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Stimulus waveform determines the characteristics of sensory nerve action potentials

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HIGHLIGHTS

- The action potential generated under the anode by submaximal stimulation is dependent on the sharpness of the stimulus shutdown.
- Assessment of anode action potential might be a simple tool to access membrane excitability of sensory nerves.
- Conventional electromyographs produce different types of stimulus configuration and this influences the ability to study anode action potentials.

ABSTRACT

Objective: In routine nerve conduction studies supramaximal electrical stimuli generate sensory nerve action potentials by depolarization of nerve fibers under the cathode. However, stimuli of submaximal intensity may give rise to action potentials generated under the anode. We tested if this phenomenon depends on the characteristics of stimulus ending.
Methods: We added a circuit to our stimulation device that allowed us to modify the end of the stimulus by increasing the time constant of the decay phase.
Results: Increasing the fall time caused a reduction of anode action potential (anAP) amplitude, and eventually abolished it, in all tested subjects. We subsequently examined the stimulus waveform in a series of available electromyographs stimulators and found that the anAP could only be obtained with stimulators that issued stimuli ending sharply.
Conclusion: Our results prove that the anAP is generated at stimulus end, and depends on the sharpness of current shut down. Electromyographs produce stimuli of varying characteristics, which limits the reproducibility of anAP results by interested researchers.
Significance: The study of anodal action potentials might be a useful tool to have a quick appraisal of distal human sensory nerve excitability.

1. Introduction

Low intensity stimuli using bipolar electrodes applied to digital branches of the median and ulnar nerves may generate a double peak response (Buchthal and Rosenfalck, 1966; Aprile et al., 2003). The first peak, or cathodal action potential (caAP), is generated under the cathode and corresponds to a submaximal sensory nerve action potential (SNAP). The second peak, or anodal action potential (anAP), is generated under the anode, as demonstrated by the proportional increase in latency after moving the position

Abbreviations: anAP, anodal action potential; caAP, cathodal action potential; FT, fall time; HCN, hyperpolarization-activated cyclic nucleotide gated; I_h, hyperpolarization-activated inward rectifying currents; PV, peak voltage; RT, rise time; SNAP, sensory nerve action potential.

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of the anode distally (Aprile et al., 2003). The two peaks are generated by fast conducting, low threshold fibers, of similar conduction velocity (Aprile et al., 2003). Aprile and colleagues noted that when the cathode is moved to the same position as the anode (and the anode moved further distally), the generated caAP has a shorter latency when compared with the anAP obtained in the original position (Aprile et al., 2003). This "anodal delay", was initially thought to be due to the activation of skin receptors. Therefore, some authors considered the clinical applicability of the technique for the diagnosis of distal axonal neuropathies (Aprile et al., 2007; Joa and Kim, 2013). Recently, though, Therimadasamy and coworkers showed that the anAP is generated at the end of the stimulus, possibly through a mechanism of anodal-break excitation, and that this could explain the "anodal delay" (Therimadasamy et al., 2015).

Anode-break excitation is an indirect manifestation of membrane accommodation to a slow polarizing stimulus, manifested by a brief rise in excitability at the end of such a stimulus. This causes a brief rebound of excitability that is able to depolarize a number of axons (Baker and Bostock, 1989). Anodal-break excitation is frequently observed in laboratory preparations of animal nerve and muscle fibers, where it is considered an undesirable artifact. Laboratory researchers have learned that anodal break excitation can be abolished by applying electrical impulses that have a slow exponential decay, known as 'triangular shape' stimulus (Accornero et al., 1977). Therefore, we carried out a study of the effects on the anAP of controlled changes in stimulus waveform. We hypothesized that, if the anAP is generated by anode-break excitation, it should be absent when the stimulus ends with slow exponential voltage decay, while this would not affect neither the caAP nor the supramaximal SNAP.

2. Materials and methods

2.1. Subjects recruited

We consecutively enrolled and examined 16 healthy volunteers at the EMG Unit of the Hospital Clinic, Barcelona, Spain. The Institutional Ethics Committee approved the study protocol, and written consent was obtained from all the subjects participating in the study. Subjects were excluded if they presented with any known neurological disorder or other medical condition that could impair peripheral nerve conduction, or if the anAP was not obtainable or lower than 2 μV.

2.2. Experimental setup

We used a conventional electromyograph (KeyPoint®, Alpine Biomed) and standard sensory nerve conduction settings (filters 20 Hz to 2 kHz; sensitivity 5–10 μV per division; sweep duration 20 ms) to examine orthodromic right median SNAPs. We applied electrical stimuli to the 3rd finger with ring electrodes (cathode at the middle of the proximal phalanx and anode placed 3 cm distally). A ground adhesive electrode was placed at the forearm. Felt pad bar electrodes mounted on a plastic support with a fixed distance of 2.5 cm were used as recording electrodes, with the active electrode placed 13 cm proximal to the cathode, at the wrist crease, overlying the median nerve. Stimulus duration of 0.5 ms was used throughout the study. All action potentials were measured after averaging 10 epochs at a frequency of 2 Hz. We made sure that the skin temperature at the base of the 3rd finger was higher than 32 °C throughout all testing.

In order to control the stimulus waveform, we added to our electromyograph stimulator a circuit with a diode and a potentiometer in parallel (Fig. 1A). Using the potentiometer, we were able to increase the resistance created by the system at the end of the stimulus, when the accumulated charges in the human tissue return to the stimulator. This allowed an effective slowdown of the decay time of the stimulus waveform originally issued by our electromyograph (KeyPoint®, Alpine Biomed). The original stimulus waveform and that of the stimulus exiting the circuit were recorded in real time, with a differential probe connected to a digital oscilloscope (PicoScope 3204®), using the Picoscope software (Picoscope 6®, Pico Technology). For the experiments reported below, we used two different stimuli waveforms: the unmodified stimulus waveform, with sharp shutting down of the stimulus, i.e., rapid voltage decay (control), and the modified waveform, with slow voltage decay (test). This circuit was prepared to receive the stimulus from the electromyograph and issue the desired stimulus waveform through suitable ring electrodes for orthodromic stimulation of digital nerves. For the observation of the stimulus waveform we used a sensitivity of 40 V per division and a time resolution of 0.5 ms per division. Signal triggering at 20 V was used to stabilize the waveform on the oscilloscope.

2.3. Control condition

The stimulating electrodes were connected to the circuit but the potentiometer was regulated to zero resistance for use of the unmodified stimulus generated by the electromyograph stimulator. In preliminary testing, we observed that adding this circuit did not change the stimulus configuration. We obtained an anAP by changing the stimulus intensity in steps of 0.1 mA. We made sure that the recorded action potential was in fact the anAP by observing a double peak response and confirming the already known characteristics of its longer latency with respect to the caAP and its progressive amplitude decrease with increasing stimulus intensity (Aprile et al., 2003; Leote et al., 2015). Afterwards, we determined the intensity that allowed us to obtain maximal anAP amplitude and recorded the intensity used as well as the anAP and caAP negative peak amplitude and peak latency at that intensity. We then increased the intensity to obtain the supramaximal SNAP and recorded its negative peak amplitude and peak latency.

2.4. Test condition

We used the external circuit to modify the voltage decay at the end of the stimulus, by increasing the resistance created by the potentiometer. Since the rising phase of the stimulus did not change no matter the amount of impedance created by the potentiometer (the diode allows for a free flow of the current during the rising phase of the stimulus), we could assure that the same amount of charge was delivered during the rising (active) phase of the stimulus in the control and test condition. This was done with a real time visual oscilloscopic control of the stimulus waveform. We quantified the change in slope using an indirect measure of the total decay time, the fall time, defined as the time ranging from the maximum peak voltage of the stimulus to the point where it decayed 80% of the maximum peak voltage (Fig. 1B). The stimulus intensity used was the one that led to obtain the maximal anAP in the control condition.

We chose to start the test using a predetermined fall time of 30 μs in all subjects. This fall time was seen, in preliminary observations, to cause some effects on the response without completely abolishing the anAP. We recorded the amplitude and latency of the caAP and anAP and, afterwards, we increased stimulus intensity to obtain the supramaximal SNAP. We then examined the effects of increasing the fall time progressively without modifying the stimulus intensity. We assessed the changes in anAP induced by the increase in fall time and, eventually, the fall time at which the anAP could not be identified anymore.