The Plateau of the Action Potential of the Frog Ventricle

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A study was made of the changes produced in action potentials of frog ventricular cells by variation in ion concentrations, by administration of NaN₃, 2:4 DNP, NaCN, NaIA and N₂ which shortened the potentials. The exposure of the perfused tissue to ionized acridines, barbiturates and desoxyglucose caused a prolongation of the action potentials. These actions as obtained were reversible. The evidence from the time-course and differential effects of inhibitors suggests that an active ion transport, modulated by K₀⁺, may be important in maintaining the plateau phase of the action potential.

The peculiarly long duration of the action potential of cardiac muscle fibers is associated with a prolonged refractory period which in turn tends to preserve a satisfactory rhythm of heart action. The prolonged plateau of ventricular cell action potentials is unique in excitable tissues; action potentials of striated skeletal muscle and of nerve under normal circumstances do not show such a phenomenon. The nature of the process that delays repolarization in the related fibers of cardiac muscle has yet to be determined satisfactorily, although several concepts have been proposed to account for the plateau of the action potential.

Weidmann in 1956¹ suggested a continued sodium permeability of the membrane which persists till potassium permeability increases at the end of the plateau. This would be satisfactory if some mechanism of action could be found which would explain the continued sodium penetration. The concept that there is delay in the occurrence of regenerative repolarization, a process completing repolarization after a critical degree of action potential decay, is favored by Cranefield and Hoffman.² The nature of the plateau is not explained, however, by this postulate nor is the slow decay preceding the quick terminal phase of repolarization. The intervention of some energy-dependent ion transfer has been suggested by Hoffman and Suckling,² by Macfarlane,⁴ and by Webb and Hollander.⁵ Brady and Woodbury⁶ conclude, also, that potassium conductance is low during the plateau (phase 2) and find it conceivable that active ion transport may be involved in the sustained depolarization. Interference with such active transport would account for the reduction of the plateau by anoxia, injury, fatigue, and metabolic inhibition, and could account for the high temperature coefficient of the plateau, as well as the immediate shortening that occurs with increase of heart rate.

The duration of the action potential (AP) may be modified by physiological reactions such as a change in heart rate, by physical agencies such as temperature change⁷ as well as by chemical agents such as those under study. For present convenience action of chemical agents may be classified in 2 categories, those shortening and those prolonging the action potential.

Shortening of the duration of the AP is induced by high K⁺ (K₀⁺) and low Na₀⁺. It has been suggested by Carmeliet and Lacquet⁸ that the shortening due to rate increase is caused by reduction of Na₀⁺ and increase in K₀⁺. Interference with inward transport of K⁺ may explain the shortening of action potentials produced by digitalis glycosides.¹² Anoxia,⁹ 2:4 dinitrophenol (DNP), sodium azide,⁴ sodium cyanide, and sodium iodoacetate (NaIA)¹⁰ produce reversible shortening of
Effect of change in rate of action potentials of frog ventricle perfused with Ringer solution at 24° C. Continuous record. Beginning (t) and end (•) of acceleration. Calibrations: 50 mV. and 100 msec. time intervals. Note gradual return of cycle length to normal control value (1200 msec.) after acceleration caused shortening to 550 msec.

the AP presumably by reduction of available phosphate energy.

Prolongation of the AP results from lower than normal K+ or increase in Na+ and from increased Ca++. There is an almost immediate prolongation of AP by veratrine alkaloids, barbiturates, and acridines like 5-amino-acridine. The lengthening persists for several hours after removal of veratrine and acridines. The initial action of 2:4 DNP is to prolong the AP. The glucose analogue, 2-deoxyglucose, also prolongs the AP, and this effect is reversed by an equimolar quantity of glucose.

The purpose of the work reported here is to compare the effects of changes in K+ with those of anoxia and a variety of metabolic blocking agents.

Methods

Excised hearts of Rana temporaria were driven by bipolar stimulation at the atrioventricular region. Hearts were maintained in Ringer solution, gassed with 1 per cent carbon dioxide in oxygen, and containing phosphate and bicarbonate buffer to give a pH of 7.2 to 7.3. The medium flowed at rates of 3 to 20 ml./min., and temperatures were in the range 20 to 27 C. Drugs and inhibitors were dissolved in the Ringer solution flowing over the heart. Long periods of exposure were avoided since recovery was less complete thereafter and since reversibility was desired. The action of inhibitors was stopped when a relatively stable state had been attained and the rate of shortening of duration reached a low value or ceased. At the end of the period of drug action fresh Ringer solution, with which the tissues were then perfused, served as the recovery medium.

The records of electrical activity were made using a microelectrode (less than 1 μ tip diameter), cathode follower and DC amplifier. Stimulation was maintained at 1200 msec. intervals except during test periods when the refractory period and rate of follow was determined, using 700, 550 and 400 msec. cycles, with driving shocks of appropriate strength and duration. When prolongation of the AP occurred, 2200 msec. cycles were used. The standard test sequence comprised recording of 10 to 20 beats at each frequency, and during the recovery process (fig. 1). Only ventricular cells were studied, since they were less likely to be influenced by neurohumors.

The threshold of excitability was estimated from the strength and duration of the driving shocks. A good deal of the current flowed through the saline medium, but the order of change of excitability was approximated. In moving tissue the resting potential could not be recorded with great accuracy especially during fast beating, but the duration of the AP was satisfactorily ascertained. At least 6 hearts were used to estimate the action of each agent. In all, 73 hearts were studied in a total of 116 action and recovery tests. Comparisons of the time of action and recovery from applied drugs were based on time required for shortening of AP to half and recovery to two thirds the initial duration.

Results

In the normal frog heart the duration of the ventricular action potential (AP) was 900 to 1000 msec. when the cycle length was maintained at 1200 msec. and the temperature at 23 C. At 27 C. summer frogs initially had an AP duration of 500 to 600 msec. After 30 min. this usually rose to 800 msec. except in a few hearts where there were pericardial adhesions and obvious myocardial damage.
Spring frogs' hearts were rarely able to follow a driving rate of 4 beats/sec. (250 msec. cycle), but in summer the hearts were usually able to sustain a rate of 5 beats/sec. (167 msec. cycle) with bath temperature at 25 C.

When the duration of the AP was steady at a 1200 msec. cycle, increase of rate shortened the duration of the AP. This change began with the first premature driving stimulus, but the shortening increased with subsequent beats. After 8 to 10 beats at the new rate, AP duration stabilized. On return to a 1200 msec. cycle, the normal heart required 10 to 12 cycles for return to and stabilization at the control level (fig. 2). The first AP at 1200 msec., after establishment of a 300 msec. cycle length, was 15 to 25 per cent shorter than those 20 seconds later. This change of AP duration on increasing the driving rate meant that a gradual increase of rate enabled the heart to follow faster stimulation than when tested by a sudden increase of rate. The unresponsive period could be gradually shortened during 10 to 15 beats. The amplitude of the AP did not necessarily fall with increased rate, up to cycle lengths of 350 msec. (fig. 1).

Two phases to recovery were observed. The first, a rapid phase requiring about 10 beats to produce approximately 90 per cent recovery of the action potential's duration, was followed by a slower rate of recovery which persisted over 3 min. and added 10 per cent to the duration (fig. 2). In the present studies the first phase has been examined rather than the second.

Chemical Modification of Action Potential

Shortened Action Potentials

A number of agents produced similar types of change in the AP. These were nitrogen (fig. 2), sodium azide (NaN3 0.5 to 2.0 mM.), 2:4 dinitrophenol (DNP 0.01 to 0.2 mM.), sodium cyanide (NaCN 1.0 to 4.0 mM.) and sodium iodoacetate (NaIA 0.4 to 2.0 mM.) (fig. 3). The time course and extent of action was a function of concentration and the effect was reciprocal in duration to recovery (fig. 4). The average times required, in groups of 4 to 9 experiments, to shorten the AP to half, and for it to recover to two thirds the initial duration, were for N2 32 min. to shorten and 8 min. to recover; 0.2 mM. DNP 2.7 min. and 23 min.; 0.02 mM. DNP 33 min. and 7 min.; 2.0 mM. NaN3 18 min. and 8 min.; 0.5 mM. NaIA 18 min. to shorten but there was no recovery even after 65 min. (fig. 3). By
Figure 4
Comparison of effects of low Na\textsuperscript{+} and various concentrations of K\textsuperscript{+} and 2:4 DNP on duration of action potential. Exposure during period before t and recovery in Ringer solution thereafter. Rate of drive the same as that which gave normal cycle length of 1200 msec. Temperature 23 to 26 C.

contrast 15 mEq./L, K\textsuperscript{+} required 3.5 min. for shortening to half normal AP duration and 3 min. for recovery in Ringer solution; 20 mEq./L, K\textsuperscript{+} required 2.0 min. for shortening and 1.8 min. for recovery to two thirds of the initial length of the AP.

Within 1 to 2 min. low concentrations of 2:4 DNP and NaIA prolonged the AP (figs. 3, 4), but this effect was lost in the shortening that followed. This was not seen with higher concentrations. When the heart was driven fast the AP shortened, but under the influence of these agents there was less recovery of the initial duration of the AP, when the rate returned to the control value at a cycle length of 1200 msec. Figure 5 shows that these substances reduced the length of the AP at any frequency, and towards the completion of their action there was little difference between slow and fast rate AP durations. Recovery of AP length failed to take place in such media as 4 mM, NaCN or 0.05 mM, DNP while the hearts were exposed to their action.

Sodium iodoacetate (0.5 mM.) initially prolonged the AP by 15 to 20 per cent, but after 5 min. slow reduction of duration began and attained a maximum in about 20 min. The action of NaIA differed from that of other substances of this group in 2 respects. First, it increased the amplitude of the ventricular AP (fig. 6) although the durations were shortened to 250 msec. at 25 C. and a cycle length of 1200 msec. Some fibers exposed to DNP or azide showed an increased AP amplitude but the increases were small compared with those produced by NaIA. Secondly, its action was not reversed by more than an hour’s washing in fresh Ringer solution. The heart became inexcitable and there was no recovery of AP duration although the amplitude remained high and contraction continued. During the late stages of NaIA action or during washing, action potentials of less than 50 msec. duration occurred and the main spike was followed by a slower process resembling an after-potential.

The resting potential and the amplitude of the AP were reduced little by low concentrations of inhibitors (0.02 mM, DNP, 0.5 mM, NaIA, 0.5 mM, NaN\textsubscript{3}) while the AP duration was reduced slowly to one third or less of its initial length (fig. 6). Higher concentrations (0.2 mM, DNP, 4 mM, NaN\textsubscript{3} but not 2 mM, NaIA) reduced the amplitude and duration of the AP, the two maintaining an approximately logarithmic relationship. This action was complete within 5 min.

Tachyphylaxis was observed with DNP and NaCN. When one heart was put through several cycles of exposure and recovery, the effect of low concentrations of these substances was less on the second and third repetition than in the first period of drug action.

The duration of the AP in hearts with an imposed 1200 msec. cycle is normally about 900 msec. When this was reduced by drug action to about 300 msec. some spontaneous activity occurred with all agents in this group. Nitrogen, NaCN, and NaN\textsubscript{3} induced repetitive discharges following driving stimuli and then after 1 to 2 min. of exposure a spontaneous firing with a cycle length of 200 msec. and AP duration of 110 msec. With NaIA there was a different pattern. A driving stimulus produced several spikes, or a decremental train of action potentials lasting about 1 sec.

The threshold for driving increased as the AP shortened, and the relative refractory...
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period extended beyond the electrical events of the AP into the diastolic zone. These changes were completely reversed within 30 min. by the return of flowing Ringer solution except in hearts treated with NaIA. Often the duration of the AP increased after such treatment (fig. 3).

Increased external concentrations of potassium caused immediate shortening of AP in surface cells. This was measurable within 1 min. and usually complete in 3 min. except with higher concentrations. In 20 mEq./L. K\textsuperscript{+} the main shortening took place in 5 min. during the first exposure to this concentration of K\textsuperscript{+}, but in subsequent exposures the major changes were complete in 3 min. With intermediate concentrations the AP shortened within 5 min. though a small additional action took place in the next 10 min. Reversal was rapid, with duration and amplitude of the AP returning to two thirds of the initial value in 2 min. The effects of removal of K\textsuperscript{+} were not complete until 20 min. had passed. The action of 60 mEq./L. Na\textsuperscript{+} (using sucrose as an osmotic substitute) was slow, requiring 15 to 20 min. to reduce the AP to a 300 msec. duration. There was, however, great reduction of amplitude when actions of 60 mEq./L. Na\textsuperscript{+} and 20 mEq./L. K\textsuperscript{+} were combined and the shortening of the AP was complete in less than 4 min.

The main difference in effect between K\textsuperscript{+} and low concentrations of the inhibitors used may be summarized: (1) The time course of reduction of the duration of AP (at 1200 msec. cycle length) to one third of initial length was slow with inhibitors and rapid with K\textsuperscript{+}. Low Na\textsuperscript{+} acted more slowly than high K\textsuperscript{+}. (2) There was more reduction in amplitude when actions of 60 mEq./L. Na\textsuperscript{+} and 20 mEq./L. K\textsuperscript{+} were combined and the shortening of the AP was complete in less than 4 min. (3) Reversal of the shortening produced by K\textsuperscript{+} was several times more rapid than from N\textsubscript{2} or low concentrations of inhibitor. Recovery from higher concentrations of inhibitor required more time and was completed only after 30 min. These findings are represented graphically in figure 6 which shows that there is a differential effect of N\textsubscript{2} and low concentrations of inhibitors on the duration rather than on the amplitude of the AP. Iodoacetate seems to have a peculiar influence on the amplitude, which increases as the duration shortens.

Lengthened Action Potentials

Several types of substance produced similar changes in ventricular muscle prolonging the electrical activity (the action potential), raising the threshold to stimulation and lengthening the refractory period. Acridines almost completely ionized at pH 7.2 produced a series of such changes in heart cells. Neomonomerin (5-amino 1-methylacridine) at 0.24 mM. concentration lengthened the AP by 100 to 200 msec. within 5 min. After 40 min. the AP again became shorter but the amplitude was unchanged. The threshold was raised throughout. On washing in Ringer solution the AP instead of decreasing slowly increased and after 20 min. occupied 1050 to 1100 msec. of...
a 1200 msec. cycle. The long AP and high threshold persisted for more than 2 hours. Similar changes were produced by proflavine (2:8 diaminoacridine, 0.1 mM.) and acridine orange (2:8 diaminomethylacridine, 0.02 mM.). These drugs continued to exert their effects even after perfusion with Ringer solution alone was reinstituted. The change in AP duration often reached its maximum of 1100 msec. 45 min. after return to Ringer solution, the tissue remaining visibly stained by the agent. At slower rates of driving the AP often expanded to 1300 to 1500 msec. Frequently there was a 100 to 150 msec. fluctuation in AP duration in successive beats. Double discharges to one stimulus occasionally occurred, the second falling on the long downslope of the AP plateau.

When 2-deoxyglucose (5 mM.) was added to glucose-free Ringer solution the AP was prolonged and the threshold rose within 4 min. The heart failed to follow a drive when the cycle length became less than 500 msec. Addition of 5 mM. glucose shortened the AP and reduced the threshold, and 10 mM. had a greater effect, but complete return to the initial threshold was not obtained (fig. 8). On washing in glucose-free Ringer solution the AP remained longer than it was initially and the threshold did not return to normal for more than 1 hour.

Barbiturates raised the driving threshold. Sodium pentobarbitone (1 mM.) during a 20-minute period gradually prolonged the AP to 1000 to 1050 msec. while the cycle length was held at 1200 msec. This change reversed on washing for 40 min. in Ringer solution. With phenobarbitone and barbitone (1 mM.) an early prolongation of the AP was followed by a reduction in duration.

A final procedure was to compare the effects of inhibitory agents on the long action potential of cardiac cells with their effects on after-potentials of frog skeletal muscle as has been done in part previously.\(^{21}\) It was found that late phases of both cardiac and frog muscle action potential and presumably the associated recovery processes in both respond to K\(^+\), Na\(^+\), N\(_2\), NaN\(_3\), 2:4 DNP, NaIA, and acridines in a similar fashion. Skeletal muscle is not so susceptible to CN as heart muscle, however. The glycolytic reserves of skeletal muscle are greater than those of the heart, and this could account for the difference. In general the heart is more sensitive by a factor of 3 to 5, when sensitivity is judged on the basis of the change in AP produced by DNP, NaN\(_3\), and NaN\(_2\), than is the after-potential of skeletal muscle. With acridines there is close similarity between the 2 repolarization potentials. Both fluctuate in duration in successive beats, after-potential and cardiac AP both fire repetitively on occasion from the long plateau, and return to Ringer solution after application of the dye increases the prolongation of both processes.

**Discussion**

When the normal heart is driven at a rate which reduces cycle length to 600 msec. or lower there is no pause between action potentials. Even at 300 msec. cycles, there is little fall of resting potential. In contrast, when K\(_+\) is raised to 20 mEq./L and the AP at any given rate is shortened, there is a diastolic
pause between action potentials, also the resting potential is reduced to about half the normal value. High K\textsuperscript{+} or low Na\textsuperscript{+} have relatively more effect on AP amplitude than on duration.

The shortening of AP that persists after rapid beating could be due to an accumulation of K\textsuperscript{+}.\textsuperscript{14} There probably would be diffusional reduction of this concentration after 10 to 12 beats. Alternatively both the shortening and lengthening processes could be regarded as due to changes in relative energy resources. In favor of this latter concept is the failure of the N\textsubscript{2} or inhibitor-treated heart cell to recover a normal duration of AP after rapid beating in spite of flowing Ringer solution which should have removed electrolytes rapidly from around the cells. The AP duration, also, remains shorter after a period of fast driving than it was initially. It is not easy to account for this on the basis of K\textsuperscript{+} or Na\textsuperscript{+} changes, nor does the relatively long period of recovery of AP duration after N\textsubscript{2} or inhibitors suggest that a pure K\textsuperscript{+} diffusion theory could account for the observations. Since reversal of the effects of high K\textsuperscript{+} takes place in flowing Ringer solution within 2 min, similar reversal of the shortening of AP of surface cells by inhibitors would be expected. But reversal is slow, or, in the case of NaI\textsubscript{A}, absent. These findings would be consistent with the intervention of an energy dependent process during the plateau\textsuperscript{13} acting presumably immediately within the cell membrane. This could operate through Na\textsuperscript{+} outward and K\textsuperscript{+} inward transport systems or through the metabolic components necessary to sustain the membrane properties of heart cells.

The exact action of the agents used cannot be determined in the living heart. Biochemical analysis of the main actions in vitro suggests that the substances shortening the AP act on oxidative or phosphorylation processes. Anoxia and CN behave similarly and presumably interfere with oxidation. Iodoacetate amongst other actions inhibits triose phosphate dehydrogenase and may prevent acetate oxidation.\textsuperscript{15,16} Azide and DNP uncouple oxidation from phosphorylation and probably hydrolyze ATP or similar high energy phosphates.\textsuperscript{17} All these substances are relatively slow in action and presumably take time to reach the inside of cells, particularly mitochondria.

The partial dependence of the duration of the AP upon resting potential shows well in the action of K\textsuperscript{+}.\textsuperscript{14} With high K\textsuperscript{+} there is an average shortening of the duration by 700 msec. for a 50 mV. fall of AP. This may be compared with 700 msec. shortening for a 15 mV. fall of AP with low DNP, NaN\textsubscript{3} and CN concentrations (fig. 6). Other agents produce even greater divergencies from the K\textsuperscript{+} determined relation of amplitude to duration. When NaI\textsubscript{A} acts upon the heart there is, for instance, an increase of amplitude to 130 mV. with reduction of duration to less than 300 msec. Conversely, acridines and desoxyglucose may double the AP duration with no consistent increase in amplitude at a constant rate of beating. Nor can the resting potential be a major determinant of the normal range of durations of AP since the AP duration varies by a factor of 5 or more with a tempera-

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure7.png}
\caption{Action of acridines. \textbf{A}—Shortening of AP duration from 1200 to 700 to 550 msec. as drive was accelerated. \textbf{B} and after \textbf{C} exposure to 1 mM. 2:8 diaminoacridine (Proflavine) heart could not follow fastest drive and subnormal action potentials occurred. \textbf{D}—Lengthening of AP during exposure to acridine orange (1 & 2) and failure to recover in Ringer solution even after 1 hour (3 & 4).}
\end{figure}
The resemblance between the effects of raised K\textsuperscript{o} and N\textsubscript{2}, NaN\textsubscript{3}, NaIA, DNP, or NaCN may mean that they act on a common chain through the inhibitors have a differentially greater effect on AP duration (fig. 6). The concentration of ions such as K\textsuperscript{+} modifies the hydrolysis of ATP and the contraction of muscle, so that a similar ionic modulation of an energy-dependent process prolonging the AP is possible. During the plateau, outward anion or inward cation movement may be dependent upon external K\textsuperscript{+} influencing oxidative phosphorylation or its local yield of energy. It seems likely that an active transport is imposed upon a basic recovery process of outward diffusion of K\textsuperscript{+} towards its equilibrium potential. The two processes may be artificially dissociated by inhibitors or local anesthetics.

The action of 2-deoxyglucose in 5 mM concentration is difficult to explain. Both threshold and duration of the AP increase. Glucose rapidly reverses most of the effect. It is thought by Wick et al.\textsuperscript{18} that the glycolytic process, particularly the conversion of glucose-6-PO\textsubscript{4} to ketose, is the primary site of action of 2-deoxyglucose in mammals. On the other hand, competition between glucose and its congener at the membrane could occur. The rapid and prolonged action of deoxyglucose suggests a surface mechanism rather than an interference with glycolysis, and the action resembles that of acridines which may attach to the surface. It could be that the piling up of glucose in the cell, inhibits lactate or acetate metabolism. Active glucose transport into red blood cells and probably other tissues like the liver is accompanied by K\textsuperscript{+} immigration and possibly deoxyglucose interferes with K\textsuperscript{+} permeability. At present those concepts do not fit into any consistent scheme.

Those substances prolonging the action potential have been grouped as "stabilizers" by Shanes.\textsuperscript{19} The acridines ionized in physiological fluids have been considered on good grounds by Albert\textsuperscript{20} to act on the cell surface of bacteria. They are quite effective dyes. On the heart cells they probably have a double action in which an early lengthening of the AP is followed by some reversible intracellular inhibition which shortens the AP; then on washing in Ringer solution the residual surface dye effect remains to prolong the action. Reduced outward passage of K\textsuperscript{+} would account for the observed long potentials although other hypotheses such as prolonged Na\textsuperscript{+} permeability must be considered. The early action of dilute DNP in prolonging the AP may be a surface dying effect, which is overcome by later intracellular uncoupling or hydrolysis of ATP.

The high takeoff and relatively long notch of the after-potential of the heated skeletal fibers\textsuperscript{13} suggests comparison of the notch of the after-potential with the plateau of the heart-cell, while the sigmoidal recovery phase of both tissues may be an homologous period of K\textsuperscript{+} permeability.

**Summary**

The behavior of the action potential (AP) of ventricular cells of the frog heart has been examined by varying rate and ionic concentration as well as by adding substances that shorten the AP (N\textsubscript{2}, NaN\textsubscript{3}, 2.4 DNP, NaCN, NaIA) or prolong it (ionized acridines, barbiturates and deoxyglucose) all of which act.
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reversibly, though it is difficult to reverse the effect of iodoacetate. The metabolic inhibitors which in low concentration shorten the AP do so by approximately 700 msec. for a 15 mV. reduction of amplitude, compared with 50 mV. for 700 msec. under the action of K+. Thresholds to electrical stimulation increase and the relative refractory periods are not proportionately reduced as the action potentials are shortened by these compounds. Spontaneous activity likewise develops as these drugs assert their maximum actions. The rate of K0+ action is more rapid than that of NaN3 or 2:4 DNP. It seems unlikely that the effects of the inhibitors are the direct response of the cardiac cell to Ko+ and Na+. The evidence from time-course and differential effect of inhibitors on AP duration suggests that an active ion transport, modulated by Ko+, may be important in maintaining the plateau.

Prolongation of the AP occurs rapidly (within 5 min.) on exposure to ionized acridines, barbiturates and deoxyglucose. Thresholds to stimulation are raised and refractory periods prolonged. The action of acridines is increased by washing in Ringer solution, and persists for hours. A surface action is suggested. There is competition between 2-deoxyglucose and glucose in relation to AP duration.

Finally, it is suggested that there is homology between the after-potential of skeletal muscle and the long action potential of cardiac cells.

**Summario in Interlingua**

Le comportamento del potential de action (PA) del cellulas ventricular del corde del rana esseva examinato per variar le frequentia cardiaca e le concentration ionie del medio de perfusione e etiam per adder substantias que (1) reduce lo PA (i.e. Nn, NaN3, 2:4 dinitrophenol, NaCN, iodoacetato de natrium) o (2) prolonga lo (ionisate acridinas, barbituratos, disoxyglucosa). Le action de omne iste agentes es reversibile. In le caso de iodoacetato, reverter le effectos non es facile. Le inhibitores metabolic que, in basse concentrationes, reduce le PA, face lo per approximativamente 700 msec pro un reduction del amplitude per 15 mV, comparate con 50 mV pro 700 msec sub le action de K+. Le limines pro lo stimulation electric monta e le periodos refractori relative non es reduite proportionalemente quando le PA es acurtata per ille compositos. Etiam un action spontane se disveloppa quando le drogas displica lor efficacia maximal. Le action de K0+ es plus rapido que illo de Na+ o 2:4 dinitrophenol. Il pare paucu probable que lo effecto del inhibitores es le responsa directe del cellula cardica a K+ e Na+.


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