Abstract—Effects of palytoxin (PTX) on isolated papillary muscles of guinea pigs were studied in an attempt to elucidate the mechanical and electrical activities. Inotropic effects of PTX above $3 \times 10^{-9} \text{ g/ml}$ were: an early positive inotropic effect, slowly developing contracture accompanied by decline in phasic tension, appearance of aftercontractions and arrhythmias at high doses. The positive inotropic effect of PTX was enhanced in high Ca$^{2+}$ medium but was not modified by propranolol. PTX induced a sustained depolarization and decrease in the amplitude, upstroke velocity and duration of action potential. During development of depolarization, arrhythmias occurred, which lasted for 5–10 min and reappeared 30–60 min after. Oscillatory afterpotential often appeared. Neither reserpine nor practolol prevented the PTX-induced arrhythmia while propranolol prevented it. Tetrodotoxin slowed the development of depolarization due to PTX and inhibited PTX-arrhythmias. In low Na$^+$ medium, PTX exerted fewer effects on resting and action potentials and produced no arrhythmia. The results suggest that PTX-induced depolarization is responsible for the generation of contracture and arrhythmia and that the depolarization is due to the change in membrane Na permeability.

Palytoxin (PTX), isolated from *Palythoa tuberculosa* (1) or other *Palythoa spp.* (2, 3), is one of the most of the potent marine toxins. Although the complete chemical structure of PTX has yet to be determined, the molecular weight has been estimated to be 3,300 (2). It has been observed that PTX induced contractions in skeletal muscle (4, 5) and smooth muscles (3–7) and that PTX depolarized the cell membrane in skeletal muscle (4, 5), smooth muscle (6) and myelinated nerve fiber (8). PTX also produced positive ino- and chronotropic effects on right atrium of guinea pig (5). *In vivo* and *in vitro* studies showed that PTX induced a variety of cardiac arrhythmias possibly involved in the lethality of PTX (3, 5). Recently, Weidmann (9) reported that unpurified extract from *Palythoa* depolarized ventricular muscles in dogs and rabbits. However, detailed electrophysiological properties of PTX on cardiac cells have apparently not been documented.

In the present paper, the effects of PTX on the mechanical and electrical activities of isolated papillary muscles of guinea pigs were studied and our findings are reported herein.
excised and papillary muscles were dissected from right ventricles, in Tyrode solution. The muscle was suspended in an organ bath containing 20 ml Tyrode solution with 0.5 g of resting tension for tension experiments, and was stimulated through bipolar platinum electrodes with a square wave pulse of 1 msec duration and three fold threshold current at a frequency of 1 Hz. About a 60 min equilibration period was allowed to elapse before drugs were applied. For the electrophysiological study, the muscle was placed horizontally in a 20 ml bath circulated with Tyrode solution and was stimulated as described above. Transmembrane potential was recorded using a conventional microelectrode technique and was displayed on cathode ray oscillograph. The microelectrode was filled with 3M KCl and had a tip resistance of 8–15 megohm. The maximum rate of rise of action potential was determined using an electronic differentiator. In some experiments, contractions were recorded together with action potentials.

Tyrode solution contained (mM): NaCl 136.8, KCl 3.0, CaCl2 1.8, MgCl2 1.0, dextrose 5.5, NaHCO₃ 11.9 and NaHPO₄ 0.4 and was gassed with 95% O₂–5% CO₂ adjusted to pH 7.2 at 37°C. 8.2% Na-medium (12.3 mM Na⁺) was prepared by replacement of NaCl for iso-osmotic choline chloride, and 30% Na-medium was made by replacement of 104 mM NaCl for iso-osmotic choline chloride. 1×10⁻⁶ g/ml atropine was added in low Na Tyrode solution to avoid the cholinergic effect of choline.

Drugs used were tetrodotoxin (TTX; Sankyo), propranolol (Tokyo Kasei), practolol (ICI) and reserpine (CIBA). The stock solution of TTX was prepared by dissolving the crystals in 0.05% acetic acid to make a concentration of 1×10⁻³ M (pH 4.6). Palytoxin, isolated from Palythoa tuberculosa by Kimura and Hashimoto (1) and having an LD50 value of 0.53 μg/kg (i.v. in mice), was dissolved in distilled water to make a concentration of 1×10⁻⁵ g/ml and then kept frozen as a stock solution. This solution was diluted just before use. The dose of PTX was expressed as (g/ml) as the chemical structure of the toxin has not been determined.

RESULTS

Effects of PTX on the contractile force of papillary muscle

PTX was applied after 1 hr of equilibration period. Fig. 1 shows a typical record of effects of 1×10⁻⁸ g/ml PTX. Immediately after the application of PTX, the contractile force increased and attained its peak within 1 min. After-contraction coupled with driven-contraction was observed. The resting tension increased with time and concomitantly the contractile force tended to decline, when observed at 7 or 25 min. High doses of PTX decreased the contractile tension resulting in cardiac arrest after a long exposure.

Arrhythmias appeared after a few minutes of exposure to 3×10⁻⁸ g/ml PTX. First, spontaneous contraction appeared as extrasystoles coupled with driven contraction and tachycardia soon followed. The duration time exhibiting arrhythmia varied with the preparation. Once exposed to PTX, removal of the toxin from the bathing medium did not alter the contractile force, after-contraction, contracture and arrhythmia. 1×10⁻⁶ or 3×10⁻⁶ M TTX suppressed the PTX-induced arrhythmia but modified little the contractile
force, contracture and aftercontraction.

Fig. 2 shows the dose-response relation with the peak inotropic effect of PTX in the muscles contracting at 1 Hz. The two-fold increase in external Ca²⁺ concentration (3.6 mM) potentiated the contractile force and PTX produced further potentiation. The degree of potentiation by PTX was greater with 3.6 mM than with 1.8 mM Ca²⁺, whereas at 3 x 10⁻⁸ g/ml PTX the muscle exhibited a maximum response in 1.8 mM Ca²⁺. 1 x 10⁻¹ to 1 x 10⁻⁶ M propranolol did not alter the contractile force in the muscle exposed to PTX.

Effects of PTX on the transmembrane potential of papillary muscles

1 x 10⁻⁸ or 3 x 10⁻⁸ g/ml PTX immediately produced a sustained depolarization after the application. Fig. 3 shows the time-course of change in resting membrane potential after exposure to 1 x 10⁻⁸ and 3 x 10⁻⁸ g/ml PTX. Higher doses reduced the resting potential more rapidly but the magnitude of maximum reduction was almost the same. The resting membrane potential was reduced to its maximum level of about -60 mV within 15 min and was sustained at this level for about 30 min, after which the potential showed a slight restoration. Washing out PTX did not restore the reduced resting potential.

With progressive depolarization, the amplitude, maximum rate of rise and duration of action potential decreased gradually. Changes in action potential and the contractile force are shown in Fig. 4. In Fig. 4-B, the resting membrane potential decreased to -74 mV after 1.5 min of application of 3 x 10⁻⁸ g/ml PTX and the contractile force increased. After
7 min, the resting potential further decreased to $-68 \text{ mV}$ and the contractile force further increased (Fig. 4-C). After 30 min the resting potential reached $-60 \text{ mV}$ and the action potential duration was markedly shortened (Fig. 4-D). At this time the resting tension

**Fig. 3.** Time course of changes in resting membrane potential in papillary muscles exposed to $1 \times 10^{-8}$ or $3 \times 10^{-8} \text{ g/ml PTX}$ and the influence of the pretreatment with $1 \times 10^{-6} \text{ M TTX}$ on the effect of $3 \times 10^{-8} \text{ g/ml PTX}$. TTX was applied 15 min prior to the addition of PTX. Each point represents a mean of 7 to 9 muscles and vertical bar represents the standard error. *; significantly different from $3 \times 10^{-8} \text{ g/ml PTX}$ alone ($P<0.05$).

**Fig. 4.** Effects of $3 \times 10^{-8} \text{ g/ml PTX}$ on the action potential and the contractile force. In each panel, upper trace is the zero potential, middle trace the action potential and lower trace the contractile force. The panels shown are before (A), 1.5 min (B), 7 min (C) and 30 min (D) after application of PTX. In this muscle, spontaneous activity appeared at 2 min and ceased at 6 min.

**Fig. 5.** Effects of $3 \times 10^{-8} \text{ g/ml PTX}$ on the generation of action potential and of spontaneous activity. In each panel, the upper trace represents the zero potential and the lower trace the action potential. Records shown are control (A), 3 min (B), 15 min (C) and 100 min (D) after the application of PTX. In this preparation the arrhythmia appeared at 2 min, ceased at 8 min and reappeared at 100 min.
was elevated while the contractile force declined and finally contracture developed. Oscillatory afterpotential preceded after-contraction. Table 1 summarizes the change of action potential in the presence of $3 \times 10^{-8}$ g/ml PTX.

PTX induced spontaneous electrical activity, particularly with $3 \times 10^{-8}$ g/ml PTX in all preparations. It appeared first as a coupled ectopic beat to the driven action potential and tachycardia soon followed as shown in Fig. 5. Spontaneous activity occurred in the voltage range of $-75$ to $-60$ mV. In some preparations, the arrhythmia was interrupted for 30–60 min after a few minutes of development. If the stimulation was stopped, the spontaneous activity ceased in 30 sec to 10 min. In the preparation shown in Fig. 5, the arrhythmia ceased but reappeared after 100 min. During this period without arrhythmia, the oscillatory afterpotential appeared as shown in Fig. 5-C. When two microelectrodes were impaled some distance apart, the coupling interval between the upstroke of preceding action potential and the peak of oscillation was the same, although amplitude of oscillation varied for the cells. In the range of resting potential of $-75$ to $-60$ mV, the amplitude of oscillatory afterpotential was 2.0 to 7.5 mV (mean 5.2 mV) and the coupling interval was 320 to 450 msec (mean 350 msec) at the frequency of 1 Hz. When PTX was washed out, the oscillatory afterpotential remained without change in its amplitude and often arrhythmias occurred.

Effects of β-adrenergic blockade or catecholamine depletion on the depolarizing and arrhythmogenic action of PTX

Practolol, a β-adrenergic blocking agent, at $5 \times 10^{-5}$ M did not prevent the arrhythmia nor the depolarization caused by PTX ($n=5$). Addition of $5 \times 10^{-5}$ M practolol during the arrhythmia did not inhibit the spontaneous activity. Another β-adrenergic blocking agent, propranolol at $1 \times 10^{-7}$ M did not inhibit the PTX-arrhythmia while pretreatment with $5 \times 10^{-7}$ or $1 \times 10^{-6}$ M propranolol prevented the generation of arrhythmia due to

| Table 1. Changes in resting membrane potential (RMP), action potential amplitude (Amp), maximum rate of rise (max dV/dT) and action potential duration (APD) in the presence of PTX for 15 min and in combination with $1 \times 10^{-6}$ M TTX or $1 \times 10^{-6}$ M propranolol. TTX or propranolol was applied 15 min prior to application of PTX. |
|---------------------------------|--------------|--------------|----------------|----------------|
|                                | RMP (mV)     | Amp (mV)     | APD (msec)     | max dV/dT(V/sec) |
|--------------------------------|--------------|--------------|----------------|-----------------|
| Control                        | $89 \pm 1.6$ | $125 \pm 2.5$ | $214 \pm 18.0$ | $197 \pm 11.7$  |
| PTX $3 \times 10^{-8}$ g/ml    | $61 \pm 3.6^*$ | $88 \pm 4.8^*$ | $120 \pm 11.8^*$ | $86 \pm 13.7^*$  |
| Control                        | $92 \pm 2.5$ | $130 \pm 3.3$ | $215 \pm 14.5$ | $228 \pm 21.2$  |
| Propranolol $10^{-6}$ M        | $91 \pm 2.6$ | $131 \pm 2.2$ | $205 \pm 15.2$ | $208 \pm 23.2$  |
| Propranolol $10^{-6}$ M + PTX  $3 \times 10^{-8}$ g/ml | $66 \pm 2.1^*$ | $93 \pm 5.1^*$ | $135 \pm 12.3^*$ | $110 \pm 24.6^*$ |
| Control                        | $88 \pm 1.7$ | $125 \pm 2.4$ | $214 \pm 14.0$ | $218 \pm 23.5$  |
| TTX $10^{-6}$ M                | $91 \pm 2.4$ | $121 \pm 1.9$ | $205 \pm 15.4$ | $196 \pm 9.2$   |
| TTX + PTX $3 \times 10^{-8}$ g/ml | $62 \pm 1.6^*$ | $77 \pm 2.9^*$ | $123 \pm 13.2^*$ | $66 \pm 12.9^*$ |

* Significantly different from controls ($P < 0.001$)
1) Action potential duration was measured as 95% repolarization time
2) $n$ = number of muscles
PTX, in most of the preparations. After the establishment of arrhythmia induced by PTX, the addition of $1 \times 10^{-6}$ M propranolol suppressed the arrhythmia in 5–10 min without altering the resting potential. Propranolol had no effect on action potential parameters, as shown in Table 1.

In the next series of experiments the role of endogenous catecholamine on the PTX-induced arrhythmia was investigated. Endogenous catecholamine was depleted when reserpine 5 mg/kg/day s.c. had been given for 2 days before sacrifice of the animals and the depletion was confirmed with chronotropic effect of tyramine. $3 \times 10^{-8}$ g/ml PTX induced arrhythmias in the muscles excised from the reserpinized animals, however the period exhibiting arrhythmia was abbreviated by 10 to 50% (n=10). Reserpinization did not prevent the development of depolarization induced by PTX.

Effects of Na removal and tetrodotoxin (TTX) on the action of PTX

Fig. 6 shows effects of PTX on the action potential amplitude and resting membrane potential. Replacement of the external medium with 8.2% Na⁺ (12.3 mM Na⁺) medium during steady depolarization due to PTX restored the membrane potential to $-82$ mV. Return to normal Tyrode solution 12 min after decreased the resting potential rapidly.

Effect of external Na concentration on the action of PTX was further examined using 30% Na⁺ (44.7 mM Na⁺) medium in which 104.4 mM NaCl was replaced by iso-osmotic choline chloride. Fig. 7 shows effects of $3 \times 10^{-8}$ g/ml PTX on the action potential and

![Fig. 6. Time course of changes in resting membrane potential (RMP: upper trace) and action potential amplitude (lower trace) after exposure to $1 \times 10^{-8}$ g/ml PTX and the effect of $1 \times 10^{-6}$ M TTX or low Na medium. These are typical data and in 4 other preparations, findings were much the same. In this muscle, the arrhythmia occurred from 1 to 7 min. PTX was washed out at 30 min. TTX was added at 45 min, for 10 min. Tyrode solution was replaced at 45 min with low Na medium in which NaCl was replaced with choline chloride. In the low Na medium the stimulation was interrupted, as an enhanced contractile force made it difficult to maintain the impalement of an electrode.](image)

![Fig. 7. Effects of $3 \times 10^{-8}$ g/ml PTX on the action potential and the contractile force in 30% Na medium. The muscle was soaked in 30% Na medium for 20 min, then PTX was applied.](image)
The contractile force of the muscle which was preincubated in 30% Na+ medium for 20 min. In 30% Na+ medium, the rate of rise and amplitude of action potential significantly decreased without change in the resting membrane potential while the contractile force was enhanced. Addition of PTX had no effect on the resting potential and action potential amplitude within 8 min, but did raise the plateau level and slightly shortened the terminal phase of repolarization. After 30 min, the resting potential was reduced by 15 mV but the shortening of action potential duration was small. Neither oscillatory "afterpotential" nor arrhythmia appeared after the application of 1 x 10^{-8} or 3 x 10^{-8} g/ml PTX. Changes in the action potential parameters following PTX in normal and 30% Na+ medium are summarized in Table 2. In 30% Na+ medium, the change in parameters due to 1 x 10^{-8} g/ml PTX were significantly less than those in normal Tyrode solution.

PTX exerted a positive inotropic effect in 30% Na Tyrode even when the resting potential was not altered. Maximum increase in contractile force was 39.6±7.5% (n=6), and such was attained 20 to 30 min after the application of 1 x 10^{-8} g/ml PTX. As the resting potential depolarized 30 min or more after the addition of PTX, the basal tension increased gradually.

Fig. 6 also shows the effect of 1 x 10^{-6} M TTX during the sustained depolarization induced by PTX. TTX did not restore the reduced resting potential. The effect of pretreatment with 1 x 10^{-6} M TTX on the reduction in resting membrane potential caused by 3 x 10^{-8} g/ml PTX is shown in Fig. 3. PTX was applied 15 min after the application of TTX. TTX slowed the development of depolarization by PTX, and such was statistically significant (P<0.05), as compared to the depolarization by PTX alone at 3 and 5 min. TTX suppressed the generation of PTX-arrhythmia in 7 of 9 preparations. In the other 2 preparations, arrhythmia appeared just after adding PTX and lasted for 2-3 min. Even in the presence of TTX, PTX elicited an oscillatory "afterpotential". In addition, TTX did not significantly affect the action potential changes induced by PTX, as shown in Table 1.

### Table 2. Comparison of the electrophysiological effects of PTX in normal and 30% Na Tyrode solution. Each value represents a mean of 6 muscles and the standard error.

|                     | Normal Tyrode      | 30% Na Tyrode     |
|---------------------|--------------------|-------------------|
|                     | control            | PTX 1 x 10^{-8} g/ml 30 min | control | PTX 1 x 10^{-8} g/ml 30 min |
| Resting membrane potential (mV) | 90±1.6 (−27±2.1%) | 62±1.6 (−21±2.9%) | 84±1.8 (−14±1.9%) |
| Action potential amplitude (mV) | 127±1.3 (−21±2.9%) | 101±3.2 (−14±5.0%) | 114±1.7 (−14±5.0%) |
| Maximum rate of rise (V/sec) | 245±43 (−37±9.2%) | 137±19 (−29±9.3%) | 120±15 (−29±9.3%) |
| Action potential duration (msec) | 205±22.3 (−25±3.0%) | 167±16.7 (−25±3.0%) | 149±9.3 (−14±4.1%) |

1) Control values in 30% Na Tyrode were obtained 20 min after the preincubation in 30% Na Tyrode. **significantly different from the % change in normal Tyrode (P<0.01) **significantly different from the % change in normal Tyrode (P<0.05)
DISCUSSION

PTX rapidly depolarized the cell membrane of guinea pig papillary muscles soon after application and reached the maximum level of about $-60$ mV in 15 min. The depolarization induced by PTX was not readily reversed with washout of the toxin. The present results are consistent in part with the Weidmann’s findings (9) that unpurified Palythoa extract produced a depolarization in dog or rabbit ventricles, although he stated that depolarization induced by $2.8 \times 10^{-8}$ g/ml was reversible. In frog skeletal muscle (5), frog myelinated fiber (8) or smooth muscle of taenia coli (6) PTX produced a depolarization which was irreversible. The depolarizing action may be a common feature of PTX-actions.

Concomitant with the progressive depolarization by PTX, the amplitude and maximum rate of rise of action potential decreased. These changes seem to be secondary to the reduced resting potential (10, 11) as such changes decreased in 30% Na medium in which the degree of depolarization by PTX was slight.

Under PTX-induced sustained depolarization, replacement of the external medium with 8.2% Na medium restored the resting potential to near $-80$ mV. In 30% Na medium, reduction in the resting potential due to PTX was significantly less than that in normal Tyrode solution. These results suggest that sodium movement across the cell membrane is associated with the depolarization induced by PTX. It has been observed that purified PTX does not have an inhibitory effect on Na+, K+-ATPase, though crude extracts from Palythoa did have such an effect (12, 13). Furthermore, 2 mM Mn2+ did not prevent the depolarization induced by PTX (in preparation). Therefore, the increase in resting Na permeability may be responsible for the depolarization due to PTX. It has already been shown that PTX increased the resting Na permeability in skeletal muscle (5) and nerve fiber (8).

TTX showed a partial antagonism to the development of depolarization due to PTX in initial stage. Deguchi et al. (5) reported that TTX partially diminished the depolarization produced by PTX in frog sartorius muscle. In frog myelinated nerve, saxitoxin which like TTX blocks the Na channel (14) abolished the major part of the inward current after PTX, within the initial stage, whereas at later times saxitoxin was less effective, thus indicating an increase in leakage current (8). In both skeletal muscle and nerve, Na deficient medium antagonized the depolarizing action of PTX (5, 8). The partial antagonism by TTX implies the possibility that PTX did not act “specifically” on the Na channel and produced a leaky state.

PTX-actions on the mechanical response are summarized as follows; 1) early positive inotropic effect, 2) later rise in basal tension accompanied by a decline in contractile force, 3) appearance of aftercontractions and, with high dose, arrhythmias. The decrease in phasic tension and the development of contracture after a long exposure to PTX were also reported by Rayner et al. (15). In their paper, PTX increased the 45Ca entry into the rabbit ventricles and it was suggested that the contracture was associated with an increment of intracellular Ca2+. The time course of the contracture was proportional to that of depolarization. On the other hand, the early positive inotropic effect could not be explained by
changes in action potential in normal Tyrode solution, but rather was enhanced in higher external Ca²⁺ concentrations. In 30% Na Tyrode, the plateau of action potential increased after PTX. Thus, there appears to be a direct effect of PTX on the Ca channel.

Arrhythmic action of PTX was observed both in in vitro and in vivo studies (3, 5, 16). The role of endogenous catecholamine in the genesis of PTX-arrhythmia could be ruled out because catecholamine depletion by reserpine or β-adrenergic blockade with practolol did not prevent the PTX-induced arrhythmias. The inhibitory effect of 1 × 10⁻⁶ M propranolol may be due to non-specific quinidine-like action (17, 18).

Arrhythmias by PTX in papillary muscle occurred in the resting membrane potential of −75 to −60 mV and depended to some extent on the stimulation. Depolarization seems to be responsible for the generation of the PTX-arrhythmia. Katzung (19) reported that an electrically-induced depolarization easily produced automaticity in guinea pig papillary muscles. Oscillatory “afterpotential” which followed each action potential appeared when the tissue was partially depolarized after PTX application. PTX induced a spontaneous action potential from the peak of oscillatory “afterpotential” when a train of stimulus with short interval was applied (in preparation). The oscillatory “afterpotential” in papillary muscles exposed to PTX may be related to the genesis of automaticity. Further experiments are expected to clarify the relationship between oscillatory “afterpotential” and automaticity induced by PTX.

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