— Original —

Effects of Some Ions and Drugs on the Aconitine-induced Fibrillation of the Purkinje Fibers*

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The effects of some ions and drugs on the aconitine-induced fibrillation and flutter of the isolated mammalian Purkinje fibers were studied from the alteration of transmembrane potentials with intracellular microelectrodes. The concentration of potassium, sodium or calcium ions contained in the perfusing Tyrode solution was varied in the stage of the fibrillation and flutter, and EDTA, tetrodotoxin and propranolol (β -blocker) were added the perfusate and their effects were observed. From the results, the ionic background of the fibrillation was estimated and the differences in nature between the fibrillation induced by aconitine and by other methods were discussed.

CONCERNING the mechanism of cardiac fibrillation, two hypotheses have been put forward: the circus-movement^{24,27} and the ectopic focus hypothesis^{7,14,28,30,31,32}. BURN and his co-workers^{3,5} supported the circus-movement hypothesis from their observations on the atrial fibrillation induced by a high rate of electrical stimulations in the presence of acetylcholine, and pointed out that the occurrence of re-entry of excitation was caused by shortening of the refractory period of cardiac muscle and was an important factor for inducing fibrillation. By means of recording the transmembrane potentials, SANO, TSUCHIHASHI and SHIMAMOTO²⁹ first studied cardiac fibrillation, and then MATSUDA, HOSHI and KAMEYAMA²⁶, SCHMIDT³³, GOTO, TAMAI and YANAGA⁹ and GOTO and TAMAI¹⁰ have investigated aconitine-induced atrial fibrillation in detail. According to these authors, the mechanism of fibrillation can be explained

by one of the following factors: (1) acceleration of the intrinsic pacemaker and depolarization of the cell membrane, (2) formation of multiple tachysystolic ectopic pacemakers, and (3) generation of a local block by interaction of the above two factors.

There is no doubt that, during the appearance and termination of fibrillation, the state of ionic permeability across the excitable membrane is changing fundamentally. HOLLAND and his co-workers^{4,17,18,19,21} have studied the change of ionic movement at the initiation of fibrillation with radioisotopes and presented the data that an increase in both inward and outward fluxes of sodium ions and a consequent decrease in uptake of potassium ions occurred. Many investigators^{2,3,8,12,13,20,26,33}, however, reported more or less different findings, contradicting the isotope studies on the ionic effect on various kinds of fibrillation. The discrepancies might result from the differences in

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the way of inducing fibrillation, the stage of fibrillation studied, or the ionic concentration tested.

This study was carried out to clarify the details of the ionic background of the aconitine-induced fibrillation and flutter on the mammalian Purkinje fibers.

METHODS

The right ventricle obtained from the isolated heart of a young rabbit was used in this experiment. The preparation was fixed in a lucite chamber (50 ml in volume) irrigated with an oxygenated Tyrode solution at a constant rate of flow (10 ml/min) and at a constant temperature (37°C). The solution contained (in mM) NaCl, 147.0; KCl, 2.68; NaH_2PO_4 , 1.5; Na_2HPO_4 , 4.5; MgCl_2 , 0.49; CaCl_2 , 1.8 and glucose, 5.5. The pH of the solution was 7.4 during aeration with 100% O_2 gas.

For inducing flutter and fibrillation of the preparation, aconitine was put into the chamber after stopping the flow of perfusate to give a final concentration of 10^{-6} g/ml.

The influences of several ions on the muscle were observed, during the flutter and fibrillatory stages, by changing the concentration of ions in the perfusing Tyrode solution. In a high potassium solution, the concentration of external potassium used was 10 mM or 20 mM, the tonicity of the solution being kept constant by reducing sodium ions. In a low potassium solution, the potassium was 1.34 mM or completely eliminated. However, in this case, the tonicity of the solution was not adjusted. In a low sodium solution, the sodium was 117.0mM, 72.5mM, or completely excluded, the tonicity being adjusted by adding equiosmolar sucrose. In a high calcium solution, the calcium was 3.6 mM or 9.0mM, sodium ions being reduced, and for a low calcium solution, EDTA of 2.5 mM was simply added.

Fig. 1. The mode of appearance and termination of the aconitine-induced fibrillation in the Purkinje fibers of the rabbit right ventricle. Upper traces (A) show the appearance of fibrillation due to aconitine (10^{-6} g/ml) and lower traces (B), a recovery by washing. Note sudden appearance of flutter and gradual alteration in pattern of the activities and transmembrane potentials. Calibrations: 1 min and 50 mV.

Fig. 2. Effects of a high potassium solution on the transmembrane potentials during the fibrillation. (A): Slow record, and (B): fast records of the membrane potentials. Arrow denotes the time of application of the high potassium solution (20 mM). Note initial acceleration of the fibrillation with a gradual depolarization. Subsequent reduction in the rhythm and in the height of the action potentials and gradual transfer to a cathodal block were observable. Voltage calibration: 50 mV. Time calibrations: 1 min in (A), 5 sec in (B).

Tetrodotoxin (Sankyo Co.) was distilled into the perfusing chamber to give a final concentration of 10^{-7} to 10^{-8} g/ml and propranolol (Inderal, Sumitomo Co.), 10^{-6} g/ml.

Microelectrodes filled with 3M-KCl with a resistance of 20 to 30 megohms were used as recording electrodes and inserted into the false tendon (Purkinje fibers).

Transmembrane potentials of the muscle cells were observed by displaying the features on a cathode-ray oscilloscope with cathode flower type preamplifier and recorded with a conventional long recording camera and an ink-writing oscillograph.

RESULTS

I. The mode of appearance and termination of aconitine-induced fibrillation and flutter of the Purkinje fibers:

About 5 minutes after administration of aconitine flutter was induced in the muscle in which tachysystolic ectopic pacemakers were produced without any noticeable depolarization of the membrane. The action potentials of the fluttering muscle showed characteristic configurations which gradually changed with time. The falling phase of the action potential gradually stabilized at the level of

about -60 mV producing a sustained negativity. Occasionally, a premature excitation, which was spontaneously brought about, elicited a fibrillation. When this fibrillatory activity became continuous, maximum diastolic potential of the cells decreased and finally fixed at the sustained negativity level. During the fibrillatory stage, which continued for a rather short time, the action potentials became gradually abortive and then all activities ceased. After introducing the normal Tyrode solution, slow pacemaker potentials in the muscle, which were quiescent, began to appear and then the fibrillation, with irregular spike discharges, followed and continued for an additional 30 to 60 minutes (Fig. 1).

II. Effects of potassium ions on fibrillation and flutter:

Since the effects of potassium ions on the excitable membrane were known to be influenced by varying the external concentration of calcium ions, the potassium concentration was varied, keeping the calcium content normal in this study.

Fig. 3. Effects of the potassium-free solution on the transmembrane potentials during the fibrillation and flutter. Arrows denote the time of application of the potassium-free solution (0 mM). (A) shows the effects in the fibrillatory stage, and (B), in the fluttering stage. The potassium-free solution recovered the resting potential temporarily to the original level and stopped the fibrillation (A). On the fluttering stage (B), the solution initially inhibited the high rate of firing without altering the resting potential, but later again increased the rate and brought about a sudden depolarization and a cathodal block. Calibrations: 1 min and 50 mV.

1) Effects of high potassium Tyrode solution :

When the high potassium (10 mM) Tyrode solution was applied at the state of fibrillation on the Purkinje fibers, the fibrillatory activity was promoted with gradual depolarization on the cell membrane from the sustained negativity level. Later, the generation of action potential was inhibited, the height of the action potential fell and the rate of discharge was reduced. Finally, the membrane activity ceased at a certain depolarized level. These results show that an inhibition of pacemaker activity in the fibrillating muscle is brought about at the final stage of the effect of excessive potassium ions, and also that a block is produced by the depolarization of the membrane. Excessive potassium ions of 20 mM effecting representative action is shown in Fig. 2.

2) Effects of low potassium Tyrode solution :

During aconitine-induced fibrillation of the Purkinje fibers, potassium-deficient (1.34 mM) Tyrode solution applied at the fibrillatory stage repolarized the membrane to the original

level, increased the amplitude of the action potential and induced a recovery of the regular rhythm. On the other hand, the low potassium Tyrode solution applied at the fluttering stage reduced only the firing rate without altering the amplitude of the resting and the action potentials and made a sinus rhythm.

However, in the case of perfusion of the Tyrode solution without any potassium ions, the sinus rhythm was accelerated and gradually shifted again to a fluttering rhythm. Then, the solution produced a sustained depolarization of the membrane, initiating fibrillation, and finally produced a complete cathodal block (Fig. 3). Based on these findings, the following conclusions were drawn: a solution of moderately low concentration of potassium ions inhibited the aconitine-induced fibrillation due to the stabilizing action on the membrane, but a solution containing extremely low concentration inhibited the permeability of the myocardial cell membrane to potassium ions and brought about the depolarization of the

Fig. 4. Effects of a sodium-deficient solution on the transmembrane potentials during the fibrillation. (A): Slow record. Arrow denotes the time of application of the sodium-deficient solution (58.5 mM). Note polarization of the membrane to the normal level inhibiting the fibrillation and increase in the height of the action potentials. (B): Fast record of the membrane potentials before application of the test solution. (C): The same but after the application. Calibrations: 1 min and 50 mV in (A), and 1 sec and 50 mV in (B) and (C).

Fig. 5. Effects of a sodium-deficient solution on the transmembrane potentials during the flutter. Arrow denotes the time of application of the sodium-deficient solution (58.5 mM). Note decrease in the rate of firing without altering the resting potential and appearance of intermittent activity of the membrane. Calibrations: 1 min and 50 mV.

membrane, producing a cathodal block in the muscle.

III. Effects of sodium ions on fibrillation and flutter:

It is conceivable that reduction of sodium ions in the external fluid suppresses the influx

of sodium ions, while aconitine enhances it. As expected, a low sodium Tyrode solution inhibited the aconitine-induced fibrillation (Fig. 4). The resting potential rose and the amplitude of the action potential increased, recovering a regular rhythm. In the fluttering stage the high rate of regular activity of the mem-

Fig. 6. Effects of a high calcium solution on the transmembrane potentials during the fibrillation. (A) shows changes of the membrane potentials after application of the high calcium solution (9.0 mM) in slow record. Calibrations: 1 min and 50 mV. (B) shows the changes in fast record. The uppermost trace is fibrillation before application of the test solution. The middle and the lower most ones show changes of the membrane potentials after application. Note polarization of the membrane to the normal level, decrease in the rate of firing and intermittent activity of the membrane accompanied by special pattern of the action potentials. Calibrations: 5 sec and 50 mV.

brane was depressed by a low sodium Tyrode solution without altering the resting potential. In this case, it was noticeable that high-and-low-frequency discharges or conduction blocks occurred intermittently (Fig. 5). These phenomena are most likely due to a decrease in threshold potential produced by the low sodium solution.

IV. Effects of calcium ions on fibrillation and flutter:

Calcium ions affect the membrane permeability to other ions (sodium and potassium in particular¹⁵), and exert complicated effects on the activity of the myocardial cell membrane. The effect of the changes in calcium concentration on the excitable membrane may be influenced by the concentration of potassium ions, since it is reported that the value of the

calcium-and-potassium ratio in the solution was directly related to the rate of fibrillation of the heart^{5, 20, 23}. The present author observed the effect of varying the concentration of calcium ions on the aconitine-induced fibrillation, keeping the concentration of potassium ions normal.

1) Effects of high calcium Tyrode solution:

Perfusion with a high calcium solution stopped the aconitine-induced fibrillation of the Purkinje fibers of the rabbit ventricle. MATSUDA et al.²⁶ and SCHMIDT³³ described the similar inhibitory effect of calcium ions on the aconitine-induced fibrillation of the dog ventricular muscle.

In the high calcium (9.0 mM) Tyrode solution, the membrane potential recovered from the depolarized state during fibrillation and increased up to the original level. The amplitude of the

Fig. 7. Effects of EDTA on the transmembrane potentials during the fibrillation. Arrow denotes the time of administration of EDTA (2.5 mM) distilled in the perfusate. (A) and (B) show a series of changes in the membrane potentials after administration of EDTA. Note depolarization and transient acceleration of fibrillation and generation of spike-like repolarizations from the completely depolarized level. Calibrations: 1 min and 50 mV.

action potential increased and the high rate of firing was depressed, restoring a regular rhythm. In this case, also, high-and-low-frequency discharges, or conduction blocks, of the membrane activity occurred intermittently, probably because of some decrease in the threshold potential caused by raising the calcium ion content (Fig. 6).

2) Effects of low calcium Tyrode solution and EDTA :

It is generally thought that reduction of external calcium ions facilitates fibrillation by lowering the threshold and producing depolarization of the membrane. Under the action of aconitine, also, the equimolar concentration of EDTA to that of calcium ions (2.5 mM) produced a depolarization of the fluttering membrane by which fibrillation was initiated. A conspicuous prolongation of the duration of the action potential that occurred subsequently, reduced the firing rhythm. But later a stage appeared in which spike-like repolarization occurred as if the spike was generated reversely from a completely depolarized level (0 mV). The generation of these spikes became gradually irregular and made a pattern of the so-called

reversal type of fibrillation. Finally, all membrane activities ceased at the completely depolarized level (Figs. 7 and 8). The remarkable prolongation of the plateau of the action potential may be a specific effect of EDTA on the myocardial cell, since this phenomenon was also observable in the absence of aconitine¹.

V. Effects of tetrodotoxin on fibrillation and flutter :

It is generally accepted that tetrodotoxin has a specific inactivating action on the sodium-carrier system. As can be expected the drug showed almost the same inhibitory effect as sodium-deficient solution did on the aconitine-induced fibrillation of the Purkinje fibers. Repolarization of the membrane to the original resting level, increase in height of the action potential, reduction of firing rate, and intermittent activity of the membrane were produced under the action of the drug (10^{-7} to 10^{-8} g/ml). A highly toxic dose of 10^{-6} g/ml blocked membrane activity. A suitable dose of this drug for inhibiting the aconitine-induced fibrillation of the Purkinje fibers was found to be 10^{-7} to 10^{-8} g/ml (Figs. 9 and 10).

Fig. 8. Effects of EDTA (2.5 mM). Faster records than those of Fig. 7. (A) shows the fibrillatory membrane potentials before administration of EDTA. (B) shows a series of changes of the membrane potentials after administration. a, 3 min; b, 4 min; c, 5 min; d, 8 min; e, 10 min after administration of the drug. Calibrations: 5 sec and 50 mV.

VI. Effects of propranolol (Inderal) on fibrillation:

This drug, which is known as a β -blocking agent, acts essentially by inactivating the sodium-carrier system^{34,36}. However, the effect of this drug on the aconitine-induced fibrillation was markedly different from that of tetrodotoxin. Propranolol (10^{-6} g/ml) depressed only the rapid rate of firing without affecting the irregularity in height and rhythm of the action potentials or the size of the resting potential (Fig. 11). As mentioned, tetrodotoxin restored not only the nearly normal resting potential, but also the regularity in amplitude of the action potential. Thus, propranolol did not always produce an ideal inhibitory effect on the fibrillation. In addition, the effect of the

Fig. 9. Effects of tetrodotoxin on the transmembrane potentials during the fibrillation. The uppermost trace shows fibrillatory stage before administration of tetrodotoxin. The lower ones show a series of changes of the membrane potentials affected by tetrodotoxin (10^{-7} g/ml). Note polarization of the membrane to the normal level, decrease in the rate of firing and intermittent activity of the membrane. Calibrations: 1 min and 50 mV.

drug was easily reversible.

DISCUSSION

GRUMBACH, HOWARD and MERRILL¹³ studied the fibrillation induced by a potassium-free Tyrode solution, and ARMITAGE, BURN and GUNNING^{2,3} studied the fibrillation induced by high frequencies of electrical stimulation in the presence of acetylcholine. They came to similar conclusions about ionic effect on fibrillation. In the present study of the aconitine-

Fig. 10. Effects of tetrodotoxin (10^{-8} g/ml) on the transmembrane potentials during the fibrillation. Note increase in the resting potential, decrease in the rate of firing and disappearance of the fibrillation. Calibrations: 500 msec and 50 mV.

Fig. 11. Effects of propranolol (Inderal) on the transmembrane potentials during the fibrillation. The arrow in the uppermost trace denotes the time of administration of the drug (10^{-6} g/ml) and the arrow in the middle trace, the time of washing. The lowermost trace shows the fibrillation reproduced after the washing. Inhibition of the rapid rate of firing without alteration of the resting potential and retention of irregularity in the rhythm and the height of the action potentials were observable under the action of the drug. Calibrations: 1 min and 50 mV.

induced fibrillation, however, the effects of exogenous ions were shown to be quite opposite to those observed by the authors mentioned above.

The serious discrepancies strongly suggest that the aconitine-induced fibrillation is entirely different in nature, or in mechanism of ap-

pearance, from the other kinds of fibrillation. In connection with this, it should be noticed that an important factor in the generation of fibrillation by electrical stimulation in the presence of acetylcholine is the initiation of re-entry of excitation of the heart muscle which resulted from shortening the refractory period

in the acetylcholine and high frequencies of electrical stimulation⁵. In that case, pacemaker activity of the membrane has been suppressed by acetylcholine. On the contrary, spontaneous acceleration of pacemaker activity and formation of ectopic pacemakers have played important roles in the generation of aconitine-induced fibrillation¹⁰.

1) On the effect of potassium ions :

GRUMBACH, HOWARD and MERRILL¹³ demonstrated that potassium free-induced fibrillation of heart muscle stopped when the external concentration of potassium ions was restored to normal. BURN⁵ also showed that the generation of acetylcholine-induced fibrillation was accelerated in proportion to the grade of potassium deficiency and suppressed by a rising concentration of potassium ions. They believed that the initiation of fibrillation resulted from an increase in the net-loss of potassium out of the myocardial cell caused by an increase in the efflux of potassium ions across the cell membrane³.

On the other hand, HOLLAND and his co-workers^{4, 18, 19, 21}, from the studies with radioisotopes on acetylcholine-induced fibrillation, concluded that fibrillation was produced at a time when transmembrane flux of sodium and potassium ions exceeded a critical value. Further, they clarified that a net loss of potassium was secondary to the increase in the influx of sodium ions which was greater than that in the efflux across the membrane²¹. Based on these findings, the inhibitory effect of a high potassium solution on fibrillation may be considered due primarily to the depression of inward movement of sodium ions and secondarily to the increase in the net entry of potassium.

According to knowledge of ionic current across the membrane during action potential, an increase in conductance of potassium ions induced by external high potassium concentration produces a shortening of action potential¹⁵ which promotes re-entry of excitation in the myocardium¹⁶ and elicits a depolarization of the cell membrane, which accelerates its excitability. While, in this experiment, high potassium reduced the rapid rate of firing discharges of the fibrillating muscle after an

initial transient acceleration of the fibrillation (Fig. 2). This may be due to the dominant effect of a depression of the inward movement of sodium ions, which leads to suppression of pacemaker activity rather than to shortening of the action potential duration. And this observation coincides well with that of DE MELLO¹⁵ that external concentration of potassium ions in 20 to 22 mM inhibited pacemaker activity. Thus, a high potassium solution has two opposite effects on the fibrillation; the inhibitory effect due to suppression of the pacemaker activity on one hand, and the accelerative effect due to shortening of the action potential duration or depolarization of the membrane, on the other.

Low potassium solution had a transient inhibitory effect on the aconitine-induced fibrillation, which possibly resulted from an increase in the resting potential and from a stabilizing action on the membrane. However, as shown in Fig. 3, potassium-free Tyrode solution altered the membrane activity to a higher rhythm. This means an appearance of the final effect of the potassium-free solution. DE MELLO¹⁵ has noted that pacemaker activity was rather accelerated below 0.5 mM of external potassium ions. The result in this report is well in accord with his observation.

In conclusion, it is quite possible that the generation of potassium free-induced fibrillation is due to the acceleration of pacemaker activity, while the inhibitory effect of potassium-deficient solution on the aconitine-induced fibrillation is chiefly due to the increase in the membrane polarization.

2) On the effects of sodium ions :

Deficiency of external sodium ions has been reported to have a promoting action on the fibrillation induced by potassium deficiency²⁰ and by high frequencies of electrical stimulation in the presence of acetylcholine³. On the contrary, the same kind of low sodium solution is known to stop the fibrillation induced by rapid injection of epinephrine¹² or by aconitine^{26, 33}. Since the latter type of fibrillations is regarded to be produced by some ectopic pacemakers which were generated by an increase in permeability of sodium ions across the cell membrane¹⁰, low sodium may reduce the inward

movement of sodium ions and prevent the generation of an action potential in the ectopic focus. The result in this report on the aconitine-induced fibrillation appeared fully in accord with these estimations.

On the other hand, the reason why the fibrillation induced by a potassium-free solution or high frequencies of electrical stimulation in the presence of acetylcholine is facilitated by a low sodium solution^{3,20} is uncertain; however, it may be partly explained by a ready occurrence of the re-entry of excitation caused by a shortening of the action potential⁶ and an appearance of the delay of excitation conduction, or a local block due to sodium deficiency⁶.

3) On the effects of tetrodotoxin and propranolol :

Tetrodotoxin has an inactivating action on the sodium-carrier system of the membrane, and it has been reported that propranolol (β -blocking agent) has the same action on the sodium-carrier system as tetrodotoxin^{34,36}.

KURIYAMA *et al.*²² showed that tetrodotoxin (10^{-7} g/ml) antagonized the aconitine-induced fibrillation of a guinea pig atria. The present study confirmed that application of 10^{-7} to 10^{-8} g/ml of tetrodotoxin inhibited the aconitine-induced fibrillation of the Purkinje fibers of rabbit ventricle. The mode of the inhibitory effect of tetrodotoxin was similar to that of a sodium-deficient Tyrode solution (Figs. 9 and 10). On the other hand, propranolol has been used clinically for stopping fibrillation of the heart, arrhythmias during digitalization in particular, since it was found that the β -blocking agent was effective on irregular activity of the heart³⁷. However, in the author's experiment on the aconitine-induced fibrillation, propranolol merely depressed the rapid rate of activity and left unchanged the irregularities in the firing rhythm and in the height of the action potential. Meanwhile, tetrodotoxin changed a fibrillatory rhythm to a regular sinus rhythm. The different actions of these two drugs might be due to some differences in administered dosage, or in sensitivity of the Purkinje fibers to these substances. But it is likely that both drugs depressed the firing rate and the spike generation in the ectopic focus owing to inhibition of permeability of sodium

ions which was accelerated preliminarily by aconitine.

4) On the effects of calcium ions :

The effect of calcium ions on the normal excitable membrane is very complicated, i.e. the direct action on the cell membrane, influences on permeability of sodium ions, and antagonism to the action of potassium ions¹⁵. The relation of calcium ions to fibrillation will be undoubtedly more complex. ARMITAGE *et al.*² showed that varying external concentrations of calcium ions gave double roles to the initiation of the atrial fibrillation induced by electrical stimulations in the presence of acetylcholine. They reported that the fibrillation never occurred in the absence of calcium ions, and then, as the concentration rose the percentage of initiation of fibrillation increased and showed maximum value in 0.75 and 4.4 mM of concentration of calcium ions, while minimum value, in 2.2 mM².

On the other hand, concerning the fibrillation induced by potassium-free solution, GRUMBACH *et al.*¹³ suggested that value of the calcium-and-potassium ratio was related to the initiation of fibrillation, and that a high calcium solution promoted the occurrence of fibrillation, and the perfusate with low calcium ions reduced it. Later, this suggestion was supported by KÄRKI²⁰ but denied by GETTS *et al.*⁸ But they reported a common observation that a high calcium solution promoted the occurrence of fibrillation, and a low calcium solution reduced it. How the fibrillation is initiated in a high calcium solution can be explained as follows: in the solution some delay of conduction velocity¹⁶ and a local block¹⁶ in the muscle take place due to decrease in the threshold potential³⁸, and the functional refractory period is shortened by a high calcium solution³⁵ which easily leads to re-entry of excitation.

On the contrary, the observation that a low calcium solution reduces fibrillation is explicable by rare occurrence of a conduction block⁸ as well as a prolongation of the refractory period of the heart muscle¹⁵. However, detailed studies on the effect of calcium ions on the frog heart by NIEDERGERKE²⁵ revealed that duration of action potential was longest in a normal concentration of calcium ions. According to

this finding, the observation by ARMITAGE *et al.*³ and BURN that the occurrence of fibrillation was reduced in a normal calcium concentration (2.2 mM) can be explained.

Meanwhile, aconitine-induced fibrillation of the Purkinje fibers was inhibited by a high calcium Tyrode solution as shown in this report (Fig. 6). The discrepancies in results between different investigators also are probably due to different ways of inducing fibrillation. As mentioned earlier, important factors of the initiation of fibrillation by aconitine are depolarization of the membrane, increase in permeability of sodium ions across the membrane, and formation of ectopic pacemakes. Therefore, the inhibitory effect of a high calcium solution on the fibrillation may result primarily from an increase in the resting potential (a stabilizing action on the cell membrane) and decrease in the threshold potential. The other aspects of the effect may be a reduction of inward movement of sodium ions and a prevention of spike generation in the ectopic focus. Conversely, the accelerative effect of low calcium on the fibrillation is explained by an increase in the threshold potential³⁸ and depolarization on the membrane.

SUMMARY

1) The effects of some ions and drugs on the aconitine-induced fibrillation and flutter were studied with intracellular micro-electrodes in Purkinje fibers of young rabbits.

2) Generally, deficiency of sodium or potassium ions and excess of calcium ions all inhibited the aconitine-induced fibrillation, by polarizing the membrane toward normal level and depressing the high rate of discharges.

3) A moderate lack of potassium ions in the solution recovered the fibrillation to a stage of flutter, but a complete elimination of potassium ions in the solution inhibited the high rate of firing of the fibrillation but gradually produced a cathodal block.

4) EDTA showed peculiar triphasic actions on the aconitine-induced fibrillation: an inhibitory effect by lengthening the duration of action potential, a production of abortive activities at slightly depolarized level, and then a generation of reversal type of fibrillation from

a completely depolarized level.

5) Tetrodotoxin and propranolol (Inderal) both depressed the high rate of discharges. The former showed a typical antifibrillatory action by polarizing the membrane. The latter, however, neither caused the polarization nor the inhibition of the irregularity in rhythm and height of the action potentials.

6) The differences in nature between the aconitine-induced fibrillation and the potassium-free-, acetylcholine-induced fibrillation were discussed.

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