within seconds after removing the magnetic arrays.

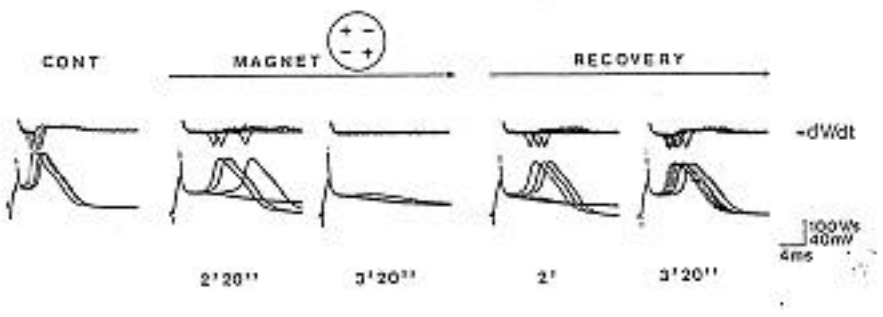

FIGURE I

Reversible blockade of action potential (APs) firing of an LD neuron. Intracellularly-applied, brief (I msec) depolarizing pulses were adjusted to elicit APs without failure (CONT). Identical stimuli began to fail to elicit APs after two minute exposure to an array of four magnets of alternating polarity positioned above the neuron under study; by three minutes, 30 seconds, all APs were blocked (MAGNET; configuration of magnets in case shown schematically; the circle represents the plastic case, polarity of each magnet indicated by a plus or minus). APs began to reappear about two minutes after removal of the array, and all stimuli elicited APs after three minutes 20 seconds (RECOVERY). Upper trace shows -dV/dt; lower trace shows transmembrane potential. Calibrations to lower right apply throughout.

Figure 2 shows recordings from a single SD neuron obtained before, during, and between exposures to magnetic fields of five different configurations. Only after exposure to the array of four magnets of alternating polarity did APs recover gradually, i.e. there was slow reversal if the effect after removal of the magnets. A two-magnet In four SD and three LD neurons, an array of four positive poles reversibly blocked firing completely. In three SD neurons, APs were blocked completely by four negative poles. In a fourth SD neuron (shown in Figure 2), only 50% of APs were blocked. In two of three LD neurons, about fifty percent of APs were blocked; in the third neuron, APs were completely blocked. Recovery occurred in all these neurons within seconds after removing the magnetic arrays.

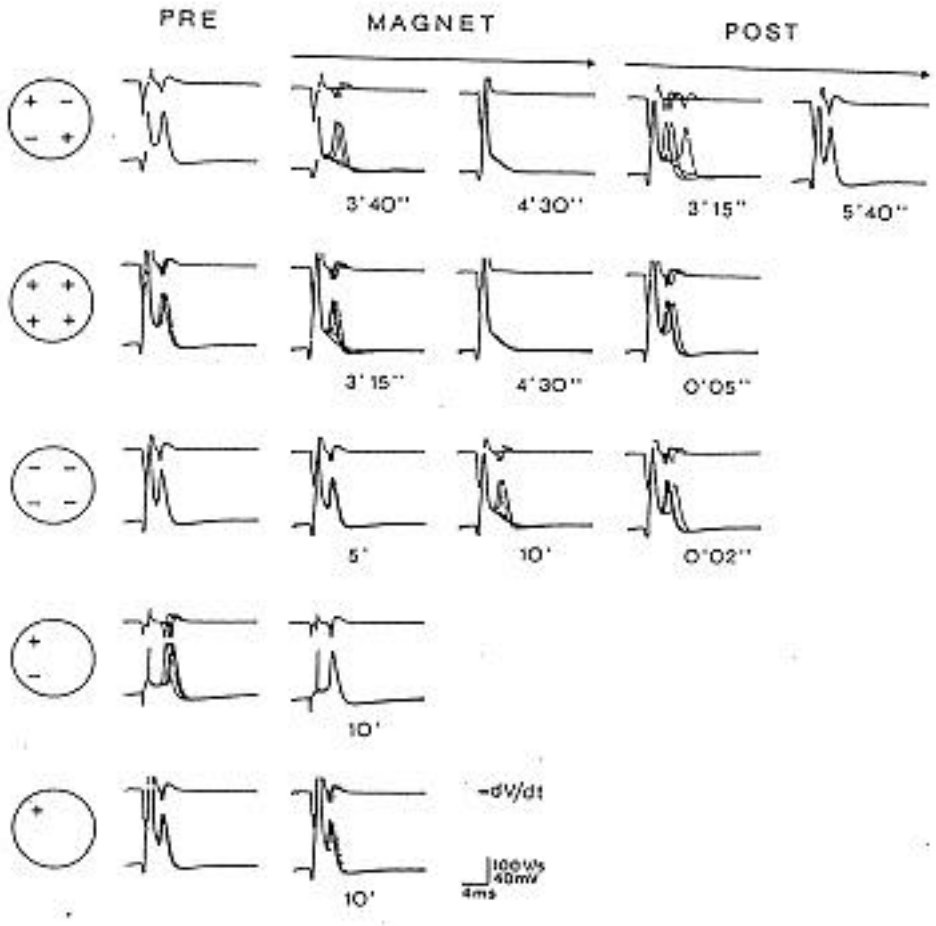

FIGURE 2

Effects of magnetic fields produced by different arrays of permanent magnets on the same dorsal root ganglion neuron. The magnetic arrays are schematized to the left of the respective rows. Intensity was set to elicit an action potential (AP) with each stimulus (PRE). After placement beneath the microscope stage of an array of four magnets with alternating polarity (side facing neuron under study; top row MAGNET) firing of APs was blocked completely in 4 minutes, 30

seconds, despite increased stimulus intensity (bridge imbalanced during stimuli). After removal of the array (POST), APs reappeared and rate rise (-dV/dt; top trace) increased gradually over five minutes, 40 seconds. An array of four magnets with positive poles aided limited firing completely within four minutes, 30 seconds (second row) and an array of four negative poles blocked about 50% of APs in ten minutes (third row). Recovery occured within seconds after removal of these arrays (POST). Two magnets of alternating polarity (fourth row) and a single magnet of positive polarity (fifth row) did not block APs after ten minutes. Calibrations apply throughout.

In an effort to quantitate effects of different magnetic fields on firing, stimuli of 1.0 msec duration were applied at 1 Hz and the number failing to elicit APs per fifty stimuli (fifty stimuli per study period, or 50 sec) was recorded. After two baseline recording periods (control periods, CI-C2), either and array of four magnets of alternating polarity or of two magnets of alternating polarity and two blanks (magnet arrangements and axially scanned field maps shown in Figure 3A and 3B, respectively) was positioned beneath the stage and 200 stimuli were applied (magnet exposure periods, M1-M4. The magnets were then removed and 200 more stimuli applied (recovery periods,R1-R4).

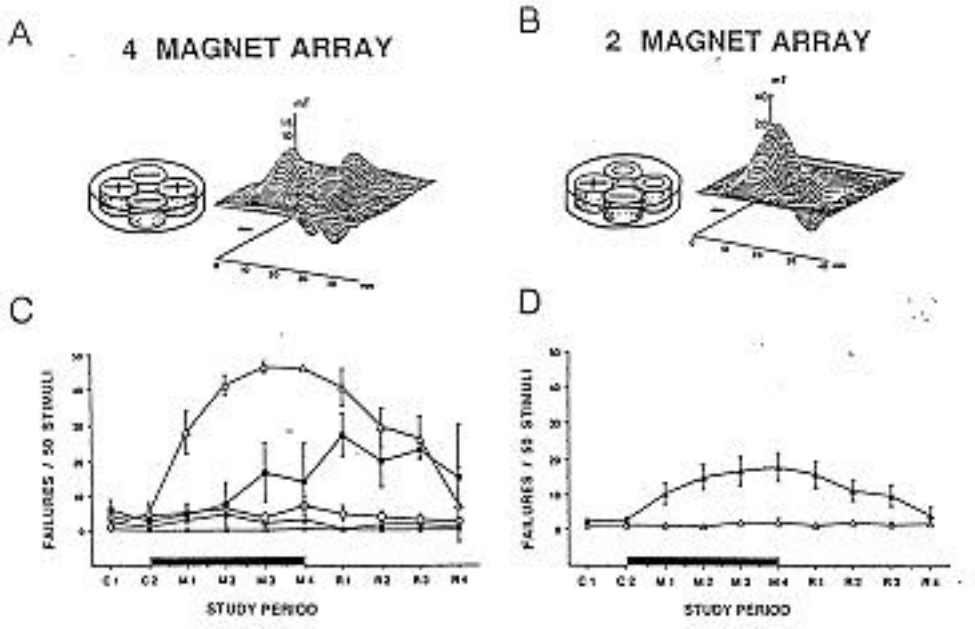

FIGURE 3

Four magnets, but not two magnets, of alternating polarity reduced AP firing. A and B show diagrams and coniputer-generated rated magnetic Field maps of the four magnet and two magnet (note two non-magnetized blanks, indicated by zeros, in the case) arrays, respectively. The maps were generated by automated scanning with a Hall effect probe 3mm from the surface of the magnetic arrays and digitization of the data. C is a graphical presentation of mean number of stimuli failing to elicit APs per fifty stimuli during control recording (study periods Cl-C2), exposure to the four magnet array (M1-M4) and during recovery after the array (RI-R4). Data were obtained from 27 SID neurons grouped to show variability of effects on the basis of % failures: open squares, 0-1 %, N =7; closed triangles, 2-10%, N=5; open circles, 10-50%, N=4; closed squares, 50-80%, N=3; and open triangles, >80%, N=8. D is pooled data from 27 neurons exposed to the four magnet array (closed triangles) compared 21 SID neurons exposed to the two magnet array (open triangles) by protocol used in C. Failures from M1 through R3 were significantly greater for neurons exposed to the four magnet array ($P<0.001$). Data points in C and D give mean ± SE. Thick black bars on abscissae delineate time of magnet exposure.

Figure 3C shows the mean number of failures in each 50 see study period for a group of twenty-seven neurons. The data were grouped arbitrarily by the maximal percentage of failures in the magnet exposure period (indicated by the heavy black line on the abscissa) to reveal variability in the effects on different neurons. Because stimulation rate was constant throughout, the abscissa was, in effect, a time base and each period represented lumped data, we have estimated pseudo-time constants (t) to compare the time course of blockade (t_b) and recovery (t_{rec}) of AP firing in different groups of neurons. In the most sensitive group of eight neurons which were almost completely blocked (open triangles; 30%), t_b = 100 sec and t_{rec} = 135 sec. Three other neurons (closed squares; 11%) had 50-80% failures with the maximum number of failures occurring after the removal of the array. For this group, t_b = 167 and t_{rec} = 200 sec. Three smaller groups (44%) were affected minimally: Five neurons (open circles; 18 %) had 10-50 % failures; four (closed triangles; 15%) had 2-10% failures; and 7 (open squares; 26%) had 2% failures or less.

Figure 3D is a graph of pooled data from the above neurons (closed triangles) exposed to the four magnet array compared to the data from twenty-one SD neurons exposed to the two magnet array (open triangles). During exposure to the four magnet array, the number of failures increased significantly above the baseline from the first period of exposure to the magnetic field to the third recovery period ($P < 0.002$, Wilcoxon signed rank test, with and without Bonferroni adjustment for baseline failures) as compared to control. The number of failures gradually decreased after removal of the array, indicating timedependent reversal of the effect of the magnetic field. Data from five additional neurons in which APs were completely abolished by the magnets but did not recover within 200 stimuli, were excluded. For the group as a whole, $t_b = t_{rec}$ = 135 sec. The number of failures during exposure to the two magnet array did not increase significantly relative to baseline ($P>0.05$, by Fisher's exact test, two-sided) and the number of failures during exposure to the four magnet array was significantly greater than during exposure to the dipolar array (treatment average, $P<0.01$; Wilcoxon rank sum test).

Resting Potentials were -49.1 $\pm$ 2.2 mV (mean $\pm$ SE; N=27) before and -44 $\pm$ 1.7 mV during exposure to the four magnet array; and, -50.1 + 2.5 mV before and -49.6 + 2.7 mV (N = 21) during exposure to the two magnet array. The magnetic arrays did not significantly affect E_m (Student's t test; $P>0.05$). Input resistance before and during, exposure to the four magnet array with APs blocked was 63.5 $\pm$ 10.3 MW (mean $\pm$ SE; N=8) and 54.4 $\pm$ 12.5 MW (N=6). This difference was not significant ($P > 0.05$). Thus, the most effective array of magnets for blocking APs had no significant effect on passive membrane properties of DRGN.

Temperature reduction had different effects on the blockade of APs of SD and LD neurons by the array of four magnets of alternating polarity. In Figure 4, pooled data from 8 SD neurons studied at 32^{o}C showed significant ($P<0.0$ 1 vs. baseline and vs. LD neurons) increase in the number of failures during exposure to the array and into the fourth recovery period (M1 to R4). The t_b was 167 sec and t_{rec} was 200 see. There was no increase in the number of failures in 9 LD neurons. Upon rewarming these same 9 LD neurons to 37^{o}C, the number of stimuli failing to elicit APs increased significantly ($P<0.01$ vs. baseline and failures at 37^{o}C to 52.2% (26.1 $\pm$ 5.5 failures per 50 stimuli) during exposure to the magnetic array. Thus temperature reduction to 37^{o}C produced a reversible abolition of the blocking effect of the magnetic field on LD neurons and slowed the effect on SD neurons.

DISCUSSION

The results demonstrate a reversible blockade of AP firing during exposure of adult mammalian sensory neurons in cell culture to inhomogeneous magnetic fields. The field produced by an array of four permanent magnets of alternating polarity was the most effective. Repeated measurements of the field produced by each array varied as much as 15%, perhaps due to changes in position of the array on the mounting post. Slight changes of position relative to the neuron under study could have accounted for the variable degree of AP blockade from cell to cell during exposure to the array. Alternatively, subgroups of neurons might respond to magnetic fields to different extents. Exposure to fields produced by an array of two magnets of alternating polarity or a single magnet had no effect on AP firing capacity.

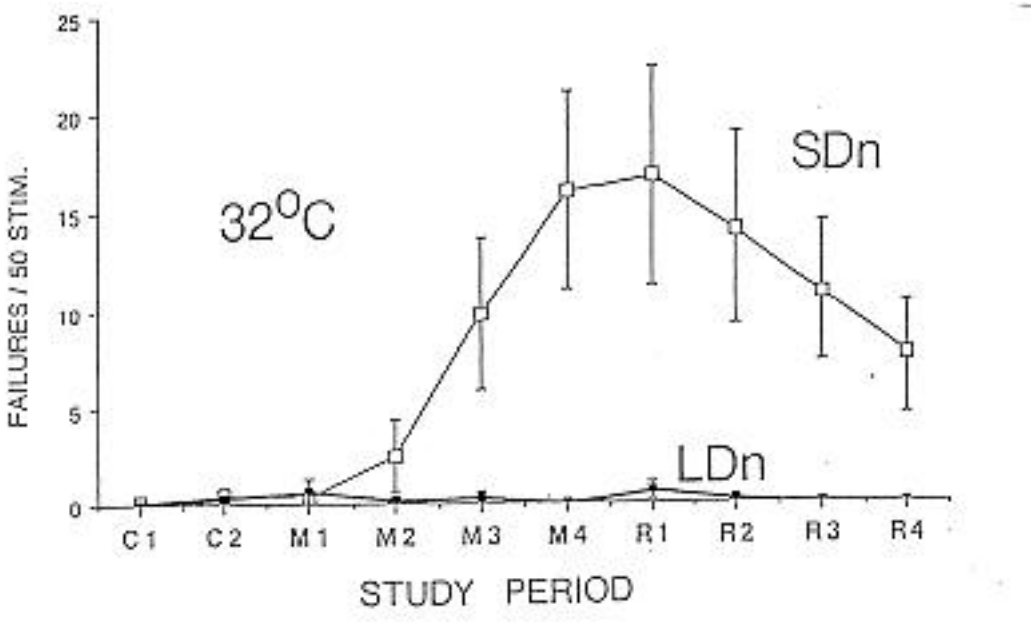

FIGURE 4

At 320C, an array of four magnets of alternating polarity reduced AP firing by SD, but not LD, neurons reversibly. Increased failures during exposure of SD neurons to the magnets was significantly different from baseline during periods M3 to R4 ($P<0.01$).

These findings suggest that the configuration of magnets in the array may determine the biological effect. 'Furthermore, of the arrays tested, the four magnet array of alternating polarity had the lowest field of strength. The field produced by this array is characterized by steep horizontal and vertical gradients (Figure 3). Thus, although the biological effect may be a product of gradients within the field and field strength, the gradients seem to be the most important.

The mechanism of the magnetic field effect is unknown. A strong field gradient could move membrane components, such as voltage-sensitive ion channel proteins. The APs of the DRGN depended on external sodium concentration.[24] In some neurons, gradual reduction of V_{max} was apparent as APs began to fail during exposure to the field. This suggested an effect on sodium channels. In preliminary patch clamp experiments, we found no effect on TTX-resistant or TTX-sensitive sodium currents of freshly dispersed DRGN. However, as shown in Figure 3, a reduction of only $5^{o}C$ abolished the effect on LD neurons and prolonged t_{b} and t_{rec} of SD neurons. The low temperature necessary to optimize patch clamp recordings may have prevented reduction of sodium currents in the magnetic field. In support of this possibility, blockade of APs and SD neurons by applied magnetic fields has not been observed in initial experiments at room temperature (McLean et al., unpublished). Longer periods of exposure to the array and/or greater field strength may be required to produce changes at reduced temperature. Alterations of temperature change the physical properties of receptors[27] and drugs.[28] Thus, it is difficult to compare data of studies on poikilotherms or on homeotherms at reduced temperature with data from homeotherms at $37^{o}C$. This suggests a need for better understanding of the effect of temperature on both membrane properties and responsiveness to magnetic fields.

More than one mechanism could be involved in the response to an imposed magnetic field. For example, evolution of the effect over several minutes suggests that biochemical processes, such as phosphorylation of ion channels, could be altered. Phosphorylation of sodium channels may be required to make the channels available for voltage activation.[29]

One potential clinical use of magnetic fields is in the treatment of medication-resistant pain. Chronic, neuropathic pain is believed to result from abnormal patterns of firing or abnormally fast firing of APs along peripheral nerves.[30] In a double blind, placebo controlled, multicenter, crossover study, a group of patients treated with multiple arrays of four magnets of alternating polarity (Magna Blocä) applied to the skin experienced significant reduction of chronic mechanical low back pain. The pain relief was significantly greater than in a group treated with placebo devices (demagnetized Magna Blocsä), but the sensation of pain was not prevented (Holcomb et al 1991, this symposium). Pain relief could have resulted from slowing conduction or decreasing the frequency of APs conducted from the periphery to the spinal cord. However, conduction

velocity of rat peripheral nerve was not slowed by the device' (McLean et al, unpublished results). The conduction velocity measurements were unable to detect the contribution of C-fibers and, thus, may not have detected an effect on those fibers. The present findings suggest that magnetic fields may affect firing patterns of both nociceptive and mechanoceptive neurons and their fibers. A potentially beneficial effect on mechano- would be decreased sensitivity of pressure receptors, thereby diminishing secondary mechanical hyperalgesia. This action could explain in part the benefit in the low back study. In support of this mechanism, we have obtained preliminary evidence in double blind trials that initial pain and secondary mechanical hyperalgesia produced by intradermal injection of capsaicin are diminished by pretreatment with the four magnet array of alternating polarity, but not a demagnetized placebo (Holcomb et al, unpublished). Other possible mechanisms of pain relief include suppression of ectopic firing (as seen in neuromas) or of hypersensitive cutaneous receptors. Both mechanisms could be important in the area of placement of the array on the patient's skin.

The above data and speculations are useful for designing further experiments to elucidate the mechanism of the membrane effect described here. Only by understanding how to control the mechanisms by which magnetic fields alter neuronal membrane function can useful devices for applications such as pain control be developed and improved.

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