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THE INFLUENCE OF POTASSIUM CONCENTRATION ON THE ACTION OF QUINIDINE AND OF SOME ANTI-MALARIAL SUBSTANCES ON CARDIAC MUSCLE

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The action of quinidine and some other antimalarial substances on cardiac muscle has been shown to be closely related to the K^+ concentration of the surrounding medium. The depression of the amplitude and rate of the contractions of the isolated perfused rabbit heart and of the isolated rabbit atria which the antimalarial substances produced seems to be due to a diminution of the permeability of the membrane to K^+, since it can be reversed by lowering the external K^+ concentration. During exposure to any of the antimalarial compounds tested, the normal inhibitory action of acetylcholine was converted to a stimulant action. This stimulant action of acetylcholine is probably due to its effect in increasing the permeability of the membrane to K^+. There were slight differences in behaviour between proguanil and quinidine on the one hand, and chloroquine, mepacrine and pyrimethamine on the other. The observations may explain the action of quinidine-like substances in abolishing fibrillation.

The experiments to be described in this paper resulted from an observation made while investigating the action of atropine on ventricular fibrillation induced in the isolated rabbit heart. Atropine sulphate perfused through the coronary vessels of the normally beating heart in a concentration of 10^{-6} g./ml. caused a large reduction in the amplitude of beat, but when perfused through the heart in a solution containing one half the normal potassium it had no such effect. Furthermore, the depression produced by atropine when the K^+ concentration was normal could be reversed by changing to a fluid containing half the normal potassium.

Observations were then made to see if the action of quinidine on the isolated perfused heart and on the isolated atria was affected in the same way by reducing the K^+ concentration. A study was also made of the action of chloroquine, mepacrine, proguanil, and pyrimethamine.

The actions of proguanil and quinidine on isolated rabbit atria, particularly their antagonism to acetylcholine, have already been described in detail (Burn and Vane, 1949; Briscoe and Burn, 1954). Two entirely unrelated antimalarials apparently antagonized the action of acetylcholine in the same way and changed the action of acetylcholine on the atria from the usual inhibitory action to a stimulant one. Experiments were therefore made to see if chloroquine, mepacrine and pyrimethamine, which all possessed a quinidine-like action on the isolated electrically-driven rabbit atria, showed similar antagonism.

METHODS

Isolated Perfused Rabbit Heart.—The heart was removed from a freshly killed rabbit and perfused with Locke solution at 36–37° C. by the Langendorff method. A record was taken of the amplitude of the ventricular contractions. Normal Locke solution, containing NaCl 9.0 g., KCl 0.42 g., $CaCl_2$ 0.2 g., dextrose 1.0 g., $NaHCO_3$ 0.5 g., distilled water to 1,000 ml., was used for all experiments except those on atropine, when a slightly modified solution described by McEwen (1956) was used.

Isolated Rabbit Atria.—The atria were carefully dissected from ventricular muscle and as much fat and connective tissue as possible removed, particular care being taken to avoid damage to the atria in the pacemaker region. They were suspended in Locke solution containing twice the normal quantity of dextrose at 29° C., in a bath of 35 ml. capacity. Contractions were recorded by a straw lever, the natural frequency of which was much greater than the highest rate of contraction.

RESULTS

Isolated Perfused Rabbit Heart.—The effect of adding atropine sulphate (10^{-6} g./ml.) to the Locke solution perfusing an isolated rabbit heart is shown in Fig. 1. The ventricular contractions were diminished in amplitude to a small fraction of their initial size in the course of 2–3 min.

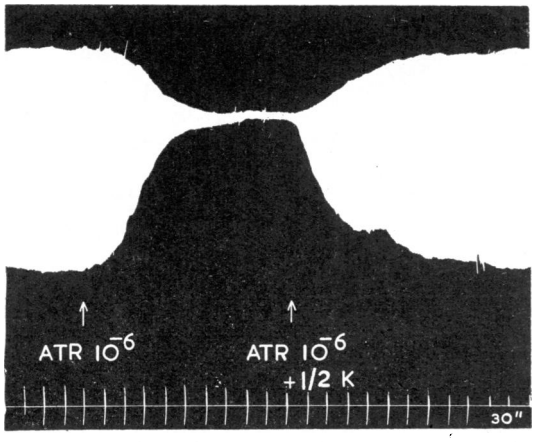

FIG. 1.—Contractions of isolated rabbit heart perfused by the Langendorff method. Record shows the effect of perfusing the heart with atropine 10^{-6} g./ml. in normal McEwen's solution. The amplitude was reduced to negligible proportions, but this depression was fully reversed on changing the perfusion fluid to McEwen's solution containing half the normal K^+.

When the perfusion fluid was changed to one containing half the K^+ concentration, but otherwise the same, this diminution was almost completely abolished.

Similar results were obtained with quinidine as shown in Fig. 2. Quinidine sulphate 3×10^{-5} g./ml. was added to the Locke solution and perfused through the heart. The amplitude was diminished as shown. The injection of 50 μg. and 100 μg. acetylcholine (ACh) into the cannula caused a very slight increase in the amplitude, and then a change to a perfusion fluid with one quarter the normal K^+ concentration produced complete recovery.

In another experiment, mepacrine hydrochloride in a concentration of 10^{-5} g./ml. reduced the amplitude and rate; this effect was abolished, though only partially, on changing to a perfusion fluid containing one quarter the concentration of K^+.

The action of chloroquine, proguanil and pyrimethamine on the isolated perfused rabbit heart was not investigated.

Isolated Rabbit Atria.—The action of quinidine on the isolated atria is clearly illustrated in Fig. 3. 0.5 mg. quinidine produced a gradual reduction in amplitude and rate. After 24 min. the beat was almost arrested, but on changing the fluid in the bath to quinidine in Locke solution containing a quarter the normal K^+ concentration, the amplitude and rate rapidly improved and became greater than at the beginning of the experiment. When conditions were steady, the bath fluid was changed back to Locke solution containing the normal K^+ concentration and the beat was arrested 12 min. later. The beat started again when the K^+ in the external medium was lowered to a quarter of the normal amount.

Pyrimethamine behaved in a similar way to quinidine. Fig. 4 shows the action of 1 mg. pyrimethamine in arresting the contractions of the atria in 15 min. and the beat restarting on changing the bath fluid to pyrimethamine in Locke solution containing a quarter the normal K^+ concentration. In section (c) after 10 min. exposure to the low K^+ concentration, when the amplitude was still small, 0.2 mg. acetylcholine caused a large increase in amplitude.

The depressant effect of chloroquine and mepacrine was also partly abolished by reducing the K^+ concentration of the solution. This is illustrated for chloroquine in Fig. 5. The longer these substances were left in the bath, the more difficult it was to reverse their effect, and when once the beat was arrested a good recovery was never

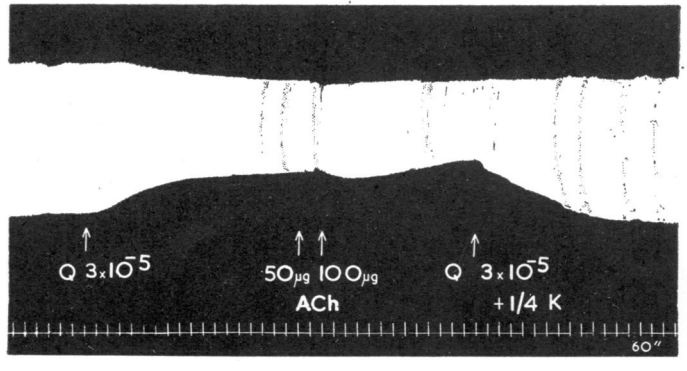

FIG. 2.—Record as in Fig. 1. The first part of the record shows the depressant effect of quinidine 3×10^{-5} g./ml. in normal Locke solution. In the presence of the quinidine, 100 μg. acetylcholine is seen to have first an inhibitory effect followed by a slight stimulant effect. On changing the perfusion fluid to one containing one quarter of the normal K^+, the amplitude returned to its original level.

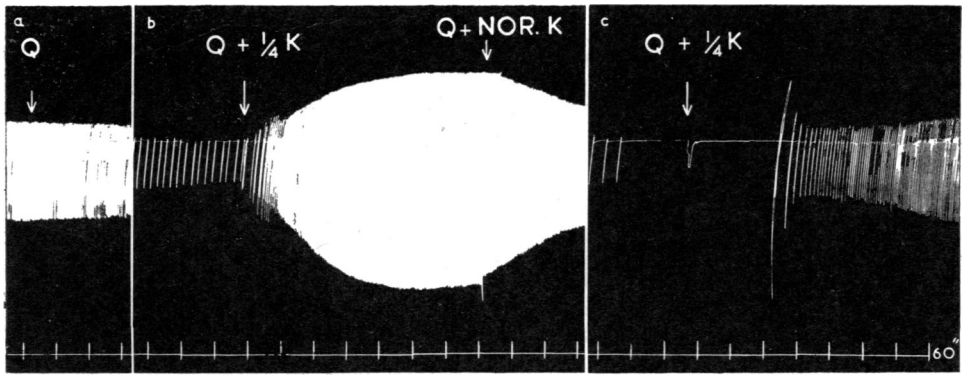

FIG. 3.—Spontaneous contractions of isolated rabbit atria in a 35 ml. bath at 29° C. (a) At Q, 0·5 mg. quinidine in normal Locke solution. (b) 24 min. later, at first arrow, bath fluid changed to Locke solution containing one quarter of the normal K^+ but the same concentration of quinidine. At second arrow, bath fluid changed again to normal Locke solution + quinidine. (c) 12 min. later, the beat was arrested, but started again when the K^+ concentration in the external medium was lowered to one quarter.

obtained merely by lowering the K^+ concentration.

In three trials on two atria, the depression produced by proguanil (10^{-4} g./ml.) could not be reversed by lowering the K^+ concentration, either before or after the beat had stopped. In this respect, proguanil differed from the other antimalarial compounds tested.

Antagonism of Antimalarials by Acetylcholine.—From observations on 18 atria, it was found that chloroquine, mepacrine, and pyrimethamine, when added to the Locke solution in which the atria were beating, reduced the amplitude and rate of beat. In sufficient dose, each antimalarial compound arrested the beat within 5 to 60 min. Doses of 0.5–1.0 mg. of mepacrine or pyrimethamine in a 35 ml. bath generally arrested the beat after about 30 min. Chloroquine was less active, and a dose of about 4 mg. was required to arrest the beat in a similar time. There was usually a gradual diminution in amplitude and rate of beat during exposure to chloroquine, mepacrine and pyrimethamine. In this behaviour, they differed from proguanil, which usually arrested the beat suddenly.

After arrest by proguanil or quinidine, addition of acetylcholine always restarted the atrial contractions. After arrest by chloroquine, mepacrine,

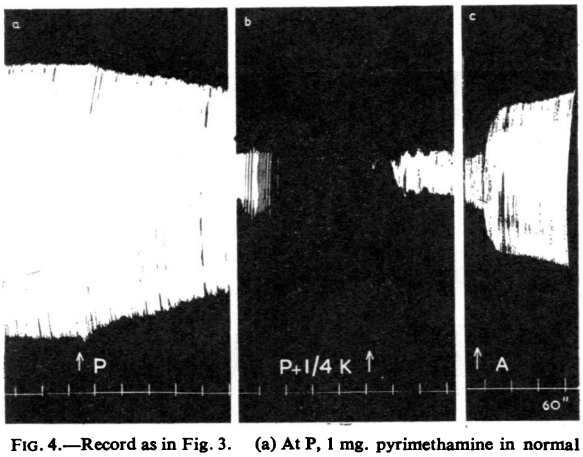

FIG. 4.—Record as in Fig. 3. (a) At P, 1 mg. pyrimethamine in normal Locke solution. (b) 15 min. later, beat arrested, but restarted on changing bath fluid to Locke solution containing one quarter of the normal K^+, but with the same concentration of pyrimethamine. (c) 10 min. later at A, 0·2 mg. acetylcholine. Note large increase in amplitude.

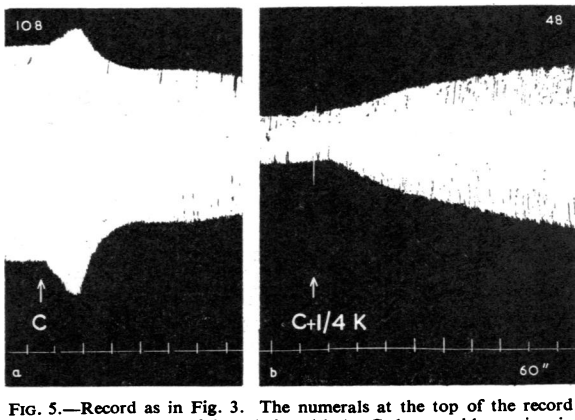

FIG. 5.—Record as in Fig. 3. The numerals at the top of the record are the number of beats/min. (a) At C, 1 mg. chloroquine in normal Locke solution. (b) 20 min. later, amplitude and rate greatly depressed. Bath fluid changed to Locke solution containing one quarter of the normal K^+, but the same concentration of chloroquine.

or pyrimethamine, however, addition of acetylcholine restored the beat in only one out of eight attempts with pyrimethamine, two out of six attempts with mepacrine and none out of three attempts with chloroquine. If the drug was first removed from the bath, acetylcholine always restarted the contractions. That the acetylcholine was responsible and not the removal of the antimalarial compound was shown by the fact that, when the acetylcholine was removed by washing out the bath, the beat was sometimes arrested again.

Before the contractions were arrested, a dose of acetylcholine which had initially caused a considerable reduction in amplitude and rate was usually without effect 10 min. after the addition of chloroquine, mepacrine, or pyrimethamine in a concentration of 10^{-5} to 3×10^{-5} g./ml. After a longer period, acetylcholine was usually observed to increase the size of the atrial contractions as shown in Fig. 6. This abolition of the inhibitory action of acetylcholine followed by conversion to a stimulant action under the influence of chloroquine, mepacrine, and pyrimethamine was identical with the behaviour of proguanil and quinidine.

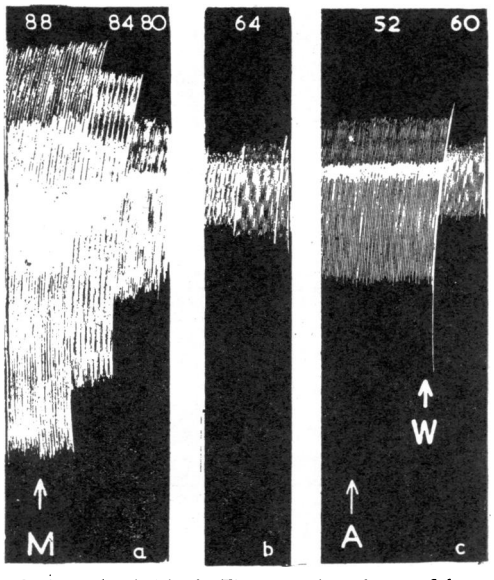

FIG. 6.—Record as in Fig. 3. The numerals at the top of the record are the number of beats/min. (a) At M, 0·7 mg. mepacrine. Amplitude and rate reduced. Rates after 5 and 10 min. (b) Half an hour later. Amplitude and rate further reduced but beat not arrested. (c) 0·6 mg. acetylcholine was added to the bath over 15 min. The last 0·1 mg. was added at A. Amplitude increased and rate hardly affected by this amount of acetylcholine. After change of bath fluid at W, amplitude and rate returned to those shown in (b).

DISCUSSION

When atropine, quinidine or mepacrine were added to the fluid perfusing the isolated rabbit heart, the amplitude was greatly diminished, and quinidine and mepacrine in addition slowed the rate. When the concentration of K^+ in the fluid was reduced these effects were reversed. Similar observations were made on isolated atria after adding either quinidine, pyrimethamine, chloroquine or mepacrine to the bath. The amplitude of beat was reduced, but the effect was reversed on changing to a fluid with a lower concentration of K^+.

During contraction potassium passes out of the cell through the depolarized and permeable cell membrane by diffusion. The foregoing observations suggest that, when perfused through the heart or when acting on the atria, quinidine renders the cell membrane less permeable to potassium ions. In consequence the efflux of K^+ is diminished and repolarization therefore becomes less and less complete. For when the external concentration of K^+ is lowered to one-half or one-quarter, the gradient for the efflux of K^+ is increased, and this compensates for the effect of quinidine. Such an explanation of the action of quinidine serves also to explain the action of acetylcholine in restarting the contractions of atria arrested by quinidine. Burgen and Terroux (1953) and Hoffman and Suckling (1953) showed that the action potential of the isolated atria was characterized by a slow rate of repolarization, and that this rate was accelerated by acetylcholine. Burgen and Terroux suggested that acetylcholine facilitated the efflux of K^+, presumably by making the membrane more permeable to K^+, and such an increased permeability has now been observed by Harris and Hutter (1956) using radioactive K^+. The stimulant action of acetylcholine in restarting the contractions when they have been arrested by quinidine is thus explained by its action in increasing the permeability to K^+.

Pyrimethamine, chloroquine and mepacrine exerted a similar depressant effect on the atrial contractions which was also reversed by changing to a fluid low in K^+. The depression caused by proguanil was not reversed in this way; but this depression, even when it proceeded as far as arrest, was always reversed by acetylcholine. Atria arrested by proguanil were shown by Burn and Vane (1949) to respond to electrical stimulation. In the present experiments it was found that, after arrest by chloroquine, mepacrine or pyrimethamine, the atria did not respond to electrical

stimulation, but after arrest by quinidine they usually did respond. Thus the evidence indicates that while the action of proguanil and quinidine may differ somewhat from that of the other substances, a diminution in the permeability of the membrane to potassium is largely responsible for causing arrest of the atria.

The particular interest of these findings lies in their application to the use of quinidine in fibrillation. Both in atrial and in ventricular fibrillation there is an increased efflux of K^+. In ventricular fibrillation of the isolated rabbit heart this has been directly observed (Armitage, Burn, and Gunning, 1957). In atrial fibrillation it is suggested by the fact that this fibrillation is arrested when the plasma K^+ concentration is gradually raised (Burn, Gunning, and Walker, 1956). This appears to be the first time that atrial fibrillation has been arrested by raising the external K^+ concentration. It is interesting to note, however, that the use of injections of potassium salts (0.1% KCl solution) in arresting ventricular fibrillation was described by Hering as long ago as 1903. The action of quinidine in arresting fibrillation may therefore be due to its effect in diminishng the permeability of the cell membrane to K^+, and thus lessening the efflux of K^+.

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