Human nerve excitability

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SUMMARY The excitabilities of separate fibre populations were examined in the ulnar nerve in 75 healthy subjects, and in the posterior tibial, peroneal, and sural nerves in 23 of these subjects. Square wave electric stimuli of varying duration were applied to the nerve in different locations, while recording the evoked muscle or nerve action potential. "Threshold" strength-duration curves were derived for motor, sensory, and mixed nerve fibre populations. These curves did not vary significantly one from another, in upper versus lower extremity, or over time. No correlations between excitability and other measures of peripheral nerve function were observed. Excitability appears to reflect some element of nerve structure or function other than myelin.

Limitations in the usefulness of nerve conduction velocity as a clinical measure of peripheral nerve function include its variability from one subject to another (Simpson, 1964), its variability over time in the same subject (McQuillen and Gorin, 1969), and the fact that it may remain normal in some instances of obvious neuropathy (Buchthal and Rosenfalck, 1971). These limitations have led to the development of new *in vivo* techniques, including analysis of compound nerve action potentials (Buchthal and Rosenfalck, 1966), and the study of nerve excitability (Heckmann, 1972; McQuillen *et al.*, 1973; Wright and McQuillen, 1973).

Until now, excitability was defined for mixed peripheral nerve only. However, many neuropathies are purely sensory, and there is some suggestion that motor and sensory nerve fibres have different excitabilities (Veale *et al.*, 1973). Many patients with neuropathy also show much more prominent involvement in the lower extremities (Thomas, 1975). Therefore, excitability was determined in separate motor and sensory fibre populations of the ulnar nerve, and in motor (posterior tibial and peroneal) and sensory (sural) nerves of the lower extremities, in normal human

volunteers. A range of values for each fibre population was established, and the long-term reproducibility of the technique investigated. Possible correlations between excitability and other measures of peripheral nerve function were investigated in an attempt to elucidate the physiological substrate of excitability.

Methods

SUBJECTS

The study group contained 75 healthy volunteers, 56 men and 19 women. Their ages ranged from 18 to 41 years (mean: 26 years). The ulnar nerve was studied in all subjects, while the lower extremity nerves were studied in 23 subjects. Motor nerve conduction velocity (NCV) and mixed nerve excitability (NE) of the ulnar nerve were within the normal range (McQuillen and Gorin, 1969; Heckmann, 1972) in all 75 subjects. Motor NCV in the peroneal nerve and sensory NCV in the sural nerve were within the normal range in each of the 23 subjects whose lower extremity nerve excitabilities were investigated (Table).

GENERAL PRINCIPLES

All studies were performed by one of the investigators (RP). With the subject in the reclining position in a room maintained at 20°C, selected nerves were stimulated at various points with bipolar saline-soaked pad electrodes (DISA 13K62). Response was recorded with surface electrodes

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Table Characteristics* of the study group

	Normal subjects	Study group
Age (yr)	24	26
NCV†		
Ulnar motor	54.8	56.4
Ulnar sensory		57.9
Peroneal		48.9
Sural		45.6
NE‡	2.2	1.8

*Mean values only given.
†NCV = nerve conduction velocity (metres per second); normal values taken from McQuillen and Gorin (1969).
‡NE = mixed ulnar nerve excitability at stimulus durations greater than 5.0 ms; normal values taken from Heckmann (1972).

(DISA 13K90), suitably amplified (DISA 14A20), and displayed on a storage oscilloscope (Tektronix RM564) for measurement. The stimulation source for excitability studies was a light-isolated electric constant current stimulator (Phipps Bird PB72).

Stimulating electrodes were placed at the point at which a minimal stimulus elicited the largest response. Next, a supramaximal stimulus with a duration of one millisecond (ms) was applied and the peak-to-peak amplitude of the maximum evoked potential measured. The current necessary to evoke a signal 10% of maximum response amplitude was taken as the reference value. This value is defined as "threshold" for the purpose of this study. To determine threshold, stimuli were applied beginning at zero milliamps (mA) and increasing in 0.5 mA increments. This process was repeated at stimulus durations ranging from 0.01 to 50 ms. The currents required to evoke responses of 50 and 80% maximum motor amplitude were investigated also, in a subgroup of 11 subjects chosen at random on the basis of availability.

Values were plotted on semilog paper using stimulus duration as abscissa and stimulus current as ordinate, to obtain excitability curves. Rheobase (threshold stimulus intensity at a stimulus duration of 50 ms) and chronaxie (the stimulus duration required to evoke a threshold response with a stimulus strength twice rheobasic value) were computed from this plot using standard methods (Wynn Parry, 1971). Motor, sensory, and mixed NE curves for the entire group were compared statistically at each duration point using Student's *t* test (Moroney, 1956).

MOTOR EXCITABILITY

Ulnar nerve In 52 subjects, separate estimates of motor NE were derived by stimulating at the elbow (proximal motor NE) and at the wrist (distal motor NE), recording the muscle action potential from the hypothenar eminence in both

instances (Fig. 1). Distal motor NE only was employed in 23 subjects. Currents required for 50 and 80% motor responses were determined with stimulation at the wrist only.

Fig. 1 Electrode placements for the study of ulnar nerve excitability. S = stimulating electrodes; R = recording electrodes.

Posterior tibial nerve Motor NE in the posterior tibial nerve was determined by stimulating at the posterior border of the medial malleolus, and recording over the abductor hallucis muscle (Fig. 2).

Peroneal nerve Motor NE in the peroneal nerve was determined proximally and distally. Proximal stimuli were applied to the common peroneal nerve at the level of the knee, in the region of the head of the fibula. Distal stimuli were applied to the deep peroneal nerve at the ankle, in the region of the retinaculum. In both settings, muscle action potentials were recorded over the surface of the extensor digitorum brevis muscle (Fig. 2).

SENSORY EXCITABILITY

Ulnar nerve Sensory NE was examined both antidromically and orthodromically in the ulnar nerve in 52 subjects and only antidromically in 23 subjects. Antidromic NE was determined by stimulating at the wrist or elbow, and recording from the lateral digital branches of the ulnar nerve to the fifth finger; stimulating and recording sites were reversed in the determination of orthodromic NE (Fig. 1).

Sural nerve Sensory NCVs and NE in the sural nerve were derived by stimulating at the junction

Fig. 2 Electrode placements for the study of nerve excitability in the leg. S=stimulating electrodes; R=recording electrodes.

of the upper two-thirds with the lower third of the calf, and recording over the posterior inferior border of the lateral malleolus (Fig. 2).

MIXED NERVE EXCITABILITY

Mixed NE was determined in the ulnar nerve by the method of Heckmann (1972), stimulating at the wrist and recording at the elbow.

REPRODUCIBILITY

Some studies were repeated after an interval of approximately one year. In the ulnar nerve, motor NEs were repeated in 18 subjects, and mixed NEs in 20 subjects. Ten subjects had repeat studies of motor NE and NCV in the posterior tibial nerves, and sensory NE and NCV in the sural nerve. Selection of subjects for re-examination was random, depending only on availability; equipment and techniques were identical.

CORRELATIONS

Correlations between conduction velocities, nerve and muscle action potential sizes, and rheobase and chronaxie were investigated. The degree of linear association between each set of values was computed in the standard fashion and expressed as a correlation coefficient (r) (Moroney, 1956). Student's t test was used to determine whether r differed significantly from zero at P values less

than 0.05. Plots were made for each set of data and inspected for possible non-linear relationships.

Results

THRESHOLD VALUES

Mean motor NE curves from the ulnar nerve, using 10, 50, and 80% of maximum values, are shown in Fig. 3. The current required to elicit a motor response 80% of the maximum evoked potential differed from the current required to elicit a motor response 10% of the maximum evoked potential at all stimulus durations ($P < 0.05$). However, the current required to elicit a motor response that was 50% of maximum differed from that required for a 10% response only at stimulus durations less than 5.0 ms ($0.05 > P > 0.22$). The standard deviation for values obtained at 10% of maximum was approximately half that of values at 50 and 80% of maximum. For this reason, the 10% threshold curve was used in the collection and analysis of all subsequent data.

Fig. 3 Ulnar motor nerve excitability curves at different stimulus strengths. Ordinate, stimulus current intensity (mA); abscissa, stimulus duration (ms). Curves are plotted for motor responses equal to 80 (○—○), 50 (△—△) and 10 (□—□) % of the maximum evoked potential.

MOTOR EXCITABILITY

Ulnar nerve Mean threshold motor NE curves are shown in Fig. 4. There was no difference ($P > 0.1$) between proximal and distal motor excitability. At stimulus durations greater than 1.0 ms, no threshold stimulus current exceeded 3.5 mA. **Peroneal and tibial nerves** Mean motor NE curves for nerves in the lower extremity are shown in Fig. 5. Although there was no significant difference ($P > 0.2$) between values obtained for proximal peroneal and distal posterior tibial NE,

Fig. 4 Threshold motor nerve excitability curves with stimulation at elbow ($\triangle$ --- $\triangle$, motor I) and at wrist ($\blacktriangle$ — $\blacktriangle$, motor II). Ordinate and abscissa, same as Fig. 3.

there were significant differences observed between proximal and distal peroneal ($P < 0.001$), and between distal peroneal and distal posterior tibial ($P < 0.05$) NE. Distal peroneal nerve is the least excitable of any motor nerve studied.

Upper versus lower extremity nerves A comparison was made between motor NE in the upper and lower extremities, in the 23 subjects where both limbs were studied. Distal peroneal NE was significantly higher than ulnar NE ($P < 0.001$), as was posterior tibial NE ($P < 0.05$). Proximal peroneal NE was marginally higher than ulnar NE ($0.02 < P < 0.05$).

Fig. 5 Threshold motor nerve excitability curves with stimulation of the posterior tibial nerve (.....), and of the peroneal nerve at the knee (-----) and at the ankle ($\blacktriangle$ — $\blacktriangle$). Ordinate and abscissa same as Fig. 3.

SENSORY EXCITABILITY

Ulnar nerve There was no difference ($P > 0.4$) between "threshold" sensory NE curves obtained with orthodromic and antidromic stimulation. No "threshold" stimulus current exceeded 3.5 mA at stimulus durations greater than one millisecond.

Sural nerve Because of the high amplification required to visualise a sural nerve action potential, stimulus artefact interfered with recording of the potential at stimulus durations greater than 5.0 ms in all but three subjects. Thus, threshold sural NE studies did not truly detect a rheobase. Sural NE as compared with motor NE in the lower extremity showed significant differences from distal peroneal NE ($P < 0.05$), and borderline differences from posterior tibial ($0.02 < P < 0.07$) and proximal peroneal ($0.05 < P < 0.1$) NE. There was no difference between sural and ulnar sensory NEs ($P > 0.1$).

COMPOSITE

Mean threshold mixed, motor, and sensory NE curves from the ulnar nerve of 52 subjects are compared in Fig. 6. There is no significant difference between these three curves ($P > 0.1$). A consistent increase in standard deviation at stimulus durations less than 0.5 ms is noted. In analysing the data from individual subjects (Fig. 7) it was noted that, with stimuli of long duration, sensory threshold was lower than motor in 21 of 52 subjects. Using stimuli of short duration, motor threshold was lower than sensory in 31 of 52 subjects, while both were the same in 21 of 52 subjects.

Fig. 6 Threshold excitability curves with stimulation at wrist ($\blacktriangle$ --- $\blacktriangle$, motor II; $\square$ — $\square$, mixed I) and of fingers ($\circ$ — $\circ$, sensory I). Ordinate and abscissa same as Fig. 3.

Fig. 7 Comparison of motor and sensory nerve excitabilities with respect to stimulus duration. Ordinate, percentage of subjects showing phenomenon.

REPRODUCIBILITY

There was no significant difference ($P > 0.4$) in threshold mixed ulnar NE curves obtained at a one year interval, nor in threshold ulnar and posterior tibial motor NE curves obtained at the same interval. In sural nerve, a significant increase in excitability was noted at one year ($0.01 < P < 0.05$), although sural NCV did not change ($P > 0.2$).

CORRELATION

Motor, sensory, and mixed ulnar nerve conduction velocities were compared with their respective

chronaxie and rheobase. Linear correlation coefficients were compared to zero with Student's t test, the comparison expressed as a P value. In all instances, no correlation ($P > 0.2$) was observed. All constructed plots showed random distribution to visual inspection; non-linear relationships were not observed.

Discussion

In 1972 Heckmann described a technique for determining excitability of mixed peripheral nerve in vivo. This measure of mixed nerve function can be abnormal in a variety of clinical neuropathies, even in the presence of normal nerve conduction velocities (Wright and McQuillen, 1973). It is useful in the serial study of patients in chronic renal failure, showing a very high correlation with the clinical evidences of uraemic neuropathy (McQuillen *et al.*, 1973) in contrast to velocity, which may vary widely (Kominami *et al.*, 1971). Until the present, however, the technique had been applied only to mixed ulnar nerve.

This study has shown that the excitability of motor and sensory nerve fibres can be determined separately in vivo with the Heckmann technique, and that such determinations do not vary significantly from one individual to another, nor from upper to lower extremity. Moreover, when a large population is considered, there is no significant difference between motor and sensory nerve excitability, with the exception of distal peroneal motor nerve—the least excitable of any nerve studied. This conclusion is in contrast to the position of Veale *et al.* (1973) who felt that electric pulses of long duration selectively stimu-

late sensory fibres while short duration pulses preferentially excite a motor response. As shown by analysis of data from individual subjects (Fig. 7), their observation may be valid sometimes, but not often enough to suggest a difference between motor and sensory nerve excitability.

Another refinement of the Heckmann technique used in this study is the use of a threshold response, defined as 10% of the amplitude of the response to a supramaximal stimulus. This refinement contributes to accuracy by replacing the subjective determination of "minimal response" with an objective measurement having a small deviation. McComas *et al.* (1971) have shown that motor units summate in an incremental fashion with finely graded stimuli. Thus, with proper amplification, a response of one or two motor neurones, as reflected by the muscle action potential, can be discerned readily. With their technique, however, it is practically impossible to delineate a response to stimulation of one or two sensory neurones, since sensory nerve action potentials are considerably smaller (in the microvolt range compared to the millivolt size of muscle action potentials). A defined threshold helps to eliminate any discrepancy in "minimal response" from one observation to another.

Two possible explanations may be offered for the observation that distal peroneal motor nerve is less excitable than any other nerve studied. In the first place, the common peroneal nerve may split above the ankle, with a significant proportion of its fibres going to the extensor digitorum brevis muscle by way of the accessory peroneal nerve (Gutmann, 1970). The accessory peroneal nerve courses behind the lateral malleolus, so it is not accessible to stimulation in the region of the retinaculum. Thus, motor nerve excitability derived from stimulation in that region may not reflect properties of the whole nerve, and may deal with muscle action potentials of a smaller size, subject to greater errors in judgment of threshold. In the second place, the distal peroneal nerve may be subject to chronic injury at the retinaculum, with the development of a chronic traumatic neuropathy (Rouselle and Stevens, 1973). Therefore, heightened nerve excitability may reflect such a neuropathy, and not normal physiology.

The excellent reproducibility of excitability studies of motor nerves in the lower extremity enlarges the usefulness of this technique in the study of polyneuropathies, many of which are associated with distal axonal degeneration (Dyck, 1975): as a clinical dictum, many such neuropathies are much more prominent in the lower extremities, at

a longer distance from the perikaryon (Thomas, 1975). The relatively poor reproducibility of sural nerve excitability may derive from its variable anatomical location from one subject to another (Gardner, 1975), and the small amplitude of its nerve action potential.

Excitability now emerges as a quality of nerve function which does not vary significantly with fibre type (motor or sensory), location of stimulus (proximal or distal, upper or lower extremity), or time. It is reproducible within narrow limits. Linear correlations or non-linear relationships which, if present, would relate excitability to other measures of nerve function, were not demonstrated. While strength-duration relationships in excitable tissue have been known for 60 years, all attempts to define their origin have been descriptive, and the functional or structural quality of peripheral nerve which governs excitability has not been delineated. It is thought that myelin sheath governs conduction velocity (Kaesler and Lambert, 1962). This evidence would suggest that some other property of nerve—such as membrane capacitance, membrane resistance, or resting membrane potential—would govern excitability.

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