Posttetanic Changes in the Human Neuromuscular System

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ABSTRACT

HUGHES, JOHN R. AND ROGER M. MORRELL. Posttetanic changes in the human neuromuscular system. J. Appl. Physiol. II(1): 51-57. 1957.- Percutaneous stimulation of the human ulnar nerve produced muscle action potentials from the adductor pollicis muscle and twitch tension responses from thumb adduction. With increase in the stimulus strength, approximately proportional increases were found in the height of the muscle action potential and twitch tension. Tetanization can produce a long lasting potentiation of twitch tension which is accompanied by either increased, decreased or unchanged amplitude of muscle action potentials. With increase in the duration, frequency or intensity of the tetanus, an additional effect producing decreased muscle action potentials and twitch tension responses appeared, particularly at 20-30 seconds after the cessation of the tetanus. Possible mechanisms and sites of action of posttetanic potentiation in the neuromuscular system are mentioned.

Posttetanic potentiation (PTP) is a term referring to the long lasting increased responsiveness that follows repetitive stimulation. Posttetanic potentiation has been found in the spinal cord (1), in various subcortical nuclei (2) and in the neuromuscular (3), sympathetic (4) auditory (5, 6) visual (7, 8) and olfactory systems (9). Most of the early work on potentiation dealt with changes in twitch tension after tetanization of the sciatic-gastrocnemius preparation. In 1858 Schiff (10) reported that after a tetanus, single test pulses produced larger responses of twitch tension than before the tetanus. Since that time the same phenomenon has been described in the cat (11), hen, pigeon (12) and rabbit (13); in addition to the gastrocnemius muscle, popliteal, tibialis anticus (14), sartorius (15) and soleus muscles have shown the phenomenon. Not only twitch tension, but also the muscle action potential and end-plate potentials (16), including the miniature end-plate potentials, have been investigated. Potentiation of twitch tension has been reported to exist in the human neuromuscular system (17, 18). The present research was designed to investigate the posttetanic changes after systematic variation of the parameters of tetanization applied to the human neuromuscular system.

METHOD

The forearm and hand of human subjects were secured firmly in a restraining apparatus (built by Dr. Paul Chatfield) consisting of a number of adjustable perpendicular metal bars that were fixed to a rigid metal base. Towels and foam rubber cushions around the forearm and hand held the limb firmly and comfortably. Percutaneous stimulation of the ulnar nerve was accomplished through a stigmatic cup electrode filled with electrode jelly placed at the ulnar notch and a large metal plate electrode placed on the upper portion of the arm.

The stimulating pulse, 0.15 milliseconds in duration and nearly rectangular in shape, was produced from a Grass Stimulator (Model S4B) and passed through a General Radio Transformer (578A) which stepped up the voltage four times. Both the muscle action potential (MAP) and twitch tension (TT) were recorded. Steel needles (entomological pins) with a tip diameter of approximately 30 µ (insulated except for the tip) were inserted into the adductor pollicis muscle and the muscle action potentials that were recorded were amplified by a Grass preamplifier (Model P4A). The indifferent electrode was placed on the skin of the back of the hand. For recording the twitch tension the thumb was inserted into a snugly fitting rigid sleeve that was attached to a strain gauge (Grass Model FT-02). The output of the strain gauge led to a direct coupled amplifier (Tektronix Type 112). The muscle action potential and twitch tension responses were displayed.
simultaneously on a dual-beam, cathode-ray oscillograph (Du Mont Type 322-A) and a Grass Kymograph Camera photographed both these responses (fig. 1). The stimulating current was periodically monitored to insure that the stimulus intensity was maintained constant throughout the experiment.

Since responses were recorded for long periods of time, the position of the stimulating and recording electrodes, the position of the thumb and the amount of tension on the musculature of the forearm and hand had to be maintained as constant as possible for many minutes. Most of the experiments were therefore conducted on two "trained" subjects (the experimenters), who were aware of the necessity for maintenance of constant position and muscular tension throughout the duration of the experiment.

Pre- and posttetanic test stimuli were presented and photographed once per second for 10-20 seconds. Submaximal test pulses were used because maximal stimulation produced such strong thumb adduction that constancy of position and tension between one test pulse and another was difficult to maintain. Furthermore, the assumption that "maximal" test pulses are preferable because they produce responses in all available fibers may be unwarranted. The intensity of the test pulse was always the same as the intensity of the tetanus, while the frequency and the duration of tetanization were systematically varied. After the tetanus, the test stimulus was again presented once per second. The posttetanic muscle action potentials and twitch tension responses were photographed once per second for approximately 2 minutes, after which time photographs were taken every 5 or 10 seconds for 10-30 minutes.

The height of the pre- and posttetanic twitch tension responses and muscle action potentials (base line to peak of negative deflection) was measured and averaged. The variation of the height of the individual responses was usually + 5% of this average. This mean value served as a base line and posttetanic responses were plotted as percentages of this pretetanic level.

RESULTS

1. Intensity Function of Muscle Action Potential and Twitch Tension. Figure 2 shows the approximately proportional increase of amplitude of the muscle action potential (MAP) and twitch tension (TT) with increase in intensity of stimulation. A measurable MAP was recorded at the intensity of 10.5 (X4) volts, but TT was not recordable until the intensity was 11.5 (X4) volts.

2. Posttetanic Changes in Twitch Tension and Muscle Action Potential. After a tetanus of 100/sec., 3 seconds in duration and submaximal in intensity, the twitch tension responses are larger than the pretetanic responses (fig. 3). These responses are largest (usually 130-160% of the pretetanic amplitude) within 1 second after the tetanus. No initial subnormality was detected, although responses occurring less than 1 second after the cessation of the tetanus were not investigated. The potentiation curve for twitch tension drops suddenly and shows a slight dip at 10-30 seconds before a small rise appears. The posttetanic responses then gradually decrease toward the pretetanic level. Figure 3 shows that the posttetanic potentiation of twitch tension may persist 5-6 or more than 11 minutes after the cessation of the tetanus.

During the posttetanic potentiation of twitch tension the muscle action potential may be supernormal (fig. 3A), subnormal (fig. 3B), or may show no significant changes, except for a short lasting subnormality, throughout most of posttetanic period (fig. 3C). In the 64 cases of potentiation of TT, 52% showed an increased muscle action potential, 30% showed a decreased response and 18% showed no change. In few instances (8%), MAP showed an increased response for approximately 4 seconds before subnormality appeared throughout the rest of the posttetanic record. Thus, when the twitch tension responses were potentiated, the muscle action potential changes were not predictable. When the twitch tension responses were subnormal (see RESULTS: 3) the muscle action potential was also subnormal in 100% of 26 instances. Figure 4 shows the subnormality of both twitch tension and muscle action potential.

3. Posttetanic Changes in Twitch Tension: Parameter: Duration of Tetanus. Figure 5 shows the posttetanic changes of TT when the duration of the tetanus was varied. The frequency of the tetanus was 100/sec. and the intensity was that which produced a MAP
of 30% its maximum. When the duration of tetanus was 1 second, the posttetanic potentiation of the twitch tension was maximal and then decreased rapidly until 20–30 seconds after the tetanus. Then the responses gradually decreased to the pretetanic level and this base line was reached at 5½ minutes. When the tetanus lasted for 3 seconds, the potentiation showed a more rapid decline than from a 1-second tetanus. The minimum point was reached at 20–30 seconds, after which the curve rose and then gradually declined to the base line. At 6 minutes after the tetanus, the posttetanic potentiation of twitch tension was still evident. When duration of tetanus was 4 seconds, the potentiation curve decreased suddenly to below the base line. The subnormality was greatest at 20–30 seconds, after which the curve rose to above the pretetanic level and then slowly decreased down to this level. With tetani of 5 and 6 seconds in duration, the posttetanic potentiation curve fell very sharply to below the base line and then gradually rose to normal by approximately 3 minutes after the cessation of the tetanus.

4. Posttetanic Changes in Twitch Tension; Parameter: Frequency of Tetanus. Figure 6 shows the posttetanic changes of TT when the frequency of the tetanus was varied. The duration of the tetanus was 3 seconds and the intensity (in fig. 6A) was 20% (of the maximum MAP elicitable). When the frequency of the tetanus was 10/sec. the potentiation curve fell quickly until about 20–30 seconds after the tetanus and then slowly declined to the pretetanic level. A similar pattern was seen when the frequency of the tetanus was 30/sec., but a posttetanic potentiation of higher percentage and longer duration was seen. When the frequency of tetanus was 100/sec. and 300/sec., the curves fell sharply toward the base line (reaching a minimum at 20–30 sec.), rose above the line and then slowly fell to this base line. Thus, with respect to producing a sudden fall in the potentiation curve, the effect of increasing the frequency of tetanus was similar to the effect of increasing the duration of tetanus (see RESULTS: 3).

When the intensity of tetanus was increased (from 20%) to 38% (fig. 6B) then the effect was to produce more suddenly an increased subnormality, similar to the effect of an increased duration or frequency of tetanus. When the frequency was 10/sec., only a slight amount of posttetanic potentiation was seen in this particular case—in 25% of the instances in which the tetanus frequency was 10/sec. no significant amount of potentiation was noted. Long lasting PTP was seen when the frequency was 30/sec. When the frequency was raised to 100/sec., the PTP curve fell sharply to beneath the pretetanic level and then slowly rose above and finally back to this level. When the frequency was 300/sec., the fall in the potentiation curve was very sudden and the subnormality was greatest at 20–30 seconds after the cessation of the tetanus. The curve gradually returned to the pretetanic level by 3–4 minutes after the cessation of the tetanus.

DISCUSSION

Figure 2 shows that the height of the twitch tension and muscle action potential increases proportionately when the stimulus intensity is
Figure 3. Posttetanic changes in twitch tension and MAP during potentiation of TT. The tetanus was 100/sec., 3 sec. in duration and submaximal in intensity. During posttetanic potentiation of twitch tension, muscle action potential may be supernormal (52%, A), subnormal (30%, B), or may show no significant change throughout most of the posttetanic period (18%, C). Posttetanic potentiation of TT lasted 5, 6, or over 11 min., and was 130–160% of the pretetanic level. Ordinate is percent of pretetanic amplitude and abscissa is time after cessation of tetanus in seconds. Note different time scale in C. Points are averages over a 5-sec. period up to approximately 2 min., after which points are averages over a 10-sec. period.

raised. However, figure 3 illustrates that with a potentiated twitch tension the muscle action potential may be either supernormal, subnormal or unchanged. For example, figure 3C shows that the twitch tension may be 160% of its pretetanic level when the muscle action potential is 80%. If the pretetanic level of TT were 105 (arbitrary units) then the posttetanic amplitude would be 168 (160% of 105) in figure 3C. Figure 2 shows that the corresponding MAP changes (if the increase in TT had occurred because of an increase in stimulus intensity) would be from 200 to 240, but in the posttetanic period of figure 3C the MAP is 160 (80% of 200). Thus, it appears that the changes in TT and MAP in the posttetanic period are unlike the changes associated with an increase in the stimulus intensity.

Various investigators working with microelectrodes on isolated animal preparations have reported subnormality of the muscle action potential during potentiated twitch tension. Von Euler and Swank (12) reported that the MAP was still 30% decreased from the pretetanic level when the twitch tension had returned to normal after the potentiated phase. Brown and von Euler (11) reported that the MAP had recovered to normal before the potentiation had disappeared. If submaximal test shocks were used, Brown and von Euler claimed that increased MAP could be seen after a tetanus. Johns et al. (19) found increased MAP after tetanization in patients with myasthenia gravis, but Botelho (17, 18) found no change of the MAP in this type of patient, nor in normal humans. With a microelectrode in a single muscle fiber, Bernhard, von Euler and Skoglund (20) found that there were no changes in the muscle action potential during the potentiated twitch tension. But if a gross electrode was inserted into the whole muscle, decreased action potentials were recorded during increased twitch tension.

Figure 3 shows that different changes in muscle action potential can be recorded during posttetanic potentiation of the twitch tension in the human neuromuscular system. The recording electrode used in the present experiments was 30 μ in diameter at the tip. Although an electrode with this tip diameter could possibly record from a single motor unit, it is more likely that the muscle action potential was recorded from an unselected sample of several units. There were two major reasons why different changes in MAP could be recorded during posttetanic potentiation of the twitch tension. The first is that a direct relationship does exist between MAP and TT during potentiation of twitch tension, but this cannot be seen for technical reasons. For example, if the electrode is too small to record a representative sample of the electrical activity of the muscle, then the MAP changes may be distinctive to the particular placement of the electrode. Also, the amplitude of the compound action potential may be a misleading index of the number of depolarized muscle fibers. The action potential of a newly
activated unit with an initial positive deflection might subtract from the amplitude of the negative compound potential. These considerations would imply that a correspondence of change between MAP and TT might be found with some different recording technique. The second reason is that a direct relationship between MAP and TT during the posttetanic potentiation of twitch tension does not actually exist.

If the first reason were correct, then one would expect that a larger electrode might show this direct relationship. However, with a relatively large silver disc electrode attached to the skin over the belly of the muscle, explored in the present study and systematically used by others (17, 18), corresponding changes between MAP and TT were not found. If the posttetanic changes in MAP were distinctive to a particular electrode placement or to a particular algebraic summation of individual potentials, then repetition of similar experimental conditions with a given electrode position should show MAP changes in the same direction. However, when similar experimental conditions were repeated (up to 5 times), potentiation of twitch tension was accompanied by muscle action potentials that showed an increase at one time, a decrease at another and no change at still a third time.

In these cases the electrode position was assumed to be constant because of the similarity of the configuration of the MAP. Therefore, it is likely that a direct relationship between the muscle action potential and twitch tension does not exist during potentiation of twitch tension. In 1941 Rosenblueth et al. (21) emphasized the independence of the changes in the MAP and TT under other conditions.

Walker (22) has reported that the muscle action potential of the gastrocnemius of the rat was decreased in height, but increased in duration during the potentiated twitch tension. However, the increase in duration of the MAP was not accompanied by proportional increases in the twitch tension. In the present study, no significant changes in the duration of the MAP were noted.

Figure 3 shows that the potentiation curve of TT falls sharply for the first 10-30 seconds after tetanization and may last for 5, 6, or more than 11 minutes. Botelho and Cander (18) showed that the posttetanic potentiation of twitch tension in the normal human being may last for over 10 minutes but their posttetanic test stimulus was not presented frequently enough to see the details of the temporal course of potentiation.

Various investigators (22, 23) have hypo-
The site of the potentiation effect has been of great interest. Ramsey and Street (24) stimulated and recorded from a single isolated muscle fiber and found posttetanic potentiation; they concluded that potentiation was a property of the muscle contractile mechanism. Walker (22) agreed with this, mainly because curare failed to reduce PTP. However, Guttman et al. (25) failed to find PTP with direct stimulation of curarized muscle; they concluded that the effect was not in the muscle fiber but at the neuromuscular junction. Others (16) have maintained that more ACh was released per nerve volley from the neural terminals at the junction. Since Brown and von Euler (11) found PTP in muscles that had been denervated for 6 days they concluded that the potentiation effect could not be at the neuromuscular junction. Others (16) have maintained that more ACh was released per nerve volley from the neural terminals at the junction. Since Brown and von Euler (11) found PTP in muscles that had been denervated for 6 days they concluded that the potentiation effect could not be at the neuromuscular junction. Von Pirquet (13) suggested that in "postetanische Potenzierung" there was an increased excitability of the nerve, end-plate and the muscle fiber. It is possible that increased muscle contractions may be due to potentiation both at the neuromuscular junction and in the muscle fiber itself. The present study was not designed to determine the mechanism and site of potentiation, but the lack of relationship between changes in twitch tension and muscle action potential during posttetanic potentiation is consistent with the hypothesis that changes in the contractile mechanism of the muscle fiber may account for potentiation.

Figure 4 shows that when the twitch tension is subnormal, the muscle action potential is also subnormal. In 1940 Rosenblueth and Cannon (26) emphasized that a tetanus conditions the subsequent responses in two opposite ways: a fatigue effect that produces a decreased response, and a facilitatory effect. In 1937 Feng (15) had stated, "Whether the facilitatory effect is able to assert itself in the face of the inhibition or not would seem to depend on the depth or completeness of the prevailing inhibition." Figures 5 and 6 show that with increased duration, frequency or intensity of tetanus this 'inhibition' asserts itself particularly at 20-30 seconds after tetanization. The fact that the muscle action potential is always subnormal during the subnormality of the twitch tension suggests
that the locus of this effect is different from the potentiation effect, in which the muscle action potential and twitch tension changes are often unrelated. This subnormality may be related to the accumulation of lactic acid. After a short period of tetanization of 5 seconds there is a marked increase in lactic acid accumulation which is usually associated with anaerobiosis. It is therefore possible that this accumulation of lactic acid depresses muscle contraction. Also, posttetanic potentiation has not been found under anaerobic or ischemic conditions in the human neuromuscular system (18).

Figures 5 and 6 show that an increase in duration, frequency or intensity of tetanus tends to produce a subnormality along with the potentiation. After a relatively short lasting potentiation, this subnormality is most evident 20–30 seconds after the cessation of the tetanus. Other studies on potentiation in the human neuromuscular system (17–19) have not reported a similar subnormality, but the tetani in these cases were relatively short lasting (17–19) and low in frequency (17, 18). The present study shows that relatively long, intense tetani of high frequency must be avoided in order to produce long lasting potentiation in the human neuromuscular system.

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REFERENCES