Effect of Stimulus (Postsynaptic Current) Shape on Fibre Excitation

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Abstract. Effects of variation of the stimulus pulse shape on the excitation of a nonmyelinated nerve fibre were studied using a mathematical model based on the Hodgkin-Huxley equations. Efficiency of smoothly changing pulses was compared with that of rectangular pulses. For pulses shorter than the time to excitation, the rate of the stimulus rise did not determine the ability of a smoothly changing pulse to excite the fibre. For a given stimulus duration, the main factor was the pulse area or the charge delivered by the pulse. The strength-duration curve for smoothly changing pulses was a nonmonotonic function, in contrast to the curve for rectangular pulses. The dependence of latency on changes in the pulse area was non-linear. It would be nonmonotonic when the pulse area variation were due to the stimulus duration or the stimulus rise duration. More that one propagating intracellular action potential (IAP) could arise upon fibre activation by a long smoothly changing threshold stimulus. Upon activation of relatively short fibres the IAP could arise not at the site of the smoothly changing stimulus injection. The rectangular pulses of long duration were more efficient than the corresponding smoothly changing ones. Irrespective of the shape, the pulses whose duration at the foot is 1–2 ms, are more suitable for a prolonged threshold fibre activation.

Key words: Strength-duration curve — Stimulus efficiency — Conduction velocity — Excitability — Computing

Introduction

The electrically excitable membranes are activated by synaptic currents. Although the postsynaptic currents (stimuli) have a smoothly changing shape, information on membrane excitation and action potential development have generally been obtained for rectangular current pulses. Such a simplification allowed to obtain and analyse the fundamental strength-duration relationship (Weiss 1901; Lapicque 1907; Hill 1936; Cole 1955; Guttman 1966; FitzHugh 1966; Noble and Stein 1966;

Khodorov 1974; Bostock 1983; Dean and Lawrence 1985).

The effects of stimuli of different shapes have also been studied. In connection with the membrane accommodation (Nernst 1908), the effects of different slopes of a linearly rising stimulus were examined (Lucas 1907; Rashevsky 1933; Monnier 1934; Hill 1936; Katz 1939; Diecke 1954; Vallbo 1964a,b; Frankenhaeuser and Vallbo 1965; Khodorov 1974), and it has been suggested (Khodorov 1975) that the strength, duration and rate of the current rise determine the stimulating effect. Offner (1946); Goldman and Klafter (1982); Dean and Lawrence (1985) have estimated the efficiency of pulses of different shapes.

As early as in 1928, Bishop and later Grundfest (1932) supposed that the course of the strength-duration curve would depend also on the stimulus shape, but this problem has not been clarified so far. Magleby and Stevens (1972); Magleby and Terrar (1975); Cohen and van der Kloot (1982); Magazanik and Giniatullin (1986) have shown that a number of factors affect the time course of the postsynaptic current decay. It is not, however, clear whether these changes influence the activation of electrically excitable membranes. Also it remains unknown whether stimuli with a shape typical of the actual postsynaptic currents could first produce IAP at a site different from that of stimulation. This could result in a very high or even negative velocity that was described for a threshold activation of relatively short fibres by rectangular pulses (Dimitrova and Dimitrov 1988). The present work was aimed at answering these questions.

Materials and Methods

Using a mathematical model based on that proposed by Hodgkin and Huxley (1952), the effects of the stimulus shape, amplitude and duration on the processes of activation of nonmyelinated nerve fibres of different lengths were analyzed. The IAPs were calculated by the method described by Joyner et al. (1978) for the structures with changing radius. The membrane parameters were the same as those employed for the Hodgkin-Huxley axon.

In order to compare the results of the present work with those obtained for rectangular pulses of stimulating current, the fibres examined had the same geometric parameters as those studied earlier (Dimitrova and Dimitrov 1988; Dimitrov et al. 1992).

The radius of the cylindrical fibres was 30 μm, and their semilength was 2.5 mm $\approx 1.25\lambda$ (short fibre), 4 mm $\approx 2\lambda$ (medium) and 10mm $\approx 5\lambda$ (long), respectively, where λ is the fibre length constant. Depending on their length, the fibres were divided into 200, 320 or 800 segments, each 12.5 μm long. The time step was 10 μs and the temperature was assumed to be 20 °C. The boundary condition at the site of the stimulus application was $V_{-1} = V_1$ and that at the fibre termination was $V_L = V_{L+1}$. The first condition reflects the origin of two symmetrical waves of excitation propagating from the site of the stimulus injection (postsynaptic membrane) towards the fibre ends. The second condition reflects the lack of longitudinal current at the insulated ends of the fibre. These boundary conditions correspond to the processes of activation of nerve terminals (Rinzel 1976) or of skeletal muscle fibres.

Studying the effects of different stimulus shapes, $I(t)$, it is insufficient to analyze the influence of the amplitude and duration that completely define a rectangular pulse only. Therefore, the current pulse area, i.e. the charge delivered to the fibre, and the ratio (K_{as}) of the entire pulse duration (T) to the duration of its rising phase were also accounted for. Tissue damage components are defined by the amplitude, charge or power delivered to the fibre by the pulse. The power is proportional to $\int_0^T I^2(t)\mathrm{d}t$, and it was also analyzed when the efficiency of smoothly changing pulses was compared with that of rectangular pulses.

The initial shape of the stimulating current pulse with K_{as}=3.5 is shown in Fig. 1*A*,*B* (filled circles). The other shapes of the stimulus tested were obtained from the initial one by proportional changes in stimulus rise (Fig. 1*A*) or decay (Fig. 1*B*) durations. The factor of proportionality was 0.5 or 1.5. To study the effects of pulse asymmetry, and thus the effects of the stimulus rise rate, the asymmetrical pulses (Fig. 1*C*, filled circles, K_{as}=7.5) and their mirror images (Fig. 1*C*, empty circles) were also used. The stimulus duration was varied within 0.2 ÷ 30 ms.

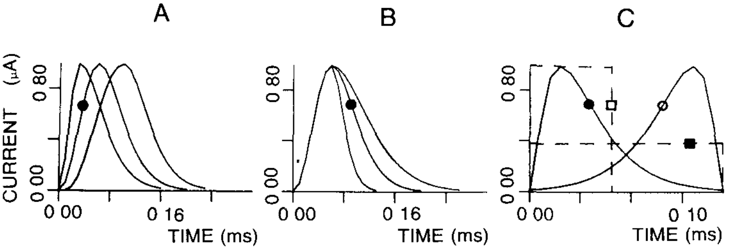

Figure 1. Shapes of the smoothly changing stimulus pulses. A, changes in the duration of rise of an initial pulse (filled circles) with K_{as} = 3.5. B, changes in the duration of decay of an initial pulse (filled circles) with with K_{as} = 3.5. C, an initial pulse with K_{as} = 7.5 (filled circles), a mirror image (empty circles) and the extreme rectangular equivalents of the smoothly changing pulses (dashed lines): identical areas and amplitudes (empty squares); identical areas and durations at the foot (filled squares).

Results

The dependence of the time to excitation (latency) on the stimulus amplitude was basically non-linear (Fig. 2, empty squares) similarly with the stimulus being a rectangular pulse (Dimitrova and Dimitrov 1988). The closer the stimulus amplitude to the threshold value the greater the latency. The latency, however, was not inversely proportional to the difference of the actual from the threshold amplitude. Due to the accommodative processes the latency was limited by the maximum time to excitation (Dimitrov et al. 1992).

Starting with a certain pulse duration, the maximum time to excitation became shorter than the stimulus duration, i.e. only a part of the charge delivered by the

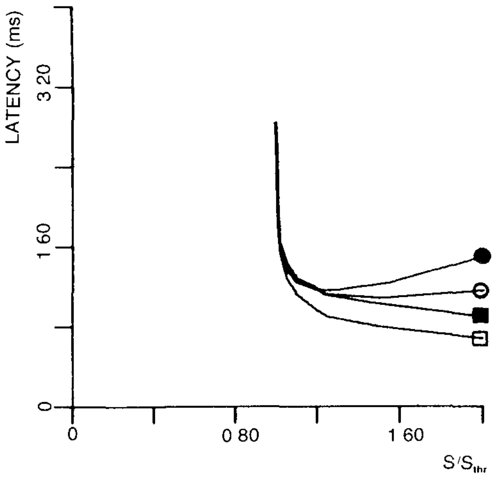

Figure 2. Latency versus changes in the pulse area (S) expressed in relative units (S/S_{thr}) in respect to the area (S_{thr}) of the threshold pulse with initial shape (K_{as} = 3.5) and 1 ms duration. The pulse area was varied at the expense of the duration of the pulse rise (filled circles), of the whole pulse (empty circles), of the pulse decay (filled squares) or at that of the pulse amplitude (empty squares). The fibre was of medium length ($2L = 8$ mm).

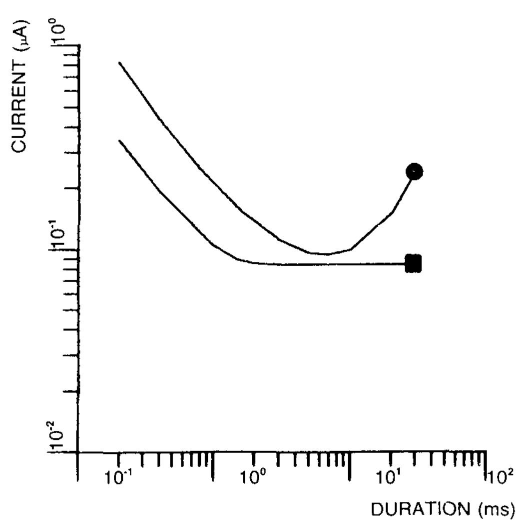

Figure 3. Strength-duration curves for smoothly changing (filled circles) and rectangular (filled squares) pulses. The fibre was of medium length ($2L = 8$ mm).

stimulus contributed to overcoming the processes that counteract the membrane excitation. The longer the smoothly changing stimulus, the smaller this portion of the charge. Moreover, the rate of the stimulus rise was also lower for longer smoothly changing pulses. As a result, the stimulus could be subthreshold if the smoothly changing stimulus amplitude was not increased. Thus, the strength-duration curve (Fig. 3) for smoothly changing stimuli (filled circles) differed from the classical one obtained for rectangular pulses (filled squares).

The investigations of the processes of fibre activation by smoothly changing pulses were divided in two parts, one dealing with short pulses with durations not exceeding the maximum time to excitation and the other one with long pulses of durations exceeding it.

1. ***Stimuli of short duration*** (0.2 – 3 *ms at the foot*)

Effects of changes in the postsynaptic current pulse amplitude

As with rectangular current pulses (Dimitrova and Dimitrov 1988), when the stimulus amplitude was substantially suprathreshold, the propagating IAP always arose at the site of the stimulus application after a relatively short latency. Upon decreasing the amplitude of the smoothly changing current stimulus applied to a short or medium fibre, also a near-threshold current amplitude could be observed for which the IAP would arise at the site of the stimulus injection or at the insulated fibre ends (Fig. 6*A*), or the whole fibre membrane could fire almost simultaneously. If the fibre was long, the IAP always arose at the site of the stimulus injection. The relationship between the threshold current amplitude and the fibre length was also similar. The shorter the fibre the smaller the threshold current value. It was 0.774 μA; 0.824 μA and 0.83 μA for the short, medium and long fibre, respectively when the stimulus had the initial shape, was 0.2 ms of duration, and $K_{as} = 3.5$. The effects described were similar for any stimulus shape when its duration was varied within 0.2–3ms.

Effect of changes in the postsynaptic current pulse duration

If the charge delivered to a fibre was varied at the expense of the pulse duration, so that the pulse amplitude and shape were unchanged, the dependence of latency on changes in the pulse area was nonmonotonic (Fig. 2, empty circles). The accommodative processes (as a result of which the charge required to induce excitation is greater for longer pulses) partially neutralized the effect of the increase in the pulse area. Thus, when the charge increase was due to the increased pulse duration, the relative exceeding of the threshold corresponding to the increased duration was smaller than that measured upon increasing the pulse amplitude. On the other hand, the longer the pulse the lower the rate of stimulus rise, and the longer the time needed for accumulation of the charge needed to induce excitation. Hence, the latency was larger than that with the variation of the charge through amplitude changes (Fig. 2, empty squares).

The duration and strength of a smoothly changing pulse (like those of any other nonrectangular pulse) are not well defined. If the duration of the smoothly changing pulse was defined at the pulse foot, and if the strength of a smoothly changing pulse was its amplitude, then the threshold strength for the smoothly changing pulse was always higher (Fig. 4*A*, filled circles), and the threshold charge was always smaller (Fig. 4*B*, empty squares and filled circles) than those corresponding to the rectangular pulse of the same duration (Fig. 4*A* and *B*, filled squares). In this case, we could conclude that the Weiss law was valid (the charge-duration relation was linear) for a wider range of pulse duration (Fig. 4*B*, empty squares and filled circles) than with the relationship obtained for rectangular pulses (Fig. 4*B*, filled squares). We could, however, substitute a rectangular pulse for a smoothly changing one. Two extreme cases requiring an equivalent rectangular pulse to have an amplitude (or duration) equal to that of the corresponding smoothly changing one, are illustrated in Fig. 1*C*- dashed lines (empty squares and filled squares, respectively). The pulse areas were identical. An equivalent alteration of the smoothly changing pulse duration (Fig. 1, empty squares) shifted the strength-duration curve closer to that for rectangular pulses (Fig. 4*A*, from filled to empty circles) and the charge-duration curve was shifted to above that for rectangular pulses (Fig. 4*B* from empty squares—filled circles to empty circles). An equivalent alteration in

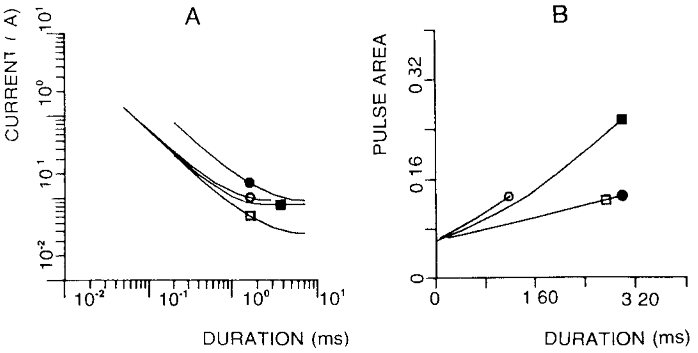

Figure 4. *A*, strength-duration curves for short pulses obtained for the medium fibre ($2L = 8$ mm). Smoothly changing pulses (filled circles). Rectangular equivalents whose amplitude and area are identical with those of the corresponding smoothly changing pulses (empty circles). Rectangular pulses (filled squares). Rectangular equivalents whose duration at the foot and area are identical with those of the corresponding smoothly changing pulses (empty squares). *B*, charge(nq)-duration curves for short pulses. Rectangular equivalents whose amplitude and area are identical with those of the corresponding smoothly changing pulses (empty circles). Rectangular pulses (filled squares). Smoothly changing pulses (filled circles) and rectangular equivalents whose duration at the foot and area are identical with those of the corresponding smoothly changing pulses (empty squares).

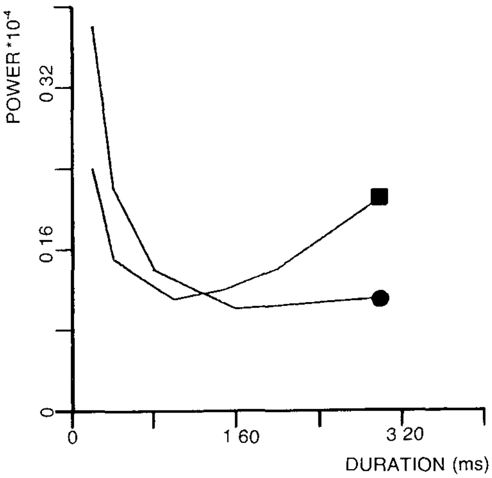

Figure 5. "Power" delivered to the fibre by short smoothly changing (filled circles) and rectangular (filled squares) pulses. The fibre was of medium length ($2L = 8$ mm).

the amplitude (Fig. 1*C*, filled squares) shifted the strength-duration curve to below that for rectangular pulses (Fig. 4*A*, from filled circles to empty squares). From the first case considered we could conclude that the rectangular pulse was more efficient as it needed a lower amplitude and charge for the threshold fibre activation than did the smoothly changing pulse of the same equivalent duration. From the second case, however, we could make an opposite conclusion.

For short stimuli ($T \leq 1.2$ ms), the rectangular pulse had to deliver less power (Fig. 5, filled squares) for the threshold fibre activation than the smoothly changing pulse of the same duration at the foot (Fig. 5, filled circles).

Effects of changes in the duration of the postsynaptic current rise or decay

The stimulus of the initial shape whose amplitude induced the occurrence of a propagating IAP at the ends of the medium fibre (Fig. 6*A*), was chosen as the basic stimulus. Its duration of rise and decay was then varied.

Shortening of the duration of rise (Fig. 1*A*) or decay (Fig. 1*B*) resulted in the conversion of the stimulus effect from a just suprathreshold (Fig. 6*A*) to a subthreshold one (Fig. 6*B*). Inversely, prolongation of any of these phases resulted in the conversion of the just suprathreshold effect to a pronounced suprathreshold one (Fig. 6*C*). These changes in the ability of the stimulus pulse to excite the fibre were in accordance with the strength-duration and charge-duration curves obtained for pulses of the initial shape. With the pulse amplitude being maintained unchanged, it was insufficient for pulses of shorter duration (requiring a higher amplitude) and too strong for pulses of longer duration. Indeed, irrespective of the initial pulse duration and the fibre length, shortening of any phase was accompanied by an

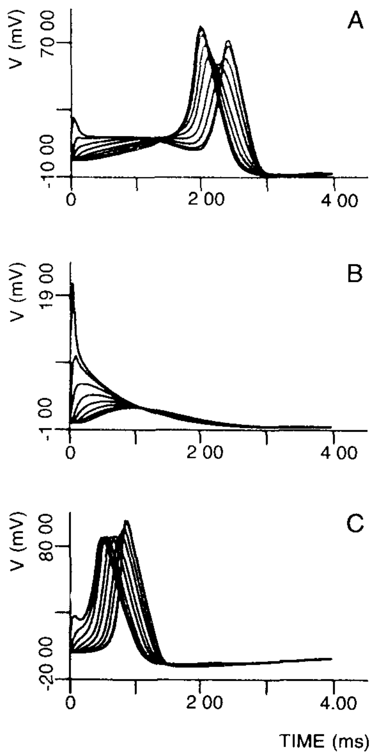

Figure 6. Effect of duration of the short pulse decay on the excitation of the medium fibre ($2L = 8$ mm). *A*, just suprathreshold strength of the smoothly changing pulse of the initial shape, $K_{as} = 3.5$, $T = 0.2$ ms. *B*, shortening (0.5) of the pulse decay duration *C*, lengthening (1.5) of the pulse decay duration. The curves are IAPs for equidistant (400 μm) points along the fibre semilength. Identical changes in the duration of the short pulse rise had similar effects.

increase in the amplitude and by a reduction in the area of the threshold stimulus pulse, and vice versa. The strength-duration and charge-duration curves for the pulses of similar shapes deviated only little from those obtained for pulses of the initial shape. However, the closer the shape to the rectangular one (i.e. the closer the area of the smoothly changing pulse under its amplitude and foot duration being 1, to 1) the closer the corresponding curves to those obtained for rectangular pulses.

The latency vs. changes in pulse area was a nonmonotonic function (Fig. 2, filled circles) or a monotonic one (Fig. 2, filled squares) when the area was varied at the expense of the rise and decay duration, respectively. It should be noted that only when the decay duration was increased, the charge increase was not accompanied by a reduction of the rise rate. The latency could reach higher values when the increase of the pulse area was due to the rise duration (Fig. 2, filled circles) as compared to the case when it was due to the whole pulse duration (Fig. 2, empty circles). Upon increasing the decay duration, a larger than threshold charge was delivered even before the initial pulse cessation. Thus, the longer the decay the more suprathreshold the charge and the shorter the time to excitation (Fig. 2, filled squares).

Effect of pulse asymmetry

In order to determine the effect of the postsynaptic current pulse asymmetry, and thus the effect of the rise rate, we used two pairs of pulses of different K_{as} (3.5 or 7.5) for every stimulus duration studied. The pulses of each pair had the same amplitudes, durations and areas but different shapes (Fig. 1*C*, filled circles and empty circles), and thus different rise rates.

The effect of the different rise rates on the time to excitation was significant. The shorter latency corresponded to a steeper rise. The differences in the latencies reached 1.7 ms.

The effect of the rise rate on the ability of a threshold stimulus pulse to excite the fibre was not as significant as usually claimed. The differences in the threshold amplitudes or charges for pulses of any pair of stimuli were within the 1–4 per cent range. The maximal difference concerned pulses with duration of approximately 1 ms. Moreover, contrary to the general belief, the threshold amplitude and charge for any pulse with a steeper rise were higher than those for an oppositely shaped pulse with a substantially lower rise rate.

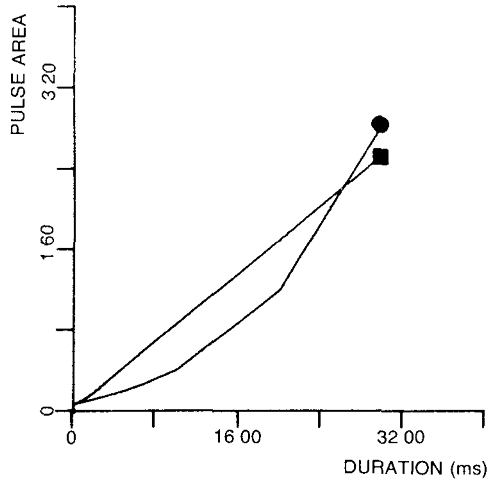

Figure 7. Charge (nq)-duration curves for smoothly changing (filled circles) and rectangular (filled squares) pulses. The fibre was of medium length ($2L = 8$ mm).

2. *Stimuli of long duration* (5 – 30 *ms at the foot*)

Even at a threshold strength of current, the IAPs occurred before the pulse cessation. Thus, the charge required for excitation to occur, was smaller than that delivered by the whole pulse. As a result, the Weiss law was not valid for this duration range. Similarly as with rectangular pulses (Dimitrov et al. 1992), the charge-duration curve was not a straight line (Fig. 7, filled circles). Contrary to rectangular pulses, the curve in this duration range did not tend to make a line passing through the zero point of the coordinates. Moreover, starting with a certain pulse duration at the foot ($T > 20$ ms), the charge delivered by the whole threshold smoothly changing pulse became higher than that delivered by the threshold rectangular pulse of the same duration (Fig. 7, filled squares).

Since the charge required to induce excitation made up only a small portion of the charge delivered by the whole threshold smoothly changing pulse, conditions could be created for more than one propagating IAP to arise (Fig. 8).

When the IAP occurred before the pulse cessation, and in particular before the pulse ceased to rise, the rise rate appeared important for the ability of the pulse to induce excitation. The steeper the rise the shorter the time used for the accumulation of the charge required to induce excitation, and the lower the threshold pulse amplitude. Contrary to the activation by short pulses, a prolongation of the stimulus rise could convert the pulse to a subthreshold one.

The power applied to the fibre by the threshold smoothly changing pulse, was an increasing function of the pulse duration (Fig. 9, filled circles). The power turned higher than that delivered by the threshold rectangular pulse (Fig. 9, filled squares) for durations exceeding 21 ms.

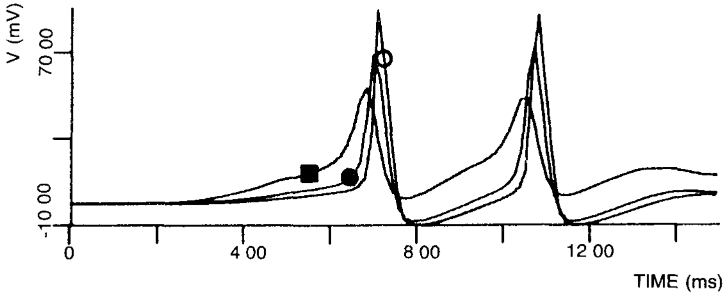

Figure 8. A series of two intracellular potentials obtained in response to a long (30 ms) smoothly changing threshold stimulus and represented for 3 equidistant points along the fibre semilength: at the site of the stimulus application (filled squares); at the middle point of the fibre (filled circles); at the insulated end of the fibre (empty circles). The fibre was of medium length ($2L$=8 mm).

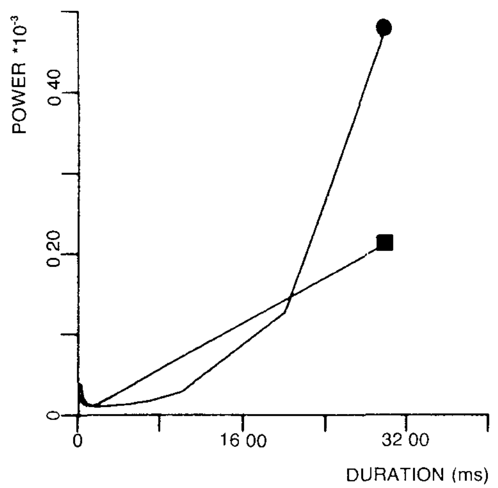

Figure 9. "Power" delivered to the fibre by smoothly changing (filled circles) and rectangular (filled squares) pulses. The fibre was of medium length ($2L$=8 mm).

With smoothly changing pulses of a duration of up to 10 ms, the excitation wave could first occur at the insulated ends of the fibre. For such an unusual onset and propagation of the IAP to occur, the IAP latency had to be larger than the pulse rise duration.

Discussion

It can be concluded from our results that for relatively short ($T \leq$ 3ms) threshold pulses, neither pulse asymmetry nor the rate of the stimulus rise determine the ability of the smoothly changing postsynaptic pulse to induce excitation of the fibre. For a given stimulus duration, the main factor is the pulse area, i.e. the charge delivered by the pulse. Conditions for an about-threshold activation can arise upon summation of subthreshold currents in neurons or upon the occurrence of disorders of synaptic transmission that result in a strong reduction of the postsynaptic currents as compared to normal activation.

The present studies cast light on some reasons for the temperature dependence of the myasthenic patients' state (Borenstein and Desmedt 1973, 1974, 1975; Ricker et al. 1977; Gutmann 1980), a phenomenon whose nature is not clear (Lisak and Barchi 1982). The increase in the postsynaptic current area due to the increased time of decay, observed at lower temperatures (Magleby and Stevens 1972; Magazanik and Giniatullin 1986) could underlie this phenomenon (compare Figs. 6*A* and 6*C*). Similar changes could also be expected when the decay time of the postsynaptic currents is altered under the effect of: membrane potential (Magleby and

Stevens 1972); acetylcholine (Magleby and Terrar 1975): different cations (Cohen and van der Kloot 1982), etc. If the increase in the postsynaptic current area is due to a prolongation of the rise time or increase in total pulse duration, the effect on the fibre excitation will depend on the relationship between the pulse duration and the maximum time to excitation. Such an increase could facilitate or depress the fibre activation if the pulse duration is shorter or longer than the maximum time to excitation, respectively.

The efficiency of pulses of different shapes could be assessed with respect to their ability to induce excitation or a less injurious effect, or to a shorter time to excitation, etc. As the duration and strength of any nonrectangular pulse are not well defined, any comparison of the efficiency of stimuli of different shapes is ambiguous unless an additional condition is specified.

With this condition being the identity of the amplitudes of short pulses to be compared, a rectangular pulse could activate the fibre with a smaller charge and for a shorter time than the smoothly changing one (compare Fig. 4*B*, filled squares and empty circles for any equivalent duration of the smoothly changing pulse). Thus, under the additional condition the rectangular pulse is more efficient than the corresponding smoothly changing one. This conclusion is in conflict with that reported by Goldman and Klafter (1982).

Another conclusion can be drawn if the additional condition is the identity of the durations of the short pulses at the foot. With respect to their ability to induce excitation, nonrectangular stimuli requiring smaller charges, are now more efficient than the rectangular ones (compare Fig. 4*B*, empty squares-filled circles and filled squares). This conclusion is now in accordance with that of Goldman and Klafter (1982). However, with respect to the threshold current amplitude, the opposite is true (Fig. 4*A*, filled circles and filled squares).

The actual duration of a nonrectangular pulse can also be defined in another way. Taking into account that the strength-duration and charge-duration curves for the short rectangular pulses (Fig. 4*A*, *B* filled squares) are between those obtained for extreme cases of conversion of the smoothly changing pulses into the equivalent rectangular ones (Fig. 4*A*, empty circles and empty squares, Fig. 4*B*, empty circles and empty squares-filled circles), and that the main factor of excitation is the threshold charge, we can consider that the actual duration of a short nonrectangular pulse is that of a rectangular pulse which requires the same charge to induce fibre excitation. Then, pulses of different shapes but identical actual duration are equally efficient with respect to their ability to induce excitation. Rectangular pulses are, however, more efficient in that they require a shorter time to induce excitation.

The power delivered to a fibre by a stimulus pulse could be a measure of the heat production (Offner 1946). The two types of the pulses considered, have similar power-duration dependences (Fig. 5). One reason for the differences in these and the charge-duration dependences (Fig. 4*B*, filled squares and empty squares-filled circles) could be the lack of coincidence between the actual duration and the duration at the foot for the smoothly changing pulses which were used to plot the dependences. The power-duration curves have minima in the proximity of 1 ms (Fig. 5). Values of stimulus duration chosen in the proximity of the minima seem to be more advantage one for prolonged fibre stimulation. These stimuli will combine a minimum power with small charge and not so high amplitude, which could protect the fibre from injury.

Threshold rectangular pulses of long duration are always more efficient than the smoothly changing ones (Figs. 3, 7, 9). This reflects a decrease in the charge delivered by a smoothly changing stimulus up to the maximum time to excitation when the stimulus is prolonged. Hence, an increase in the amplitude of the physiologically adequate smoothly changing pulse is necessary to reach the threshold. No such problem ever arises upon threshold activation by rectangular pulses. For rectangular pulses, non-monotonic strength-duration curves cannot be obtained. A prolongation of a rectangular pulse of the rheobasic amplitude does not, in fact, change the development of the processes until excitation occurs. Thus, the rheobase, i.e. the threshold current that is independent of the duration of long pulses, is a consequence of the conventional method for obtaining the strength-duration dependences using rectangular pulses.

References

Bishop G. H. (1928): The relation between the threshold of nerve response and polarization by galvanic current stimuli. Amer. J. Physiol. **84**, 417—436

Borenstein S., Desmedt J. E. (1973): New diagnostic procedures in myasthenia gravis. In: New Developments in Electromyography and Clinical Neurophysiology (Ed. Desmedt J. E.), vol. 1, pp. 350—374, Karger, Basel

Borenstein S., Desmedt J. E. (1974): Temperature and weather correlates of myasthenia fatigue. Lancet **2**, 63—66

Borenstein S., Desmedt J. E. (1975): Local cooling in myasthenia. Arch. Neurol. **32**, 152—157

Bostock H. (1983): The strength-duration relationship for excitation of myelinated nerve: computed dependence on membrane parameters. J. Physiol. (London) **341**, 59—74

Cohen I., van der Kloot W. (1982): The interaction of extracellular H^+, Na^+, Ca^{2+} and Sr^{2+} on the decay of miniature end-plate currents. Brain Res. **241**, 285—290

Cole K. S.. (1955): Ions, potentials, and the nerve impulse. In: Electrochemistry in Biology and Medicine (Ed. Shedlovsky T.), pp. 121—140, John Wiley and Sons, New York

Dean D., Lawrence P. D. (1985): Optimization of neural stimuli based upon a variable threshold potential. IEEE Trans. Biomed. Eng. BME-**32**, 8—14

Diecke F. (1954): Die "Akkommodation" des Nervenstammes und des isolierten Ranvierschen Schnurringes. Naturforschung **96**, 713—729

Dimitrov G. V., Dimitrova N. A., Pajeva I. K. (1992): Threshold stimulation and accommodation of the Hodgkin-Huxley axon. Gen. Physiol. Biophys. **11**, 59—68

Dimitrova N. A., Dimitrov G. V. (1988): Effect of electrical stimulus parameters on the development and propagation of action potentials in short excitable fibers. Electroencephalogr. Clin. Neurophysiol. **70**, 453—459

FitzHugh R. (1966): Theoretical effect of temperature on threshold in the Hodgkin-Huxley nerve model. J. Gen. Physiol. **49**, 989—1005

Frankenhaeuser B., Vallbo A. B. (1965): Accommodation in myelinated nerve fibres of *Xenopus laevis* as compute on the basis of voltage clamp data. Acta Physiol. Scand. **65**, 1—20

Goldman R. J., Klafter R. D. (1982): Reduced charge in nerve stimulation by waveform modification. Proc. 35th Ann. Conf. Eng. Med. Biol. - Philadelphia 24, 193

Grundfest H. (1932): Excitability of the single fibre nerve-muscle complex. J. Physiol. (London) **76**, 95—115

Gutmann L. (1980): Heat-induced myasthenic crisis. Arch. Neurol. **31**, 671—672

Guttman R. (1966): Temperature characteristics of excitation in space-clamped squid axons. J. Gen. Physiol. **49**, 1007—1018

Hill A. V. (1936): Excitation and accommodation in nerve. Proc. Roy. Soc. B **119**, 305—355

Hodgkin A. L., Huxley A. F. (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. (London) **117**, 500—544

Joyner R. W., Westerfield M., Moore J. W., Stockbridge N. (1978): A numerical method to model excitable cells. Biophys. J. **22**, 155—170

Katz B. (1939): Electrical Excitation of Nerve. Oxford University Press, London

Khodorov B. I. (1974): The Problem of Excitability. Plenum Press, New York

Khodorov B. I. (1975): General Physiology of Excitable Membranes. Nauka, Moscow (in Russian)

Lapicque L. (1907): Recherches quantitatives sur l' excitation electrique des nerfs traitee comme une polarization. J. Physiol. (Paris) **9**, 622—635

Lisak R. P., Barchi R. L. (1982): Myasthenia Gravis. W. B. Saunders Company, Philadelphia

Lucas K. (1907): The excitable substance of amphibian muscle. J. Physiol (London) **36**, 113—135

Magazanik L. C., Giniatullin R. A. (1986): Effects of voltage and temperature on the postsynaptic potentiation in neuromuscular junction of frog. Neirofiziologiya **18**, 512—518 (in Russian)

Magleby K. L., Stevens C. F. (1972): A quantitative description of end-plate currents. J. Physiol. (London) **223**, 173—197

Magleby K. L., Terrar D. A. (1975): Factors affecting the time course of decay of end-plate currents: a possible cooperative action of acetylcholine on receptors at the frog neuromuscular junction. J. Physiol (London) **244**, 467—495

Monnier A. M. (1934): L' Excitation Electrique des Tissus. Hermann et Cie, Paris

Nernst W. (1908): Zur Theorie des electrischen Reizes. Pflugers Arch. Ges. Physiol. **122**, 275—314

Noble D., Stein R. B. (1966): The threshold conditions for initiation of action potentials by excitable cells. J. Physiol. (London) **187**, 129—162

Offner, F. (1946): Stimulation with minimum power. J. Neurophysiol. **9**, 387—390

Rashevsky N. (1933): Outline of a physico-mathematical theory of excitation and inhibition. Protoplasma **20**, 42—56

Ricker K., Hertel G., Stodieck S. (1977): Influence of temperature on neuromuscular transmission in myasthenia gravis. J. Neurol. **216**, 273—283

Rinzel J. (1976): Simple model equations for active nerve conduction and passive neuronal integration. Lectures on Math. in the Life Sci. **8**, 125—164

Vallbo A. B. (1964a): Accommodation of single myelinated nerve fibres from *Xenopus laevis* related to type and end organ. Acta Physiol. Scand. **61**, 413—428

Vallbo A. B. (1964b): Accommodation related to inactivation of the sodium permeability in single myelinated nerve fibres from *Xenopus laevis*. Acta Physiol. Scand. **61**, 429—444

Weiss G. (1901): Sur la possibilite de rendre comparables entre eux les appareils servant a l' excitation electrique. Arch. Ital. Biol. **35**, 413—446

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