EFFECTS OF LOCAL ANESTHETICS, TETRODOTOXIN,
ACONITINE AND VERAPAMIL ON THE MECHANORECEPTORS
OF ISOLATED FROG HEART*

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Abstract—Effects of local anesthetics, tetrodotoxin (TTX), aconitine and verapamil on the rate of afferent discharges from the mechanoreceptors of isolated hearts of the bullfrog were studied. When procaine (1×10^{-4} M), tetracaine (1×10^{-6} M) and dibucaine (1×10^{-5} M) decreased the contractile force and beating rate of the heart, high frequency discharges that were synchronized with the contraction of the heart appeared. When concentrations of these local anesthetics were increased, the afferent discharges were abolished. When TTX (1×10^{-8} M - 1×10^{-7} M) caused a cardiac arrest, high frequency discharges, consisting of maintained discharges and the discharges synchronized with small contractions of the ventricle, appeared. Occasionally, in the presence of TTX (1×10^{-7} M) the cardiac arrest occurred, and then very irregular contractions appeared. At that time, high frequency discharges synchronized with contractions appeared. On the other hand, aconitine (1×10^{-7} M - 1×10^{-6} M) initially increased the rate of afferent discharges from mechanoreceptors in the atrium and ventricle and then abolished the discharges without significantly affecting beating rhythms and contractile force. When verapamil (1×10^{-6} M - 1×10^{-5} M) was applied, the beating rate and contractile force were significantly decreased, but high frequency discharges synchronized with contractions were observed. These results indicate that local anesthetics, TTX and verapamil at those concentrations which depressed the cardiac functions did not inhibit the heart mechanoreceptor excitability and the concentration of aconitine that markedly affected the cardiac functions stimulated the heart mechanoreceptor.

Previously, we (1) reported that the rate of afferent discharges from the isolated frog heart was increased when Ca^{2+} or Mg^{2+} was added to Ringer's solution, but was decreased when Mn^{2+} was added to that solution. Kontani et al. (2) reported that the rate of afferent discharges from the frog muscle spindle, a kind of stretch receptor, was reduced by Ca^{2+}, Mg^{2+} and Mn^{2+}, in a concentration-dependent manner. Therefore, it is supposed that the mechanoreceptors generating afferent discharges in the frog heart may be different from the frog muscle spindle in the responsiveness to drugs. In this paper, we studied the effects of some local anesthetics and aconitine on the rate of afferent discharges from the frog heart mechanoreceptor and discussed the results in comparison with those from the frog muscle spindle. Local anesthetics and aconitine caused a decrease and an increase in rate of afferent discharges from the frog muscle spindle, respectively (3). When the frog heart was perfused with Mn^{2+} (1.1 mM)-containing Ringer's solution or low Ca^{2+}
Ringer's solution (Ca\(^{2+}\) 0.37 mM), the afferent discharges disappeared within 3 min (1). When the frog heart was perfused with those modified Ringer's solutions, the reduction of the receptor potential of heart mechanoreceptors may occur. Mn\(^{2+}\) is known to block the Ca entry in various preparations, e.g., in barnacle muscles and smooth muscles (4, 5). Therefore, we also studied the effect of the organic Ca antagonist, verapamil, which suppresses the Ca\(^{2+}\) influx in heart and smooth muscles (6), on the rate of afferent discharges from the frog heart mechanoreceptors.

**Materials and Methods**

The experiments were performed on bullfrogs (*Rana catesbeiana*) weighing 250–350g. Preparations and recording methods were described in a previous paper (1). The heart was isolated together with the cardiac branches of right vagosympathetic nerves, and then the heart was perfused with amphibian Ringer’s solution according to the Yagi-Hartung method. When the atrium alone was perfused with Ringer’s solution, the venous cannula was inserted into the vena cava posterior, and the aorta was ligated. The ventricle was cut right in two from the apex cordis, and a cannula whose top was in the shape of a globe (7 mm in diameter) was inserted into the ventricle. The perfusion solution from the right atrium could drain through the cannula, and the ventricle was tied as near as the atrium so that the afferent discharges from the ventricular mechanoreceptors could be excluded. When the ventricle alone was perfused, a cannula of 8 cm in length was retrogradely inserted into the ventricle, and Ringer’s solution was flowed into the cannula from its branch and overflowed at the top of the cannula. The vena cava posterior was not ligated to avoid the expansion of the atrium.

The cardiac nerve branch was placed on a pair of platinum electrodes. Afferent impulses were amplified with an amplifier (Nihon Kohden AVB-2) and displayed on an oscilloscope (Nihon Kohden VC-9). The same impulses were then transformed into square waves and fed into an integrator. The trigger level of the integrator was adjusted a little higher than the noise level. The output of the integrator was recorded by a D.C. recorder (Hitachi 056). The isotonic contraction of the atrium or ventricle was picked up with an isotonic transducer (Nihon Kohden TD 112S), displayed on an oscilloscope and recorded by a D.C. recorder. The effect of one concentration of each drug was examined in 2 or 4 different preparations. All of the experiments studying the effects of drugs were performed in the perfused heart preparation according to the Yagi-Hartung method unless otherwise indicated. Amphibian Ringer’s solution was of the following composition (mM): NaCl, 115.5; KCl, 2.7; CaCl\(_2\), 1.8; NaHCO\(_3\), 3.0; and glucose, 5.5 (pH was adjusted to 7.5±0.2 by adding HCl). When the effects of drugs were investigated, Ringer’s solution was exchanged for drug-containing solutions.

Drugs used were procaine HCl (Bancain®, Banyu Pharm. Co.), tetracaine HCl (Tetocain®, Kyorin Pharm. Co.), dibucaine HCl (Nagase Iyaku-hin), tetrodotoxin (TTX) (Sigma), aconitine (Merck) and verapamil (a gift from Eisai).

**Results**

1. **Relationship between afferent discharges and perfusion pressure:** As described by previous investigators (7, 8), afferent discharges synchronized with beating of the frog heart were observed. In the present experiments performed on the perfused frog heart according to the Yagi-Hartung method, the rate of afferent discharges was below 5 spikes/sec when Ringer’s solution in the venous reservoir was drained off (the level
of Ringer's solution was approximately 0.5 cm H2O). When the level of Ringer's solution in the reservoir was increased to 1.5 and 2.5 cm H2O, the mean rate of afferent discharges was increased to 26.0±1.6 and 31.8±1.8 spikes/sec (n=20), respectively. When the level was increased to 3.5 cm H2O, the cardiac rhythms became irregular. Therefore, the level of Ringer's solution in the reservoir was kept constantly at 2.5 cm H2O when the effect of a drug on the rate of afferent discharges was examined. When the atrium alone was perfused, the level of Ringer's solution in the venous reservoir was also kept at 2.5 cm H2O. When the ventricle alone was perfused and the level of Ringer's solution in the cannula was increased from 1 cm H2O to 8 cm H2O gradually, the rate of afferent discharges from the ventricular mechanoreceptors was increased. When the level of the solution in the cannula was below 4 cm H2O, however, the nerve fiber on the electrodes was shaken by ventricular contractions, and the recording of the afferent discharges was often interrupted. Therefore, the level of Ringer's solution in the cannula was kept at 8 cm H2O when the effect of a drug on the rate of afferent discharges was observed. In short, in the whole frog heart, atrium and ventricle, the rate of afferent discharges was increased by the elevation of the level of Ringer's solution. This finding indicates that most afferent discharges recorded in our preparations originated from the baroreceptors of the atrium and ventricle.

2. Effects of procaine, tetracaine and

Fig. 1. The effect of procaine on the rate of afferent discharges from the perfused heart of a bullfrog and the cardiac contraction. Records (A): integrated afferent discharges recorded by using an integrator and a D.C. recorder. Vertical bar of records (A): frequency of 20 or 40 spikes/sec. Records (B): contraction of the heart recorded by using an isotonic transducer and a D.C. recorder. Vertical bar of records (B): contraction of 1 mm. Horizontal bar: time for drug perfusion. Photographs of oscilloscope display which show the afferent discharges synchronized with cardiac contractions are added. Traces (C): cardiac contractions recorded by using an isotonic transducer. Traces (D): afferent discharges. Horizontal bars on the photographs: time of 1 sec. The first two photographs show the afferent discharges before perfusion with drug containing solution. The last photograph shows the afferent discharges after washing out of the drug.
Fig. 2. The effect of tetracaine on the rate of afferent discharges from the perfused heart of a bullfrog and the cardiac contraction. For details of legend, see Fig. 1.

Fig. 3. The effect of dibucaine on the rate of afferent discharges from the perfused heart of a bullfrog and the cardiac contraction. For details of legend, see Fig. 1.
dibucaine: The effects of procaine ($1 \times 10^{-4}$ M - $1 \times 10^{-3}$ M), tetracaine ($1 \times 10^{-6}$ M - $1 \times 10^{-5}$ M) and dibucaine ($1 \times 10^{-6}$ M - $1 \times 10^{-4}$ M) on the rate of afferent discharges from mechanoreceptors of the perfused heart and cardiac contractions are shown in Figs. 1, 2 and 3, respectively. Procaine ($1 \times 10^{-4}$ M) and dibucaine ($1 \times 10^{-6}$ M) caused more relaxation of the heart during diastole; and tetracaine ($1 \times 10^{-6}$ M) and dibucaine ($1 \times 10^{-5}$ M) caused disturbances of cardiac rhythms, but did not decrease the rate of afferent discharges synchronized with contractions of the heart appeared. When heart was perfused with solutions containing procaine ($1 \times 10^{-3}$ M) or tetracaine ($1 \times 10^{-5}$ M), the rate of afferent discharges was decreased gradually and disappeared within 3 min, but irregular contractions of the heart remained. When dibucaine ($1 \times 10^{-4}$ M) was applied, the contraction of the heart and the afferent discharges disappeared within 2 min. After washing out of procaine or tetracaine for 15 min, the contraction of the heart and the rate of afferent discharges were almost restored to the levels before the treatment. After washing out of dibucaine ($1 \times 10^{-5}$ M) for 15 min, the cardiac rhythms only became regular, and high frequency discharges synchronized with the contraction appeared. After washing out of dibucaine ($1 \times 10^{-4}$ M), the cardiac contraction appeared periodically, but no afferent discharges were generated.

3. Effect of TTX: The effects of TTX ($1 \times 10^{-8}$ M - $1 \times 10^{-7}$ M) are shown in Fig. 4. TTX caused a cardiac arrest, and the time required to cause it was shortened with increasing concentrations of TTX. When the heart was arrested at diastole, maintained discharges appeared, and the frequency was gradually decreased and disappeared within 30 sec. While small contractions of ventricular muscle remained, high frequency discharges synchronized with contractions appeared.

Fig. 4. The effect of tetrodotoxin on the rate of afferent discharges from the perfused heart of a bullfrog and the cardiac contraction. For details of legend, see in Fig. 1. Note that high frequency discharges appeared while the small cardiac contractions remained.
When the solution containing TTX was exchanged for normal Ringer's solution, irregular contractions and high frequency discharges synchronized with the contraction soon appeared, and then the heart rate and the rate of afferent discharges were almost restored to the levels before the treatment within 5 min. As shown in Fig. 4, we observed in 2 of 4 experiments with $1 \times 10^{-7}$ M TTX the transient cardiac arrest and the disappearance of afferent discharges followed by the irregular contraction of the ventricle and afferent discharges synchronized with the contraction, and the firing rate of afferent discharges synchronized with the contraction was very high when the heart was relaxed sufficiently during diastole and then contracted. It was suggested that TTX ($1 \times 10^{-7}$ M) could not inhibit the generation of afferent discharges, and the disappearance of afferent discharges may result from the cardiac arrest.

4. Effect of aconitine: Effects of aconitine ($1 \times 10^{-7}$ M - $1 \times 10^{-6}$ M) are shown in Figs. 5 and 6. When the heart was perfused with aconitine containing solutions, the rate of afferent discharges synchronized with the contraction of the heart was significantly increased initially, and the discharges became independent of the cardiac rhythms and finally the discharges almost disappeared; but the cardiac rhythms and the contraction of the heart were little affected. The time required to attain the maximum effect was shortened from $5.0 \pm 0.7$ to $1.4 \pm 0.3$ min (mean±S.E., n=4) as the concentration of aconitine was increased from $1 \times 10^{-7}$ M to $1 \times 10^{-6}$ M. After washing out of aconitine for 20 min, the afferent discharges did not appear. In order to study the effect of aconitine on the atrial or ventricular mechanoreceptors, aconitine ($1 \times 10^{-7}$ M) containing solution was perfused into the atrium or ventricle alone. Both the rates of afferent discharges from atrial and ventricular mechanoreceptors were increased (Fig. 6). The effect of local anesthetic on the increase in rate of afferent discharges induced by aconitine was also studied. Procaine

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![Figure 5](image-url)

**Fig. 5.** The effect of aconitine on the rate of afferent discharges from the perfused heart of a bullfrog and the cardiac contraction. For details of legend, see Fig. 1. The vertical bar of records (A) indicates frequencies of 25, 50 and 100 spikes/sec.
Fig. 6. The effect of aconitine on the rate of afferent discharges from the perfused atrium and the atrial contraction (I) and the rate of afferent discharges from the perfused ventricle and ventricular contraction (II) of a bullfrog. For details of legend, see Fig. 1. The vertical bar of records (A) indicates frequencies of 25, 50 and 100 spikes/sec.

Fig. 7. The effect of aconitine on the rate of afferent discharges from the perfused heart of a bullfrog and the cardiac contraction in the presence of procaine. For details of legend, see Fig. 1. The vertical bar of records (A) indicates frequencies of 10, 25, 50 and 100 spikes/sec.
(1×10⁻⁴ M), which did not significantly affect the beating rate and contractile force of the heart at least for 15 min, was applied for 3 min; and then aconitine (1×10⁻⁷ M) was added in the presence of procaine (1×10⁻⁴ M). Even in the presence of procaine (1×10⁻⁴ M), aconitine (1×10⁻⁷ M) caused an equivalent increase in rate of afferent discharges to that in the absence of procaine (Fig. 7).

5. Effect of verapamil: The effects of verapamil (1×10⁻⁶ M - 1×10⁻⁵ M) are shown in Fig. 8. The contractile force and beating rate of the heart were decreased in a concentration-dependent manner, but high frequency discharges synchronized with contractions of the heart were observed even in the presence of verapamil (1×10⁻⁵ M). When the heart was perfused with verapamil-containing solutions, the heart was relaxed significantly during diastole, and maintained discharges appeared and the rate of those discharges was gradually decreased. While weak contractions remained, high frequency discharges synchronized with the contraction appeared. When verapamil containing solution was exchanged for Ringer’s solution and the heart was perfused with Ringer’s solution for 10 to 20 min, slow heart beats were resumed, and high frequency discharges synchronized with the contraction appeared.

Discussion

In the present experiments, procaine (1×10⁻⁴ M), tetracaine (1×10⁻⁶ M), dibucaine (1×10⁻⁵ M) and TTX (1×10⁻⁷ M) caused decreases in beating rate and contractile force of the heart, but high frequency discharges synchronized with cardiac contractions appeared. These results suggested that the membrane excitability of the frog heart mechanoreceptor was not inhibited at those concentrations of the drugs which caused a decrease in contractile force and beating rate of the heart. When the high concentration of procaine (1×10⁻³ M), tetracaine (1×10⁻⁶ M) or dibucaine (1×10⁻⁴ M) was applied, the rate of afferent discharges

Fig. 8. The effect of verapamil on the rate of afferent discharges from the perfused heart of a bullfrog and cardiac contraction. For details of legend, see Fig. 1. Note that high frequency discharges appeared while the small cardiac contractions remained.
from the heart mechanoreceptors was gradually decreased and finally abolished. Thus, it is evident that such high concentrations of local anesthetics were necessary to cause the inhibition of the membrane excitability of mechanoreceptor or the conduction block of sensory nerve fibers. In the previous study (3), procaine \(1 \times 10^{-4} \text{ M}\) reduced the rate of afferent discharges from the frog muscle spindle to 30% of the control level, and TTX \(1 \times 10^{-7} \text{ M}\) abolished it. Since procaine \(1 \times 10^{-4} \text{ M}\) or TTX \(1 \times 10^{-7} \text{ M}\) could not reduce the rate of afferent discharges from the frog heart mechanoreceptors, the frog heart mechanoreceptors may be resistant to the effects of local anesthetics in comparison with the frog muscle spindle. On the other hand, aconitine \(1 \times 10^{-7} \text{ M}\) increased the rate of afferent discharges from the frog heart mechanoreceptors in the atrium and ventricle of the frog heart without significantly affecting cardiac rhythms and contractile force. Fukuda and Ishiko (8) reported that veratridine caused an increase in the rate of afferent discharges from the frog heart mechanoreceptors. When we converted the reported value of veratridine to the molar concentration, it was \(7.5 \times 10^{-6} \text{ M}\). In the frog muscle spindle, the minimum effective concentration of aconitine or veratridine which caused an increase in the rate of afferent discharges was reported to be \(3 \times 10^{-7} \text{ M}\) or \(1 \times 10^{-6} \text{ M}\), respectively (3). We could not know whether the concentration of veratridine in the report of Fukuda and Ishiko (8) was the minimum effective concentration, but those values on aconitine or veratridine between the frog muscle spindle and frog heart mechanoreceptor were not significantly different, and so the sensitivity of frog heart mechanoreceptor to those drugs may be almost the same as that of the frog muscle spindle. It was reported that the excitatory effect of aconitine on the frog muscle spindle or crayfish stretch receptor was inhibited by procaine or TTX pretreatment, respectively (3, 9). The increase in the rate of afferent discharges from the frog heart mechanoreceptor induced by aconitine \(1 \times 10^{-7} \text{ M}\) could not be inhibited by procaine \(1 \times 10^{-4} \text{ M}\) at the concentration which did not significantly affect the cardiac rhythms or contractions (Fig. 7). In the experiments which were performed on cat heart to study the effects of local anesthetics on the afferent impulses activities from the cat heart mechanoreceptors (10), it was reported that local anesthetics diminished the impulse activity from the atrial stretch receptors, but the inhibitory effects were not marked and only for a short time in the anesthetized cat and that the continuous firing of spikes from the veratridine-sensitized cat heart receptors was totally suppressed with procaine or other local anesthetics, but the disturbances in the electrocardiogram were observed at the dose of procaine which caused those depressive effects.

Since it is very difficult to record the generator potential produced in the heart mechanoreceptor and to study the mechanisms of impulse initiation there, most of studies on the heart mechanoreceptor have been performed by recording impulses in their sensory fibers. Paintal (11) applied the impulse initiation mechanisms which had been studied in other mechanoreceptors (e.g., frog muscle spindle and crayfish stretch receptor) to those of the heart mechanoreceptor and suggested that there are the generator region and regenerative region in the sensory endings, and the former is relatively unsusceptible to drugs, but the latter is susceptible. In the present experiments, it was considered that the regenerative region of frog heart mechanoreceptors would be more susceptible to aconitine or veratridine, which sensitized the receptor, than local anesthetics or TTX, which inhibited its excitability, in comparison with those of the
frog muscle spindle.

Verapamil is used as an antianginal agent, but the effects on the heart mechanoreceptors have been little studied. Verapamil is known to depress the Ca entry into the squid giant axon (12) and the contractility of cardiac muscle, and vascular and non-vascular smooth muscles (6, 13–15). It was reported that Ca\(^{2+}\) as well as Na\(^+\) played an important role in the generating process of receptor potential in the frog muscle spindle (16–18), and D 600 reduced the receptor potential in the mammalian muscle spindle in Na\(^+\)-free bathing solution, but had no effect on the receptor potential amplitude in the presence of Na\(^+\) (19). At the concentration of verapamil which significantly decreased the contractile force and beating rate of the frog heart, high frequency discharges synchronized with weak contractions could be observed (Fig. 8). If the generator process of receptor potential in the frog heart mechanoreceptor is inhibited by verapamil, the receptor potential induced by weak contraction of the heart would be effectively reduced. Verapamil (1 \(\times 10^{-5}\) M) which was dissolved in Ringer’s solution may have had little effect on the generator region in frog heart mechanoreceptor. The effects of verapamil on the frog heart mechanoreceptor were different from those of Mn\(^{2+}\). At present, we have no information to explain why Mn\(^{2+}\) but not Ca\(^{2+}\) or Mg\(^{2+}\) abolished the afferent discharges from the heart mechanoreceptors. The sites of action of Mn\(^{2+}\) in the heart mechanoreceptor may be different from those of verapamil.

Most of the afferent activities from the heart mechanoreceptors may originate from the baroreceptors, and it was reported that the increase in the rate of afferent discharges was associated with the positive inotropic action of epinephrine in the isolated frog heart (8). When local anesthetics, TTX and verapamil were administered to the perfused frog heart, high frequency discharges synchronized with contractions following large relaxation during diastole appeared, but the rate of discharges was very low which was synchronized with contractions following insufficient relaxation of the heart during diastole. It is suggested that the relaxation of the heart during diastole may increase the sensitivity of mechanoreceptors, and the drugs which have a negative inotropic action may also generate the high frequency discharges synchronized with cardiac contractions.

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