Afterpotentials and Triggered Activity in Hypertrophied Myocardium from Rats with Renal Hypertension

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SUMMARY We have found that afterpotentials can be induced selectively in hypertrophied myocardium from rats with renal hypertension. Three kinds of afterpotentials were recorded by standard microelectrode techniques: early afterdepolarizations, delayed afterdepolarizations, and early afterhyperpolarizations. The first two kinds of afterpotentials could give rise to triggered spontaneous activity, whereas the last kind did not. Delayed afterdepolarizations were induced in hypertrophied fibers exposed to Tyrode's solution containing high extracellular calcium ([Ca$^{2+}$]o = 7.2-12 mM) and early afterdepolarizations occurred in hypertrophied fibers exposed to Tyrode's solution containing tetraethylammonium (TEA = 10-30 mM). Neither of these treatments produced afterpotentials in normal myocardium. We found that delayed afterdepolarizations became larger when the stimulation frequency, number of preceding driven beats, or [Ca$^{2+}$]o was increased. The coupling interval from the upstroke of the last driven action potential to the peak of the delayed afterdepolarization decreased when the stimulation frequency or number of preceding driven beats increased. Hypertrophied fibers treated with high [Ca$^{2+}$]o that gave rise to triggered activity showed a characteristic relationship between delayed afterpotential magnitude and drive cycle length. In hypertrophied muscles treated with TEA, triggered activity developed from an early afterdepolarizations but terminated with a delayed afterdepolarization. The occurrence of afterpotentials in hypertrophied, but not in normal myocardium, appears to reflect the development of an important electrophysiological alteration that may predispose hypertrophied fibers to develop arrhythmias.


AFTERPOTENTIALS have been reported previously in studies on a number of cardiac tissues under a variety of experimental conditions including exposure to toxic levels of digitalis (see Discussion for references). Afterpotentials and aftercontractions also have been reported to occur in papillary muscles from rats with cardiac hypertrophy (Heller, 1979; Heller and Stauffer, 1979). Heller (1979) has previously suggested that hypertrophied hearts may be more sensitive to digitalis-induced arrhythmias because aftercontractions and afterdepolarizations are associated with cardiac hypertrophy and exposure to digitalis.

The purpose of this study was to analyze the effect of increased extracellular calcium [Ca$^{2+}$]o, tetraethylammonium (TEA), and the rate and duration of drive on the afterpotentials we have observed in hypertrophied myocardium. The results of this study suggest that the development of afterpotentials may be an important electrophysiological mechanism for generating arrhythmias in hypertrophied hearts.

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phied myocardium was based on: (1) previous studies (see Discussion for references) showing that cardiac afterpotentials are dependent on \([\text{Ca}^{2+}]_o\) and (2) the assumption that afterpotentials in hypertrophied preparations must be the result of a critical alteration in the balance between inward and outward transmembrane currents. Accordingly, \([\text{Ca}^{2+}]_o\) was increased to enhance the inward current and TEA was used to decrease the outward current (Kenyon and Gibbons, 1979).

Animals were studied 7–14 weeks postoperatively. After anesthetization with ether, hearts were excised and papillary muscles were removed from the left ventricles of hypertensive and normotensive animals. The papillary muscles were mounted in a tissue bath perfused with Tyrode’s solution maintained at 34–35°C. No tension was applied to the muscles.

Transmembrane action potentials were recorded by standard glass microelectrode techniques. Continuous recordings of electrical activity were obtained on a 6-channel strip chart recorder (Gould Brush model 260). Selected photographic records of action potentials were also obtained from oscilloscopic recordings with a Polaroid camera (Tektronix C5A).

**Electrical Stimulation**

External stimulating pulses lasting 0.2–0.8 msec were delivered to the tissue by bipolar Teflon-coated silver wires. The pattern of the stimulating pulses was selected by a programmable digital timing system (Rockefeller University) interfaced with a pulse generator connected to a stimulus isolation unit.

Two types of stimulation protocols were used. (1) Preparations were driven regularly at a cycle length of 1000 msec with periodic (every 5–10 minutes) interruption of stimulation for 1–2 minutes, after which a single stimulus was applied. This stimulation sequence was used in 20 of 26 hypertrophied and 18 of 24 normal preparations. (2) Preparations received a programmed sequence of pulses as follows: (a) regular drive for 20 seconds at a cycle length of 2000 msec, (b) a quiescent interval lasting 1000 msec followed by (c) 10 pulses at cycle lengths varying from 1000 to 200 msec in 100-msec decrements and then by (d) trains of stimuli consisting of 2–20 pulses at a cycle length of 200 msec and increasing in length by increments of 2 pulses. This stimulation protocol was used in 6 of 26 hypertensive and 6 of 24 normal preparations.

**Terminology**

The following terms are used to describe afterpotentials and rhythmic activity (Wit and Cranefield, 1976, 1977; Cranefield, 1975, 1977):

**Early Afterhyperpolarization**

An afterpotential that is continuous with phase 3, but that carries the membrane potential to a level more negative than that recorded later in diastole in fibers that normally lack spontaneous diastolic depolarization.

**Early Afterdepolarization**

An afterpotential that interrupts the usual course of repolarization thereby preventing the membrane potential from returning to the level prevailing prior to the action potential upstroke. Nondriven action potentials can occur during an early afterdepolarization.

**Delayed Afterdepolarization**

An afterpotential that occurs after completion of repolarization and carries the membrane potential to a level more positive than that recorded later in diastole.

**Spontaneous or Automatic Activity**

Electrical activity that occurs in the absence of external stimulation. Automatic fibers are inherently rhythmic and perpetually active without any prior external stimulation being required to create the conditions necessary for their activity.

**Triggered Activity**

Nondriven electrical activity initiated by one or more driven or spontaneous action potentials. Triggered activity differs from automatic activity in that triggerable fibers remain inactive until excited by one or more driven or spontaneous action potentials. These action potentials cause triggerable fibers to develop afterpotentials which may give rise to single or repetitive nondriven (triggered) action potentials.

**Sustained Rhythmic Activity**

Repetitive, nondriven activity arising from any cause, i.e., triggered or automatic, as well as reentry.

**Data Analysis**

The following parameters were measured from strip chart recordings:

**Afterpotential Amplitude**

For afterpotentials consisting of delayed afterdepolarizations preceded by early afterhyperpolarizations, this measurement was made from the most negative level reached by the afterhyperpolarization to the peak positive level reached by the afterdepolarization. For afterpotentials consisting of only early afterhyperpolarizations or delayed afterdepolarizations, the peak magnitude was measured as the most negative or positive potential level reached relative to the level of steady diastolic potential seen later in diastole.

**Coupling Interval**

This interval was measured as the time from the onset of the upstroke of the last driven action potential to the peak of the following afterpotential. This measurement was obtained only for fibers
generating delayed afterdepolarizations so that this parameter could be analyzed over a wide range of cycle lengths.

Results

The characteristics of the groups of animals used in these experiments are summarized in Table 1. These data show that the mean systolic blood pressure of animals whose left renal arteries were clipped (HBP) was significantly higher than that of sham-operated (SHAM) rats. The presence of myocardial hypertrophy in HBP animals is indicated by the significantly higher mean heart weight in the face of lower mean body weight of HBP as compared to SHAM animals.

Afterpotentials were obtained in all 15 HBP preparations superfused with Tyrode’s solution containing increased [Ca\(^{2+}\)]_o (7.2–12.0 mM) and in 10 of 11 preparations superfused with TEA (10–30 mM)-containing Tyrode’s solution. Only 2 of these 26 preparations produced afterpotentials in normal Tyrode’s solution ([Ca\(^{2+}\)]_o = 2.4 mM). Triggered activity was recorded in 18 of the 26 HBP preparations (8 of 15 in high [Ca\(^{2+}\)]_o, and 10 of 11 in TEA).

In contrast, 24 SHAM preparations subjected to the same treatments failed to show either afterpotentials or triggered activity.

The most commonly recorded type of afterpotential was the delayed afterdepolarization. This was recorded from all 15 HBP muscles treated with increased [Ca\(^{2+}\)]_o, and 10 of 11 muscles treated with TEA. The configuration of the afterpotential as well as the presence of triggered activity depended upon the frequency of prior stimulation and the number of preceding driven action potentials.

The effects of stimulation frequency and [Ca\(^{2+}\)]_o on afterpotential configuration are illustrated in Figure 1. Following the last driven HBP action potential at a cycle length of 900 and 500 msec in normal Tyrode’s solution (Fig. 1A) only small early afterhyperpolarizations occurred. After the last driven HBP action potential at a cycle length of 200 msec (Fig. 1A), a delayed afterdepolarization, without a preceding early afterhyperpolarization, was recorded. During perfusion with high [Ca\(^{2+}\)]_o (Fig. 1B), the membrane potential following the last driven HBP action potentials at the longer cycle lengths (900, 500 msec) showed an early afterhyperpolarization and then a delayed afterdepolarization.

**Table 1** Characteristics of Experimental Animals

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>HW (g)</th>
<th>BW (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBP</td>
<td>211 ± 21 (26)</td>
<td>1.34 ± 0.21 (26)</td>
</tr>
<tr>
<td>SHAM</td>
<td>132 ± 21 (24)</td>
<td>1.02 ± 0.10 (24)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are given as mean ± so numbers in parentheses = number of animals; HBP = hypertensive rats; SHAM = sham-operated normal rats; BP = systolic blood pressure; HW = heart weight; BW = body weight. Statistical significance was determined by Student’s t-test for unpaired data.

Figure 1 Effects of drive cycle length (CL) and [Ca\(^{2+}\)]_o on afterpotential characteristics. A and B show that the magnitude and configuration of both early afterhyperpolarizations and delayed afterdepolarizations in HBP fibers vary according to the CL and [Ca\(^{2+}\)]_o. C and D show that SHAM fibers did not develop afterpotentials at any cycle length at either [Ca\(^{2+}\)]_o.

At a driven cycle length of 200 msec, the configuration of afterpotentials showed a dependence on the number of preceding driven action potentials (Fig. 2). After 2 driven HBP action potentials in normal Tyrode’s solution (Fig. 2A) only an early afterhyperpolarization occurred. After 8 driven HBP action potentials, a slow delayed afterdepolarization was recorded. Increasing the number of driven HBP action potentials to 14 and 20 produced progressively larger and more rapid delayed afterdepolarizations (Fig. 2A). In the presence of high [Ca\(^{2+}\)]_o, generating delayed afterdepolarizations so that this parameter could be analyzed over a wide range of cycle lengths.
[Ca\textsuperscript{2+}]\textsubscript{o}, after 2 driven HBP action potentials the membrane potential showed an early afterhyperpolarization followed by a slow delayed afterdepolarization. After 8 and 14 driven HBP action potentials, the delayed afterdepolarizations recorded in high [Ca\textsuperscript{2+}]\textsubscript{o}, (Fig. 2B) were greater in magnitude and had more rapid upstrokes than those seen in normal Tyrode's solution (Fig. 2A). After 20 driven HBP action potentials, a single nondriven triggered action potential occurred and was followed by a large delayed afterdepolarization (Fig. 2B). The membrane potential then gradually returned to a steady diastolic level and the muscle remained quiescent. Under the same experimental conditions, the SHAM muscle showed neither afterpotentials nor triggered activity in either normal (Fig. 2C) or high [Ca\textsuperscript{2+}]\textsubscript{o} Tyrode's solution (Fig. 2D).

The relationship between the preceding drive cycle length and both afterpotential amplitude and the coupling interval was studied in 6 HBP preparations exposed to high [Ca\textsuperscript{2+}]\textsubscript{o}, including the preparations used in Figure 1. Figure 3A shows that 4 preparations had a biphasic relation between cycle length and afterpotential amplitude. In these muscles, afterpotential amplitude reaches an initial peak or plateau level at cycle lengths between 900 and 600 msec followed by a nadir at cycle lengths between 600 and 400 msec. The nadir is followed by an ascending limb that reaches a second and larger peak at a cycle length of 200 msec. All 4 preparations having this kind of relation gave rise to triggered activity. Two other muscles showed no afterpotentials or only an early afterhyperpolarization over a wide range of cycle lengths (1000-300 msec). These preparations developed very small afterdepolarizations only at a cycle length of 200 msec, and neither of them gave rise to triggered activity.

Figure 3B shows that HBP preparations that produced triggered activity also had a characteristic relationship between the preceding drive cycle length and the coupling interval. The 4 preparations in which the coupling intervals shortened with decreasing drive cycle length all developed triggered activity. The two muscles represented by single points at a cycle length of 200 msec developed delayed afterdepolarizations only at that cycle length. These two muscles had the longest coupling intervals and neither developed triggered activity.

Figure 4 shows the relationship between the number of driven action potentials at a cycle length of 200 msec and both the peak amplitude and coupling interval of afterpotentials recorded in the presence of high [Ca\textsuperscript{2+}]\textsubscript{o}, for the same 6 HBP muscles analyzed in Figure 3.

Figure 4A shows that, as the number of driven action potentials increased from 2 to 20, the magnitude of the delayed afterdepolarizations increased. In the 3 preparations showing the largest afterdepolarizations, the slope of the curve relating the number of driven responses to afterpotential amplitude was quite steep. All of the these muscles gave rise to triggered activity. For this reason, the last plotted point for these preparations is the longest driven train giving an afterpotential but no triggered activity. The two preparations with the smallest afterpotentials had a much flatter relationship and neither of these muscles gave rise to trig-
Effect of the number of preceding driven action potentials on afterpotential magnitude (A) and coupling interval (B) in HBP preparations perfused with 10–12 μM [Ca\textsuperscript{2+}]\textsubscript{o}. The preparations and symbols are the same as in Figure 3. Fibers in which triggered activity could be induced showed a steeper relation between afterpotential magnitude and number of beats and shorter coupling intervals than fibers that did not develop triggered activity.

One preparation had a relationship intermediate between the first and second type. This muscle gave rise to triggered activity when the number of driven responses exceeded ten.

Figure 4B shows that, in general, the coupling interval decreased as the number of driven action potentials increased. Preparations with large afterpotentials (Fig. 4A) had shorter coupling intervals than those with small afterpotentials. The 4 preparations with the shortest coupling intervals all gave rise to triggered activity, whereas the two muscles with the longest coupling intervals failed to generate triggered activity.

To determine whether the amplitude of the afterpotentials was uniform, recordings were obtained simultaneously from 2 or 3 sites separated by 0.4–4.0 mm in 10 HBP and 5 SHAM muscles perfused with high [Ca\textsuperscript{2+}]\textsubscript{o} Tyrode's solution. Figure 5 shows the results of a typical experiment. During slow stimulation, the HBP preparation (Fig. 5A) developed synchronous early afterhyperpolarizations after each driven action potential at all recording sites. During rapid stimulation there was a progressive loss of maximum diastolic potential, and following termination of rapid stimulation a delayed afterdepolarization occurred at all recording sites. The delayed afterdepolarizations were synchronous but varied in amplitude according to recording site. There was no consistent pattern in the distribution of afterpotential amplitude in the preparations studied. The recordings obtained from the SHAM muscle under identical conditions (Fig. 5B) show a uniform lack of afterpotentials at all recording sites.

Early afterdepolarizations were much less common than delayed afterdepolarizations and almost...
always occurred in HBP muscles treated with TEA. Early afterdepolarizations developed most often, but not exclusively, when a driven action potential was provoked after a preceding quiescent period of 1-2 minutes. Early afterdepolarizations were recorded in 5 of 11 HBP preparations treated with TEA and were always associated with triggered activity that terminated with a subthreshold delayed afterdepolarization.

Figure 6 shows typical records of early afterdepolarizations leading to triggered activity. In Figure 6A a single stimulus evoked a single driven action potential in the SHAM muscle; following this response the SHAM fiber remained quiescent. In contrast, a single stimulus applied simultaneously to the HBP muscle produced a driven action potential whose normal course of repolarization was interrupted by repetitive, nondriven responses, i.e., triggered activity.

Figure 6B shows simultaneous recordings from 2 sites in an HBP preparation treated with TEA. After a single stimulus, both recording sites show upstrokes followed by an initial phase of repolarization which is interrupted by a prolonged early afterdepolarization. After an initial period of quiescence, progressively larger, nondriven oscillatory responses are seen at both sites, and this activity terminates when the membrane potential reaches a level of maximum diastolic potential close to the prior resting potential. A similar sequence of events is repeated three times, but each of these subsequent sequences is initiated by a nondriven upstroke. The triggered activity then continues in a more regular fashion and terminates with a small and slow delayed afterdepolarization.

The records in Figure 6 suggest that triggered activity can be initiated and sustained by an alternating sequence involving an early afterdepolarization giving rise to slow response type action potentials at very depolarized levels of membrane potential and delayed afterdepolarizations giving rise to action potentials of large amplitude at more negative levels of membrane potentials. The synchrony of electrical activity at two recording sites separated by more than a length constant indicates that the membrane electrical activity is uniform and makes reentrant excitation an unlikely explanation for this activity.

**Discussion**

The results of this study show that myocardial hypertrophy induced by renal hypertension in the rat is associated with afterpotentials and triggered activity. Hypertrophied fibers giving rise to triggered activity in high [Ca\(^{2+}\)] showed physiological characteristics which distinguished them from fibers that did not. Such HBP preparations showed: (1) larger delayed afterdepolarizations, (2) a biphasic relation between afterpotential amplitude and drive cycle length (Fig. 3A), (3) a steep increase in the magnitude of delayed afterdepolarizations with an increasing number of preceding driven beats (Fig. 4A), and (4) shorter coupling intervals between the last driven action potential and the
delayed afterdepolarization (Figs. 3B and 4B). Those HBP fibers giving rise to triggered activity did so at a critical drive cycle length of 200 msec whereas fibers that did not produce triggered activity developed only a small delayed afterdepolarization at this same cycle length. 

The delayed afterdepolarizations recorded from HBP muscles exposed to high [Ca\(^{2+}\)]o have certain features in common with apparently similar electrical activity reported to occur in other cardiac tissues. For example, cardiac Purkinje fibers exposed to toxic concentrations of cardiac glycosides develop delayed afterpotentials which become larger as the rate of stimulation (Rosen et al., 1973a, 1973b; Davis, 1973; Ferrier et al., 1973; Ferrier and Moe, 1973; Ferrier, 1976; Rosen and Danilo, 1980) or number of preceding driven beats (Ferrier et al., 1973) increases. Purkinje fibers exposed to cardiac glycosides also develop triggered activity arising from delayed afterdepolarizations when the drive cycle length reaches a critical value of <600 msec (Ferrier et al., 1973) to 200-300 msec (Davis, 1973; Ferrier and Moe, 1973; Rosen and Danilo, 1980). The delayed afterdepolarizations obtained in digitalis-intoxicated Purkinje fibers also demonstrate a decrease in coupling interval as the drive cycle length decreases (Davis, 1973; Ferrier et al., 1973; Ferrier, 1976; Rosen and Danilo, 1980) and an increase in magnitude when [Ca\(^{2+}\)]o is increased (Ferrier and Moe, 1973). As reported for fibers of the simian mitral valve exposed to catecholamines (Wit and Cranefield, 1976), HBP fibers treated with high [Ca\(^{2+}\)], that give rise to triggered activity demonstrated a characteristic relationship between the magnitude of delayed afterdepolarizations and drive cycle length. 

HBP fibers treated with TEA also developed triggered activity, but this activity arises initially from an early afterdepolarization rather than a delayed afterdepolarization. An interesting feature of this kind of activity is that, even though it develops from an early afterdepolarization, it always terminates with a delayed afterdepolarization which may itself be capable of initiating a spontaneous action potential at a more negative level of membrane potential. The records in Figure 6B are compatible with such a sequence of events and suggest that the mechanism responsible for provoking triggered activity can alternate between early afterdepolarizations and delayed afterdepolarizations.

The results of previous studies on digitalis-induced delayed afterdepolarizations suggest that these afterpotentials are in some way dependent on [Ca\(^{2+}\)], since their magnitude increases when [Ca\(^{2+}\)]o increases and their magnitude is decreased by "slow channel blockers" such as verapamil and Mn\(^{2+}\) (see Cranefield, 1973, 1977; Rosen and Danilo, 1980). The delayed afterdepolarization of hypertrophied fibers show a similar dependence on [Ca\(^{2+}\)]. An important role for [Ca\(^{2+}\)] in the development of delayed afterdepolarizations is also suggested by our observation that these afterpotentials are accompanied by aftercontractions (Capasso and Aronson, unpublished observations), as previously reported (Ferrier, 1976; Heller, 1979). Although the afterpotentials recorded simultaneously from two or three sites separated by a length constant or more in the same HBP papillary muscle were synchronous in occurrence, they often varied in magnitude. This finding may be the result of variable electrotonic coupling between the surface and underlying cells in different parts of the muscle. Evidence supporting this view was reported in a study of digitalis-induced afterpotentials in canine Purkinje fibers (Saunders et al., 1973). In that study, the delayed afterdepolarizations recorded from completely isolated Purkinje fiber bundles were "essentially synchronous and similar in amplitude and configuration" at different recording sites. However, when the Purkinje fiber remained attached at both ends to pieces of ventricular muscle, simultaneous recordings showed that the afterpotential amplitude was small at sites near the muscle attachment and large at sites widely separated from the muscle attachment.

We previously have reported that HBP fibers have longer action potentials than those of SHAM fibers (Aronson, 1980). However, we were not able to establish a clear or simple relationship between the degree of action potential prolongation and the propensity of an HBP preparation to develop afterpotentials or triggered activity. In addition, high [Ca\(^{2+}\)], can both induce afterpotentials and shorten the duration of HBP action potentials.

Ultrastructural (Loud et al., 1978; Anversa et al., 1978; Wendt-Gallitelli et al., 1979) and biochemical (Jacob et al., 1977) alterations have been described in the model of cardiac hypertrophy used in this study. After 4-8 weeks of hypertension, these ultrastructural changes include enlargement of myocytes, an increase in contractile mass, expansion of capillary lumina, reduction in the mitochondria to-myofibril ratio, and a 2- to 3-fold increase in both smooth endoplasmic reticulum and T-system volume and surface area. Cardiac hypertrophy induced by renal hypertension is also associated with decreased activity of specific actomyosin Ca\(^{2+}\)-ATPase activity (Jacob et al., 1977). The relationship of these changes to the occurrence of afterpotentials is uncertain. It is possible that the ultrastructural changes influence the distribution and perhaps the free concentration of ions, such as Ca\(^{2+}\), and affect membrane electrical activity in this fashion. Alternatively, the Ca\(^{2+}\) binding and uptake capacity of newly synthesized membrane structures in hypertrophied fibers may be reduced and thereby lead to increased concentrations of intracellular Ca\(^{2+}\) which could, in turn, influence membrane electrical activity. Further studies are needed to investigate these possibilities.

Although the reduced activity of actomyosin
Ca\(^{2+}\)-ATPase may explain the reduced velocity of shortening observed in this model of cardiac hypertrophy (Jacob, 1977), the relation of this biochemical alteration to the development of afterpotentials is unclear. Further biochemical studies of the Ca\(^{2+}\) release and uptake system and of sarcolemmal Na\(^+\)-K\(^+\) ATPase will be required to establish whether biochemical alterations may contribute to the generation of afterpotentials in this model of cardiac hypertrophy.

Whatever the mechanism underlying the afterpotentials and triggered activity associated with cardiac hypertrophy, this kind of electrical activity could predispose hypertrophied hearts to a wide variety of rhythm disorders. The occurrence of sustained rhythmic activity that depends on afterpotentials for its initiation in our experimental model of myocardial hypertrophy as well as in human atrial fibers from diseased hearts (Mary-Rabine et al., 1980) suggests that triggered activity may be an important mechanism underlying arrhythmias in pathological cardiac tissues.

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