Threshold Stimulation and Accommodation of the Hodgkin-Huxley Axon

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Abstract. The charge-duration and strength-duration relations for just threshold rectangular stimuli were numerically investigated for the Hodgkin-Huxley axons of different lengths and different membrane capacitances under normal conditions and blockage of the development of accommodative processes. Two linear portions could be distinguished on the charge-duration curve. One of them followed the Weiss law. The other one represented a portion of a straight line passing through the zero point of the coordinates. The slope of the second portion was determined by the charge for very short stimuli (Q_0), the slope of the first portion, and the maximum time to excitation ($\tau_{\max}$). The rheobase reflected the slope of the second portion. Upon varying the fibre length the slope of the first and the second linear portions and the rheobase changed. The membrane capacitance substantially affected both the value of Q_0 (as in the case of myelinated fibres) and the rheobase. The accommodative processes affected the Q_0, the slope of the first line, $\tau_{\max}$, and, consequently, the rheobase. The effect of potassium activation was stronger than that of sodium inactivation. The slope of the first line, $\tau_{\max}$, and the rheobase might be considered more comprehensive indicators of the accommodative processes than the usually used indicators.

Key words: Charge-duration curve — Strength-duration curve — Accommodation — Excitability — Computing

Introduction

Starting with investigations of Du Bois-Reymond (1848), it has been shown that if the slope of a linearly rising stimulus becomes smaller than a critical one called "minimum current gradient for excitation" (Lucas 1907), the excitable cells fail to produce action potentials. When the slope is reduced, not only increases the time to excitation, but also the absolute stimulus level that must be reached to induce excitation. This phenomenon has been termed accommodation (Nernst 1908).

The increase in membrane voltage threshold upon increasing the time to excitation, is considered the reason for accommodation and an indicator of the latter (Monnier 1934; Rashevsky 1933; Noble and Stein 1966; Noble 1972; Fozzard and Shoenberg 1972). The accommodation constant determined as a value inversely proportional to the rate of membrane voltage threshold change is employed as a measure of accommodation (Solandt 1936; Kugelberg 1944). Another indicator is the increase in the current threshold of a testing stimulus applied on the background of a subthreshold linearly rising stimulus whose slope is close to the minimal gradient (Diecke 1954; Vallbo 1964a,b; Khodorov 1974) or on the background of subthreshold rectangular pulses (Baker and Bostock 1989).

However, reports also appeared showing that the voltage threshold can increase very slightly or not at all when the time to excitation increases (Knutsson 1964; Knutsson and Scoglund 1966; Sugi 1968; Fozzard and Schoenberg 1972; Krinsky and Kokoz 1973). It has been suggested that there are cells which do not accommodate. Moreover, when the time to excitation increases, the current threshold measured by linearly rising (Jakobsson and Guttman 1980; - "reverse accommodation") or testing stimuli (Baker and Bostock 1989 - "negative accommodation") can decrease instead of increasing.

Blair and Erlanger (1936), Katz (1939), Granit et al. (1963), Vallbo (1964a,b), Kernell (1965), Cooley and Dogde (1966) and Khodorov (1974) have demonstrated that excitable cells can produce repetitive action potentials when the stimulus is a constant depolarizing current; i.e. every pulse, with the exception of the first one, is a response of the cell to a stimulus whose slope is zero. However, there is a pronounced correlation between the firing rate of the repetitive responses and the membrane accommodation (Katz 1939; Vallbo 1964a,b; Kernell 1965; Khodorov 1974).

Thus, each of the indicators mentioned above fails to describe manifestations of accommodation under certain conditions. Are there better, i.e. more comprehensive, indicators of the processes of accommodation?

Materials and Methods

The model of Hodgkin and Huxley (1952) describes well the peculiarities of fibre activation (Cole 1965; FitzHugh 1966; Noble 1966; Khodorov 1974). This model was used as a basis for calculating the intracellular action potentials by the method of Joyner et al. (1978) for the structures with changing radius. The membrane parameters were the same as in the Hodgkin-Huxley model. Fibres of 30μ radius and different semilengths were activated by threshold rectangular pulses of different duration ($T_s = 0.02 \div 3$ ms). The semilength of short, medium, and long fibre was 2.5 mm $\approx 1.25\lambda$, 4 mm $\approx 2\lambda$, and 10 mm $\approx 5\lambda$, respectively (λ is the fibre space constant). The boundary condition at the site of stimulation was $V_{-1} = V_1$. It corresponds to symmetrical propagation of the excitation waves to the insulated fibre ends, where $V_L = V_{L+1}$. The time step, space step and the

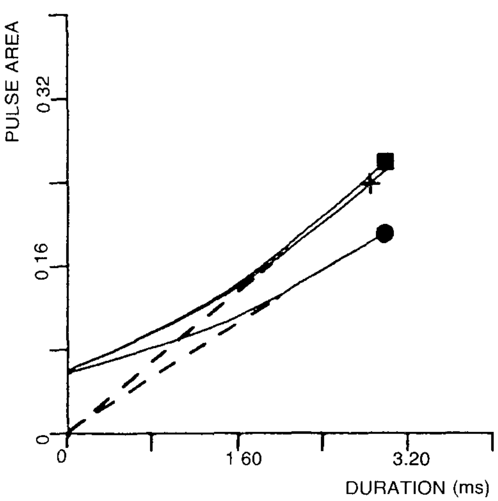


Figure 1. Charge (nq) - duration curves for fibres of different lengths; the fibre semilength for long (filled squares), medium (crosses) and short (filled circles) fibre was 5λ, 2λ and 1.25λ, respectively. Dashed lines: straight lines whose slopes define the corresponding rheobases.

temperature were 10 μs, 12.5 μm and 20 °C, respectively.

Results

Two linear portions with different slopes could be distinguished on the charge (pulse area)—duration curve (Fig. 1 – solid lines). They were separated by a transition section with the pulse duration ($T_s \approx 1.5 \div 2$ ms) being almost equal to the time to excitation, i.e. to the latency of the origin of the propagating action potential. The first linear portion ($T_s \leq 1.5$ ms) followed the Weiss law (Weiss 1901). With similar stimulus durations the action potentials always occurred with a delay after the pulse cessation. The second linear portion corresponded to the activation of the fibre by a current of the rheobasic strength (I_{rh}) and duration longer than the maximum time to excitation ($T_s > 2$ ms for the Hodgkin-Huxley axon with the standard membrane parameters). Under these conditions, the action potentials always occurred before the pulse cessation, i. e. the stimulating current that continued after the onset of the regenerative process delivered a charge greater than that necessary to excite the fibre. Thus, the slope of the second linear portion of the charge-duration curve was higher than that of the first linear one, and defined the rheobase. Within this duration range the charge-duration curve was a portion of a straight line passing through the zero point of the coordinates (Fig. 1 – dashed lines).

The interpretation of the constant defining the slope of the first linear portion expressed by the Weiss law: $Q = Q_0 + I_{\mathrm{rh}}.t$ (where Q_0 is the threshold charge

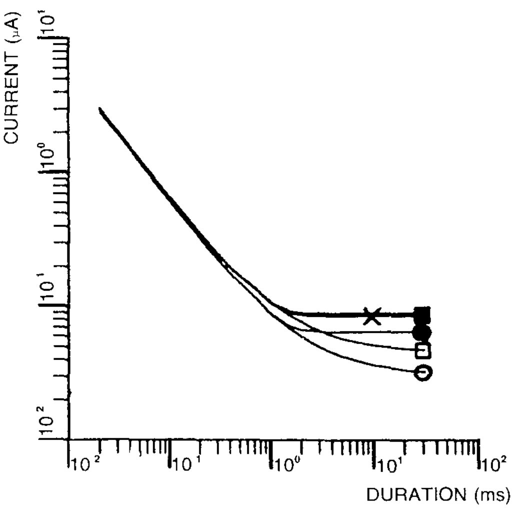


Figure 2. Strength-duration curves for fibres of different lengths. Actual Hodgkin-Huxley fibres: long (filled squares), medium (crosses), short (filled circles). An artificial case assuming the Weiss law being valid for any pulse duration for long (empty squares) and short (empty circles) fibres.

for very short stimuli) as the rheobase (Bostock 1983) would be true only when the maximum time to excitation goes into infinity. In any other case such an interpretation would lead to an underestimated value of the rheobase. This is illustrated in Fig. 2. If the Weiss law were valid for all pulse durations (Fig. 2 empty squares and circles for a long and short fibre, respectively) the rheobase would be smaller, and the strength-duration time constant ($\tau_{sd} = Q_0/I_{rh}$) higher than those in the case of the actual curves (Fig. 2 filled squares and circles).

The slope of the second linear portion of the charge-duration curve and, consequently, the rheobase, should depend on the charge Q_0, the slope of the first linear portion, and the maximum time to excitation. Indeed, for shorter fibres the slope of the extra charge in the first linear portion and, consequently, the slope of the second linear portion and the rheobase decreased (Fig. 1, from filled squares to crosses and filled circles).

Variation of membrane capacitance (C_m) led to pronounced changes in Q_0 and, consequently, in the slope of the second linear portion (Fig. 3) and in the rheobase. With C_m doubling, the short stimulus threshold current increased by 71 per cent and the rheobase by 54 per cent. This result differs considerably from the data for myelinated fibers reported by Frankenhaeuser (1965): 41.5 for the threshold for short stimuli, and 6.5 per cent for the rheobase; and by Bostock (1983): (−1) per cent for the rheobase.

The relation between the processes of excitation and those counteracting the excitation determine not only the charge Q_0 and the slope of the first linear portion, but also the maximum time to excitation. Hence, the slope of the second linear

Figure 3. Effect of membrane capacitance (C_m) on the charge (nq)-duration curve. (filled circles), – $C_m = 1\,\mu\mathrm{F/cm}^2$; (empty circles), – $C_m = 2\,\mu\mathrm{F/cm}^2$. The fibre was of medium length.

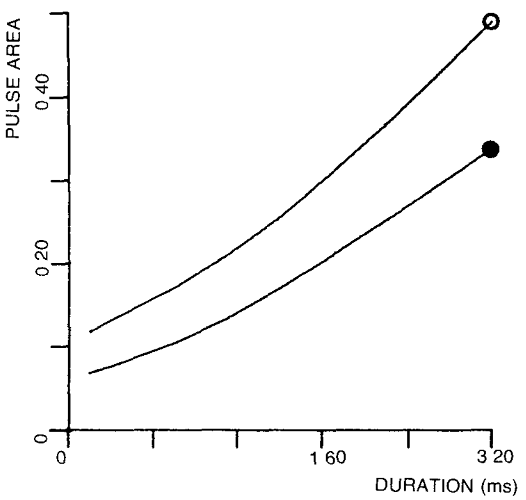
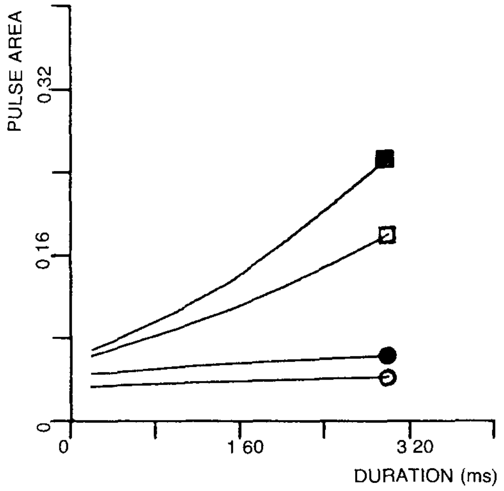


Figure 4. Charge (nq)-duration curves for a fibre of medium length with normal Hodgkin-Huxley membrane parameters (filled squares) or with blockage of development of: sodium inactivation (empty squares), i.e. $h = h_0$; potassium activation (filled circles), i.e. $n = n_0$; sodium inactivation and potassium activation (empty circles), i.e. $h = h_0$ and $n = n_0$.



portion and the rheobase were considerably affected.

In order to block the development of the processes counteracting the excitation, i. e. the accommodative processes (inactivation of the sodium and activation of the potassium system) the values of the Hodgkin-Huxley variables h or/and n were fixed at their initial resting levels (h_0, n_0), whereby the charge and the extra charge (Fig. 4), as well as the threshold current and the rheobase (Fig. 5)

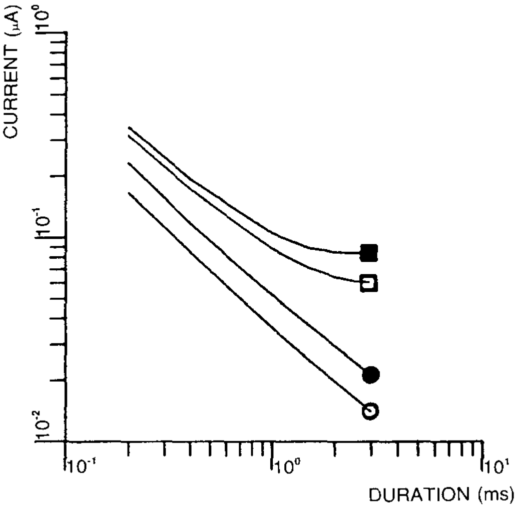


Figure 5. Strength-duration curves for a fibre of medium length with normal Hodgkin-Huxley membrane parameters (filled squares) or with blockage of development of: sodium inactivation (empty squares), i.e. $h = h_0$; potassium activation (filled circles), i.e. $n = n_0$; sodium inactivation and potassium activation (empty circles), i.e. $h = h_0$ and $n = n_0$.

were reduced. When only the development of the sodium inactivation was blocked (Figs. 4 and 5, empty squares), the effects were less pronounced than with the development of potassium activation being blocked only (filled circles) or than with the development of both processes being simultaneously blocked (empty circles).

The blockage of the accommodative processes led to a high increase in the maximum time to excitation. Under normal conditions or when only sodium inactivation was blocked, this time was only 2–3 ms but it was 10–35 ms when only potassium inactivation or both processes were blocked. Thus, the threshold charge-duration curve was linear within a broader range of pulse durations when both systems (Fig. 4, empty circles) or at least potassium activation (Fig. 4, filled circles) were blocked.

The increase in the maximum time to excitation combined with the decrease in the charge necessary to induce excitation were the reasons for the pronounced decrease in the rheobase, reflecting the slope of the second linear portion of the charge-duration curve.

The rate of the extra charge increasing was affected by the fibre length (Fig. 1) and by membrane capacitance (Fig. 3), but it was almost zero only when the development of accommodative processes was blocked. The small residual extra charge for longer stimuli could result from the fibre cable properties being manifested in a different actual (not steady state) fibre length constant for stimuli of different duration or from the membrane conductivity shunting the membrane capacitance.

Discussion

Each new generation tries to comprehend the classical conceptions in the corresponding field of science in the light of new results. Papers of Jakobsson and Guttman (1980); Bostock (1983); and Baker and Bostock (1989) mark the beginning of the interest of the fifth generation in basic problems of bioelectricity - the threshold excitation and accommodation of biological membranes.

Experimental results (Guttman 1966) and calculations based on the Hodgkin - Huxley model (Cole 1955; FitzHugh 1966) have shown that the amplitude of a stimulus with a duration $\tau = Q_0/I_{\mathrm{rh}}$ is 1.31–1.38 I_{rh} instead of $2I_{\mathrm{rh}}$ as it could be expected (Lapicque 1926) from the Weiss law.

The present results showed that this discrepancy might be due to the higher actual value of the rheobase (Fig. 2 filled squares and circles) as compared to the values that would be expected from the Weiss law (Fig. 2 empty squares and circles). An increase in the current strength corresponding to the shorter actual τ ($\tau_{\mathrm{act}} = Q_0/I_{\mathrm{rh\,act}}$) is not sufficient to compensate for the effect of a higher actual value of the rheobase.

The linear character of the charge-duration dependence found within a restricted range of durations (Bostock 1983) suggests a general validity of the Weiss law. However, this character could only point out that the stimulus duration is shorter than the maximum time to excitation. The deviation of the actual strength-duration curve from the Weiss law (Fig. 2) made Lapicque (1907) and Hill (1936) to use more rapidly varying exponential functions with one or two time constants to fit the experimental data instead of the inversely proportional function. Thus, it is not surprising that within the range of stimulus durations for which the Weiss law is valid, Bostock (1983) found that the Weiss law fitted his data better than did the equations of Lapicque (1907) or Hill (1936).

The accommodative processes determine both the slope (other than zero) of the first linear portion of the charge-duration curve described by the Weiss law, and the maximum time to excitation restricting the validity of this law. Due to the accommodative processes, the longer the stimulus, the higher the threshold charge, i. e. the higher the stimulus level that must be reached before excitation occurs. An extra charge for activation of an actual fibre was also necessary with short pulses. Thus, we can conclude that the accommodation can be manifested not only at long time stimuli, as it can be assumed on the basis of the usually used indicators (changes in membrane voltage of current threshold), but also at short time stimuli.

An increase in the charge required to induce excitation can also be observed in cells that do not seem to accommodate (Fozzard and Schoenberg 1972) or in cells showing reverse (Jakobsson and Guttman 1980) or negative (Knutsson and Scoglund 1966; Baker and Bostock 1989) accommodation. Thus, unlike Jakobsson and Guttman (1980), we agree with Hodgkin and Huxley (1952) that their axon does show accommodation.

Besides, a pronounced rheobase can be observed even with the voltage threshold not changing (Fozzard and Schoenberg 1972).

We can conclude that the slope of the charge-duration curve before the maximum time to excitation, as well as the maximum time to excitation and the rheobase might be considered more comprehensive indicators of the accommodative processes than the indicators used so far.

The experimental data of FitzHugh (1966) and Guttman (1966) and the present results lead us to believe that the effect of the accommodative processes increases (the *rheobase increases* and the *maximum time to excitation decreases*) with the increasing temperature.

When the fibre is stimulated by a linearly rising stimulus whose slope is close to the critical one, the action potential amplitude and the rate of the potential rise decrease (Diecke 1954; Frankenhaeuser and Vallbo 1965; Vallbo 1964a,b). This, however, is typical of activation by any threshold stimulus (Cooley and Dogde 1966; Cole et al. 1970; Khodorov 1974; Dimitrova and Dimitrov 1988) as a result of a slight predominance of the excitation processes over the accommodative ones. The higher the temperature, the wider the range of the suprathreshold stimulus strength within which a gradual response is observed (Cole et al. 1970). This can be explained by a strengthening of the effect of the accommodative processes with the increasing temperature.

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