NEUROMUSCULAR FACILITATION DURING
TRAIN-OF-FOUR AND TETANIC STIMULATION IN
HEALTHY VOLUNTEERS: OBSERVATIONS WITH
HALF-REFRACTORY PAIRED RESPONSES

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SUMMARY
The compound electromyographic response of the thenar musculature was elicited by supramaximal stimulation of the ulnar nerve in 12 awake healthy volunteers. The half-refractory period of the neuromuscular transmission was determined. Twin stimuli separated by the half-refractory interval were repeated as a unit at 2 Hz and at 50 Hz. Thus two trains of responses, one beginning with a maximal response, the other with a half-maximal response, were obtained with each frequency of stimulation. Marked facilitation of the electromyographic response began with the train of stimulation, especially with tetanic stimulation. A secondary fade occurred occasionally. These changes were more remarkable in the train of half-refractory responses. We conclude that nerve stimulation facilitates neuromuscular transmission and deduce that the characteristic fade observed with a curariform block, rather than being an uncovered physiological phenomenon, is caused by tubocurarine and related drugs.

Muscular responses, elicited by a train of supramaximal nerve stimuli during the non-depolarizing neuromuscular block produced by tubocurarine, fade whether the stimulus frequency is tetanic or subtetanic (train-of-four) (Ali, Utting and Gray, 1970; Lee and Katz, 1977). Without neuromuscular block, the response has been observed to fade only occasionally, and to a minor degree. Indeed the opposite, an increase in the response, has occurred. Critical observation has depended on an analysis of the train of electromyographic responses to nerve stimulation (Epstein and Epstein, 1973; Katz, 1973). Previous investigations have established that most changes, facilitation or fade, occurred within a fraction of a second of the application of the train of stimulation (Ali, Utting and Gray, 1970; Epstein and Epstein, 1973; Katz, 1973; Lee and Katz, 1977).

However, the failure to demonstrate changes in the train of responses in the absence of block and the apparently minor degree of those changes observed may not signify that the state, or the reserve, of the neuromuscular transmission does not change significantly during the stimulation. Maximal responses elicited by supramaximal stimulation will not reveal such occult changes as long as the response remains maximal. It is not known if fade is an occult physiological phenomenon uncovered by a curariform block of the neuromuscular transmission, or a characteristic drug effect.

To elicit a submaximal response with the standard supramaximal stimulation, necessary for the revelation of such occult changes, we studied the effects of nerve stimulation during the relative refractory period of the neuromuscular transmission.

METHODS
Nine male and three female anaesthetists volunteered for the study. The ages ranged from 25 to 35 yr except for one volunteer who was 53. No medication was used. All subjects were performing their normal professional activity, except during the period of the study.

The ulnar nerve of the non-dominant side was stimulated at the wrist by use of two surface electrodes. The stimuli were 0.2-ms square pulses of supramaximal voltage (120–150 V) derived from a Grass S88 nerve stimulator through a Grass S1U5 Stimulus Isolation Unit.

The electromyographic response (compound e.m.g.) of the thenar musculature was analysed by a special computing device described elsewhere (Lee, Katz...
and Lee, 1977). The compound e.m.g. was amplified (300–1000 ×), dissected and counted digitally (64 times during a 12-ms window, each time to an accuracy of 0.2%), stored briefly with electronic memory, reconstructed to analog (with steps) and fed to an ink-writing oscillograph with time-expansion (160 ×). This process permitted the compound e.m.g., the frequency of which is too great for a hot-stylus or ink-writing recorder, to be recorded with ease “on-line” in an immediately available permanent form. Thus, the oscillograph had 1600 ms to write out a 10-ms response. Three Grass e.e.g. surface electrodes were used on the dorsum of the hand to pick up the compound e.m.g. The active electrode was placed directly over the bulk of the thenar musculature, and the reference electrode over the middle phalanx of the index finger. The third, connected to the shield of the cable, was placed between them.

The neuromuscular refractory period was determined first by applying twin stimuli of increasing interval (1.0–6.0 ms, in increments of 0.2 ms). The half-refractory period specific to each individual (the interval with which twin stimuli elicited two unequal responses (R1 and R2), one half the other (R2 = ½R1)) was determined. This pair of stimuli was then repeated every 0.5 s for 2 s (train-of-four), and 50 times per second for 1 or one-half second (50 Hz tetanus). From any train, the device collected up to 16 single or paired responses, each during a 12-ms window, and displayed them as a group stacked window by window. Thus train responses elicited at any frequency were recorded with equal ease.

The R1 train and the R2 train of responses, 1st–4th in a train-of-four and 1st–16th from a 50 Hz tetanus, were analysed.

![Figure 1: Refractory period, half-refractory interval, train-of-four (2 Hz) and tetanic (50 Hz) trains of neurally evoked paired compound e.m.g. responses of the thenar musculature in a normal healthy volunteer. Upper panel: Determination of the refractory period. In parentheses are time intervals, in milliseconds, between the twin stimuli which elicited the paired responses. The absolute refractory period was 1.8 ms. The half-refractory interval was 3.2 ms. Lower panel: Twin stimuli separated by the half-refractory interval were repeated at 2 Hz as a train-of-four, and at 50 Hz for a tetanus. As many as 16 pairs of responses from the beginning of the train were processed, and displayed at equal intervals as a session irrespective of frequency of stimulation. Each pair occupied a 12-ms window. The biphasic triangular calibration signal at the right lower corner was 8 ms in duration, amid a 12-ms window, 6 mV (for the upper panel) or 12 mV (for the lower panel) in amplitude. Only the second stimulus twin was recorded as the stimulus artefact, the first having been eliminated deliberately. Both stimulus artefacts were eliminated from the paired responses in the right upper portion of the figure by a delay in the opening of the window so that the latter portion of the paired e.m.g. responses could be recorded.
RESULTS

Refractory periods
The absolute refractory period was 1.7 (SD 0.4) ms. The half-refractory interval was 3.3 (SD 0.7) ms. Twin stimuli 4.9 (SD 0.9) ms apart, or more, elicited two maximal responses (fig. 1).

Repetitive responses to single stimulus
In three of the 12 subjects, a single stimulus elicited a double-peaked compound e.m.g. The repetitive response was minor in amplitude, and could not be differentiated from a small R2 elicited by a twin stimulus. Under these circumstances, the repetitive response would increase its amplitude, or the twin stimuli would begin to elicit three or four responses, when twin stimuli with intervals beyond the absolute refractory period were applied.

Train-of-four responses
When twin stimuli separated by the half-refractory interval were repeated twice per second, the 4th R1 averaged 4 (SD 4) % larger than the 1st R1, the 4th R2, 18 (SD 10) % larger than the 1st R2. Train-of-four therefore did not fade, but facilitated slightly (fig. 1, 2 Hz).

Tetanic responses
When the twin stimuli were repeated at 50 Hz, both the R1 and the R2 responses showed invariably an initial increase followed by a plateau or a secondary decline (fig. 1, 50 Hz). The increase began at the second pair of responses in the train. The R1 train peaked between the 2nd and the 9th (except in one case where it peaked at the 15th), with an average increase of 28 (SD 34) % at the peak. The R2 train peaked between the 2nd and the 10th pair of responses, with an average increase of 170 (SD 93) % at the peak. R1 and R2 trains of responses had similar trends but did not progress in parallel (fig. 2). On five occasions, the R2 train facilitated markedly and exceeded the corresponding R1 during the tetanus.

Fade resulted when the secondary decline more than offset the initial facilitation. At the 16th responses, however, 6 out of 10 R1 responses and 7 out of 10 R2 responses were facilitated (fig. 2). Overall, the 16th R1 responses averaged 16 (SD 36) % larger than the 1st R1 responses; the 16th R2, 89 (SD 121) % larger than the 1st R2 responses.

The sum of corresponding (R1 + R2) responses showed a similar trend of initial facilitation with a secondary decline (fig. 2). Trains of single stimuli elicited a train of single responses similar to the R1 train.

DISCUSSION
The refractory nature of neuromuscular transmission (Berry, 1966; Katz, 1966, 1973; Epstein and Jackson, 1970; Aidley, 1971; Epstein and Epstein, 1973; Suzuki et al., 1975) should be differentiated from that of the nerve or the muscle. Also the refractory nature of the whole nerve, the whole muscle or their transmission should be differentiated from that of the axon, the muscle fibre, or the transmission between the two (Farmer and Buchthal, 1960; Katz, 1966; Aidley, 1971). The refractoriness studied
here concerns the transmission between a whole nerve and a whole muscle. It is caused probably by failure of some nerve fibres of the ulnar nerve to excite those muscle fibres which they innervate. This occurs because 50% of the muscle fibres do not cause an action potential. Less probably, it may be a result of failure of 50% of the nerve fibres to fire an action potential because the nerve has a shorter refractory period (Berry, 1966). As the muscle fibre responds in an all-or-nothing manner, when the whole muscle response is 50% of the maximum, most muscle fibres must be near to their stimulation threshold, half responding maximally and half not responding at all. Consequently, the half-maximal R2 response should be a sensitive indicator of the changes in the state of neuromuscular transmission, because some maximally responding muscle fibres may readily become unresponsive, and vice versa.

An increase in the amplitude of the R2 response elicited by twin stimuli with a fixed interval suggests a shortened refractory period, and vice versa. When it is impractical to repeat the determination of the refractory period by varying twin intervals, changes in the amplitude of the R2 response relative to the corresponding R1 response serve as a convenient indicator of the changes in the state of neuromuscular transmission, because some maximally responding muscle fibres may readily become unresponsive, and vice versa.

Facilitation in the R2 train, on the other hand, may be a result of improved transmitter output, decreased refractoriness or repetitive firing (Katz, 1966), all of which may increase the number of muscle fibres responding to the second twin stimulus of the nerve. It is unlikely that acetylcholine, accumulated from one stimulus, potentiates the response to the next stimulus in a 2-Hz or 50-Hz train (Katz, 1966).

In respect of e.m.g., facilitation is short-lived, and does not occur following a tetanic stimulus. Previously, Epstein and Epstein (1973) and Katz (1973) have reported that no significant post-tetanic facilitation occurred in anaesthetized man without neuromuscular block. In this study we consistently observed facilitation of the post-tetanic response. However, the increase in the magnitude was trivial, being of approximately the same order as previously reported, 2% according to Epstein and Epstein (1973) or less than 7% according to Katz (1973). The prominent post-tetanic facilitation observed in the mechanical response cannot be explained electromyographically.

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In contrast to the normal situation, neuromuscular transmission during tubocurarine block is characterized by a marked fade in the train of responses which is detectable from the second response onwards (Katz, 1973; Lee and Katz, 1977). This is not simply an occult physiological phenomenon uncovered by non-depolarizing neuromuscular block in general, but a characteristic pharmacological effect of this group of neuromuscular blocking agents. It is not a necessary sign of non-depolarizing neuromuscular block because alaphabungarotoxin produces an almost pure post-junctional non-depolarizing block (Lee, 1972) which is not characterized by comparable fade (personal observations).

The subsequent reversal of the trend of the tetanic train (which results in a secondary fade in some subjects) results probably from fatigue or depletion of immediately available transmitter, the availability and the replenishment of which are limited (Katz, 1966).

In conclusion, the compound electromyographic response of the thenar musculature is facilitated markedly by stimulation of the ulnar nerve. We deduce that the characteristic fade observed during neuromuscular block produced by tubocurarine must not be an occult physiological phenomenon uncovered by the drug, but a specific product of drug action.
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REFERENCES


FACILITACION NEUROMUSCULAR DURANTE ESTIMULACION TETANICA Y "TREN DE CUATRO" EN VOLUNTARIOS SANOS: OBSERVACIONES CON RESPUESTAS EMPIREJADAS SEMI-REFRACTARIAS

RESUME

La réaction électromyographique composée de la musculature thenar a été éclaircie par une stimulation supramaximale du nerf ulnaire sur douze volontaires éveillés en bonne santé. On a déterminé la période semi-refractaire de la transmission neuromusculaire. Des stimulations jumelées séparées par l'intervalle semi-refractaire ont été répétées sous forme unitaire à 2 Hz et à 50 Hz. On a donc obtenu deux groupes de réactions, un groupe commençant par une réaction maximale, et l'autre par une réaction semi-maximale, avec chaque fréquence de stimulation. Une facilité marquée de la réaction électromyographique a commencé par le groupe de stimulation, surtout avec la stimulation tétranique. Un affaiblissement secondaire s'est produit occasionnellement. Ces variations ont été davantage remarquées dans le groupe de réactions semi-refractaires. Nous en concluons que la stimulation des nerfs facilite la transmission neuromusculaire et en déduisons que l'affaiblissement caractéristique observé dans le cas d'un blocage curariforme est provoqué par la tubocurarine et autres médicaments associés, plutôt que d'être un phénomène physiologique découvert.

NEUROMUSKULÄRE FAZILITATION WAHREND EINER VIERERSERIE-STIMULIERUNG UND WAHREND TETANISCHER STIMULIERUNG BEI GESUNDEN FREIWILLIGEN: BEOBACHTUNGEN MIT HALBREFRAKTÄREN PAAR-REAKTIONEN

ZUSAMMENFASSUNG


FACILITACIÓN DE COMPOUND E.M.G. ELICITED IN TRAIN

SUMARIO

La respuesta electromiográfica compuesta de la musculatura tenar fue obtenida mediante estimulación supramáxima del nervio ulnar en 12 voluntarios sanos despiertos. Se determinó el periodo semi-refractario de la transmisión neuromuscular. Se repitieron los estímulos gemelos separados por intervalo semi-refractario, como una unidad a 2 Hz y a 50 Hz. De esa forma se obtuvieron dos trenes de respuestas, uno comenzando con una respuesta máxima, y el otro con una respuesta semi-máxima, para cada frecuencia de estimulación. Una señalada facilitación de la respuesta electromiográfica comenzó con el tren de estimulación,
especialmente con la estimulación tetánica. Una amortiguación secundaria apareció de vez en cuando. Estos cambios fueron más evidentes en el tren de respuestas semi-refractarias. Concluimos que la estimulación del nervio facilita la transmisión neuromuscular y deducimos que la amortiguación característica observada con un bloqueo curariforme, más bien que un fenómeno fisiológico puesto de relieve, constituye un efecto causado por la tubocurarina y fármacos afines.