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THE STABILIZING ACTION OF CHLORPROMAZINE ON AMPHIBIAN HEART

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Since the elaborate work has been performed by *Courboisier* and his co-workers (5), many investigators have described the pharmacological action of chlorpromazine. Most of these works have been preformed on central nervous system and its depressant action has been unanimously mentioned.

In addition to these reports, the action on the circulatory system has been studied by various investigators. According to these workers, chlorpromazine dilatates the peripheral blood vessel (5,6,7,8,) and acts on the heart muscle as a stabilizing agent (6). Furthermore some authors point out that the stabilizing action can be naturally expected (5,14), because chlorpromazine possesses pharmacologically similar properties as quinidine. In fact, not only on the heart muscle, but also on the striated muscle or on the smooth muscle, the lowering of motility by the administration of chlorpromazine has been described by some authors (13,14). However, on the mechanism concerning with the stabilizing action of chlorpromazine, any distinct conclusion has not been obtained.

The present investigation was performed on the purpose of elucidating its stabilizing action by observing the changes of contraction curve of perfused heart and the electrorophysiological features of single fibre of isolated heart muscle with the aid of microelectrode technique.

METHOD

All the experiments were performed on the excised heart of Japanese toad. In order to examine the changes of contraction force and beating frequency, the contraction curve was drawn on the smoked drum by means of the perfusing method after Yagi-Haltung. The changes of electrophysiological features were examined with microelectrode techique and both resting and action potential were photographed on the double beam oscilloscope. The membrane potential was separately recorded from atrial muscle and the sinus region.

RESULTS

1. Mechanical contraction curve

When chlorpromazine is applied to the regularly beating heart, any effects

hardly observed as far as the concentration is ranged in the order of 10^{-6}g/ml. But with increasing the concentration to 1×10^{-5}g/ml, the height of contraction curve decreases to about 50–70% of control value and the decrease of heart rate reaches to half a value of control approximately (Fig. 1). These changes are easily possible to recover to the ordinary state by changing the perfusing Ringer solution.

Fig. 1. Effects of chlorpromazine on regularly beating heart.

Also chlorpromazine demonstrates a remakable stabilizing action on the irregularly beating heart: e.g. the irregular beat caused by addition of adrenaline ($5\times10^{-6}-1\times10^{-5}$g/ml) or nicotine ($1\times10^{-6}-2\times10^{-6}$g/ml) to perfusing Ringer solution could be stabilized by chlorpromazine of $1-2\times10^{-5}$g/ml. (Fig. 2). In these cases, though the heart rate decreases to approximately half a value of

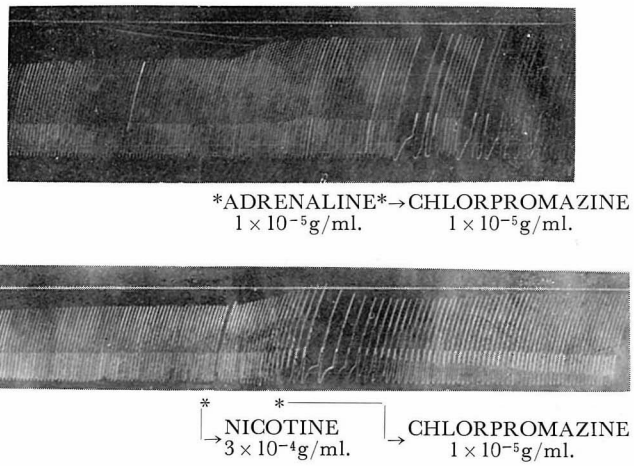

Fig. 2. Effects of chlorpromazine on irregularly beating heart.
Record was obtained by using the same preparation in Fig. 1.

normal beating, the height of contraction curve does not so differ from that of the normal heart or rather more increased. The excised heart under such a condition could beat for days.

Similar effects of chlorpromazine on the irregular beating induced by electrical shock could be also obtained. In this case, however, the contraction height

decreased to about one third of control by chlorpromazine and the beating stopped after 5 hours of the procedure.

When the solution perfusing in such a heart is exchanged for the fresh Ringer solution, the arrhythmia appears again. This phenomenon appeared more frequently in the case of irregularly beating heart caused by drugs than that induced electrically.

In such a series of experiments, the lowered sensitivity to adrenaline was observed on the heart pre-treated with chlorpromazine; i.e. by applying $1-5\times 10^{-5}$ g/ml of adrenaline, the arrhythmia arose within several minutes after the application and on the heart pre-treated with chlorpromazine it did not appeared, although the contraction height increased slightly in the latter case. Moreover by applying the electrical shock with moderate intensity, the arrhythmia was easily possible to cause on such a preparation. In this case, as long as the stimulus is applied the magnitude of contraction was slightly incresed. However the magnified height falls down to the original state as soon as the stimulation was interrupted. These findings may demonstrate that the positive inotropic action by adrenaline or nicotine balances to the decrease of frequency by chlorpromazine. Similar results have been already described on mammalia or man (5,6).

2. *Electrophysiological features*

a) *The atrial muscle*

As shown in the records of Fig. 3. and Fig. 4., chlorpromazine decreases slightly the amplitude of both resting and action potential, the decrease in heart rate being also clear. In addition to these findings, it is recognized that the slow repol-

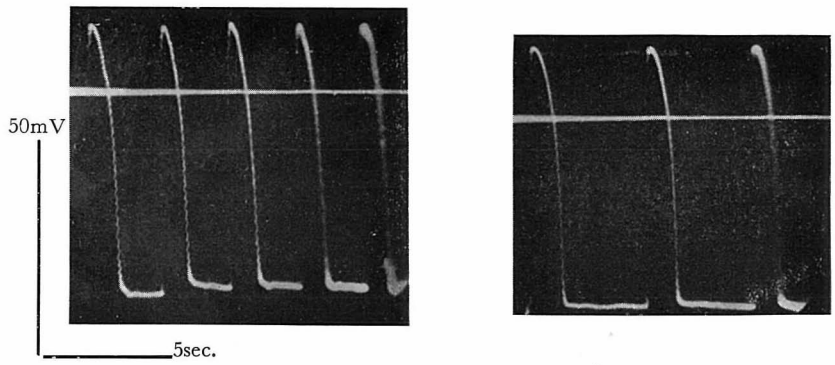

Fig. 3. Changes of membrane potential in atrial muscle following adinistration of chlorpromazine (1×10^{-5}g/ml). Note the potential level and the beating frequency.

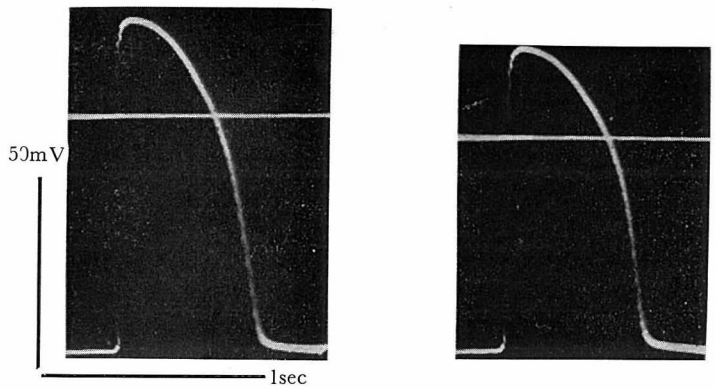

Fig. 4. Changes of membrane potential in auricular muscle following administration of chlorpromazine (1×10^{-5}g/ml). Note the potential level and the duration of plateau. See text.

arization phase is prolonged in small degree. The prolongation of plateau duration reaches approximately to 120% of control value (Fig. 4). When adrenaline or nicotine in such a concentration as mentioned in "Mechanical contraction curve" is applied to this preparation, the electrophysiological features are scarecely influenced.

It must be noted that the changes of both resting and action potential are not remarkable as that of sinus.

b) *The pace maker region*

As already well-known, the action potential recorded from amphibian sinus takes a characteristic shape; i.e. prior to the rising phase of action potential, the

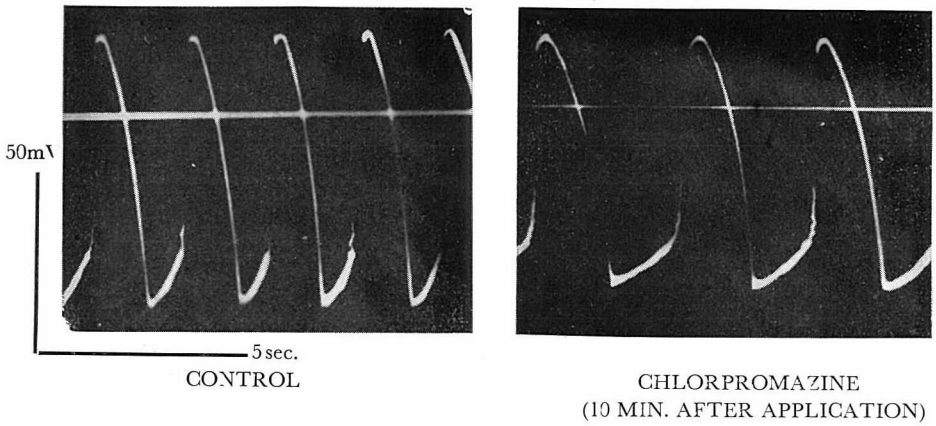

Fig. 5. Changes of membrane potential in sinus region in ten minutes after administration of chlorpromazine (2×10^{-5}g/ml). Note the potential level and the slope of generator potential.

slowly developed falling of resting potential is always found in spontaneously beating preparation. Similar records can easily be obtained from mammalian Purkinje fibres.

Chlorpromazine influences chiefly on the slow depolarization phase (generator potential) and on the slow repolarization phase (plateau). Of course, as mentioned above, both resting and action pototential are also more decreased in height compared with that of atrial muscle.

As shown in Fig. 5., chlorpromazine makes the decrease of the slope of generator potential and the prolongation of plateau. It must be interested that any changes of critical voltage for the rising phase are hardly recognized in spite of the changes on other parts. In generally, as observed on the experiment by means of vagal stimulation or administration of acetylcholine (2, 3, 10, 18, 19), the bradycardia takes place due to the increase of resting potential and the decrease of the inclination of generator potential. The lowering in heart rate produced by chlorpromazine, however, seems to occur chiefly depending upon the latter. In other word, it may be concluded that the decrease of resting potential does not participate in the bradycardia caused by chlorpromazine, because the absolute value of resting potential is rather decreased in height.

On the other hand, contrasting with the case of vagal stimulation or administration of acetylcholine, the duration of plateau is not shortened, but rather prolonged. These findings may be likely assumed that the bradycardia caused by chlorpromazine differs from that by acetylcholine or vagal stimulation in its nature.

Discussion

The results mentioned above demonstrate clearly that chlorpromazine acts inhibitorily on the heart muscle itself.

The depressant action of chlorpromazine was consisted of the lowering of contraction force and the decrease of heart rate. With respect to the lowering force, it has been reported by some authors that chlorpromazine lowered the motility of striated muscle or smooth muscle (14). Moreover *Courboisier* et al (5) has already suggested that chlorpromazine posesses the quinidine-like action.

On the other hand, the negative inotropic action of quinidine on cardiac muscle has been established (1, 11, 12). From these point of view its stabilizing action is naturally expected. But it is very difficult to explain reasonably the menchanism of producing the lowering of contraction force.

Accompanying the lowering of contraction force by chlorpromazine, both resting and action potential are slightly decreased in electrophysiological examination. Changes in the former, however, are fairly obviously recognized compared with that in the latter. This fact indicates that there is no direct relationship be-

tween both changes of mechanical and electrophysiological features. Similar conclusion are already pointed out by *Trautwein* (16, 17). As mentioning below, concerning these points, the reasonable interpretation could not be obtained from results observed in the present experiment. Perhaps chlorpromazine may act on the metabolic process of the contraction of cardiac muscle and cause the lowering of contraction force. In fact, the declining action of chlorpromazine on the metabolic precess has already been described (5).

On the other hand, based on the electrophysiological records, the bradycardia caused by chlorpromazine takes place as a result of the decrease of inclination in slow depolarization phase, as well as other stabilizing agents. It is noteworthy that both resting and action potential of sinus are rather decreased compared with the case of acetylcholine or vagal stimulation. Indeed acetylcholine brings about the decrease of both resting and action potential in some case, but, in general, these procedures produce the elevation of resting potential: the membrane is highly hyperpolarized. From these fact, chlorpromazine may act on heart muscle directly without the intermediate process such as the secretion of acetylcholine. Hence the action of chlorpromazine on heart muscle, especially on sinus, seems to be not secondarily without any mediator as actylcholine, but primarily. In other word, the depressant action caused by acetylcholine accompanies with the hyperpolarization of membrane, and naturally the shortening of plateau. It has been already pointed out that these findings are based on the increase of K-conductance (18, 19, 25). Then chlorpromazine may decrease the potassium conductance, because the depolarzation of membrane and the prolongation of plateau duration are evidently recognized. Moreover it is worthy to note that the sodium carring system may be influenced through the disfunction resulted from the action of chlorpromazine as a metabolic poison. It seems also likely to assumed that the disfunction of sodium pump may give rise secondarily by the lowering of potassium conductance (9, 18, 19, 20, 21, 22, 23). Changes of electrophysiological features by chlorpromazine should be considered as a consequence caused by combining these many factors as mentioned above. In fact, the finding that the shape of plateau is remarkablly altered under unfavorable conditions have been frequently observed (4, 15, 16, 17).

The stabilizing action of chlorpromazine may be considered as a results by lowering of function of sinus: the stabilization of chlorpromazine may be resulted from the decrease of spontaneous frequency in sinus cited firstly out of three fundamental features pointed out by *Weidmann* (24). In the present work, indeed, the artificially produced blocking should be named the atrio-ventricular block, a ventricular contraction occurs in corresponding with two contractions of sinus or atrium. On the other hand, the blocking between the sinus and the atrium could be observed in no case. If the sinus frequency falls down approximately to half a rate, the heart carries on appearently without the blocking. So that

the stabilization by chlorpromazine may proceed through such a way, and it may be not produced by recovering the function of impulse conducting system which fell in functional disorder by drugs or electrical shock, but the contraction of heart may be carried out on the lowered functional level. It may hardly be considered that the function of impules conduction system is independently elevated by chlorpromazine, whereas the function of other parts (ventricle, atrium, sinus) seems to be lowered as shown by the mechanical and the electrophysiological records.

SUMMARY

1. Effects of chlorpromazine were examined on excised toads heart by means of the mechanogramm and the microelectrode technique.

2. Within several minutes after the administration of chlorpromazine (1×10^{-5} g/ml), the height of contraction and heart rate are lowered approximately in half a value of control.

3. On the heart pre-treated with chlorpromazine (1×10^{-5}g/ml), the conduction block by artificial procedures does not so easily occur comparaed with the non-treated.

4. The membrane potential is lowered by chlorpromazine, the lowering is more marked in the sinus region than the auricular muscle.

5. It is discussed that the stabilization by chlorpromazine may be carried out on the functional level lowered by the drug.

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