The Opposing Effects of Chronic Angiotensin-Converting Enzyme Blockade by Captopril on the Responses to Exogenous Angiotensin II and Vasopressin vs. Norepinephrine in Rats

FRANÇOIS SPERTINI, HANS R. BRUNNER, BERNARD WAEBER, AND HARALAMBOS GAVRAS

SUMMARY To study the influence of acute and chronic angiotensin-converting enzyme blockade on the pressor response to exogenous angiotensin II, vasopressin and norepinephrine, we gave normal female Wistar rats 100 mg of captopril or 1 ml of 5% glucose twice daily by gavage for 2 weeks. On the 15th day, rats were anesthetized with pentobarbital, and dose-response curves to angiotensin II, lysine-vasopressin, and norepinephrine were obtained before and after intraperitoneal injection of 100 mg/kg of captopril or 1 ml of 5% glucose. Acute as well as chronic converting enzyme blockade enhanced the pressor response to exogenous angiotensin II. Similarly, sensitivity to exogenous vasopressin was increased by both acute and chronic converting enzyme inhibition. In contrast, chronic converting enzyme blockade significantly blunted the response to exogenous norepinephrine, whereas acute blockade tended to accentuate its pressor effect. These results suggest that chronic angiotensin-converting enzyme blockade may partly inhibit sympathetic activity which, in turn, might contribute to the antihypertensive efficacy of this therapeutic approach. These results also point to an important physiological interaction between the two pressor hormones, angiotensin II and vasopressin.


OVER the past years, three pressor principles have been implicated in regulating normal blood pressure and in the pathogenesis of hypertensive diseases; i.e., (1) norepinephrine and the sympathetic nervous system (Louis et al., 1973), (2) angiotensin II and the renin system (Brunner et al., 1974), and (3) vasopressin (Mohring et al., 1976). Some interactions have been identified among these pressor systems (Gordon et al., 1967; Vander 1968; Malvin 1971; Peach 1974), but their precise role in maintaining normal and elevated blood pressure levels still is poorly understood.

Recently, a compound (captopril) (Ondetti et al., 1977) became available which can be taken by mouth and which blocks the conversion of the inactive angiotensin I to the pressor hormone, angiotensin II (Ferguson et al., 1977). Supposedly, this antagonist interferes specifically with only one of the three pressor systems mentioned. In this context, the considerable antihypertensive efficacy of this drug, when used to treat hypertensive patients, seems surprising (Gavras et al., 1978; Case et al., 1978; Brunner et al., 1979; Fouad et al., 1980). Some have attributed this effectiveness of converting enzyme blockade to possible bradykinin accumulation (Williams and Hollenberg, 1977) or overactivity of the kallikrein-bradykinin system. Because converting enzyme is identical to kininase II, its blockade could be expected to inhibit partly the inactivation of bradykinin (Érdös, 1975). However, with chronic converting enzyme inhibition, this hypothesis seems less likely, since, in rats with hypertension due to long-term angiotensin II administration, converting enzyme blockade did not reduce blood pressure (Tejedor et al., in press). Another possible explanation for the surprising efficacy of converting enzyme blockade in reducing blood pressure may derive from the influence of reduced angiotensin II levels on the pressor effect of the other vasoactive principles. Particularly, it seems important to find out whether reduced angiotensin II levels may change the pressor responsiveness to norepinephrine and thus to sympathetic activity. Accordingly, the present study was designed to investigate the pressor response to exogenous angiotensin II, vasopressin, and norepinephrine in normal rats before and after acute as well as chronic angiotensin-converting enzyme blockade.

Methods

Animals and Procedures

Female albino rats (Institut für biologisch-medicinische Forschung AG, Füllinsdorf, Switzerland)
TABLE 1  Experimental Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Gavage (15 days)</th>
<th>Intraperitoneal injection (final day)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1 ml b.i.d.</td>
<td>D5W</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D5W</td>
</tr>
<tr>
<td>2</td>
<td>D5W</td>
<td>1 ml b.i.d.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEI</td>
</tr>
<tr>
<td>3</td>
<td>CEI</td>
<td>100 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg/kg</td>
</tr>
</tbody>
</table>

D5W: 5% dextrose in water; CEI: converting enzyme inhibitor—captopril (E. R. Squibb).

weighing 180–200 g were maintained on a normal rat chow diet (U.A.R., Geneva) containing 103 mEq/kg of sodium and 197 mEq/kg of potassium. Prior to study, the rats were trained to accept medication by gavage twice daily.

Three groups, consisting of seven rats each, were studied. Group 1 received 1 ml of 5% glucose twice daily by gavage for 15 days. On the last day, as will be discussed later, 1 ml of 5% glucose was administered intraperitoneally during the final experiment (see Table 1). In group 2, treatment during the initial 15 days was identical. On the final day, captopril (Squibb Institute) 100 mg/kg in 1 ml of 5% glucose was injected intraperitoneally. Group 3 was treated for the first 2 weeks by twice daily gavage with captopril, 100 mg/kg in 1 ml of 5% glucose. On the last day, captopril, 100 mg/kg in 1 ml of 5% glucose, was administered intraperitoneally.

On the day of the experiment, all rats were anesthetized with sodium pentobarbital (Nembutal; Abbott) injected intraperitoneally. The dose of anesthesia was adapted in each group to maintain blood pressure at levels as close as possible to those obtained in awake animals. To this purpose, two additional series of rats (Groups 1' and 3') were maintained similarly to groups 1 and 3, but on the final day their blood pressure was measured intra-arterially in the awake state following surgical preparation under light ether anesthesia. Based on the findings of these additional studies, animals of group 3, 50 mg/kg of pentobarbital. Following anesthesia, the trachea was cannulated. Then venous catheters (PP10) were placed in each jugular vein. Both had been filled previously with 0.9% saline containing heparin, 50 U/ml. A PP50 catheter filled with the same heparin solution was introduced into the carotid artery and connected to a pressure transducer (Statham P23Dd; Hato Rey) for continuous blood pressure recording. This was monitored by means of an electro-galvanometer (Philips 2000; Eindhoven) and recorded on a light sensitive oscillograph (Manarp Electronic Institute Ltd.). The body temperature was maintained constant at 37°C (rectal) by a light placed over the animal. Following the surgical procedure, blood pressure was allowed to stabilize for at least 20 minutes. Subsequently, dose-response curves to norepinephrine, angiotensin I and II, and lysine-vasopressin were established as described below.

Solutions

Norepinephrine (Arterenol R; Hoechst) 1 mg/ml, was diluted 1:20 with 5% glucose to attain a final concentration of 50 mg/l of norepinephrine. Angiotensin I (Schwarz-Mann) was dissolved in water to a final concentration of 10 mg/liter. Angiotensin II (Hypertensin R, Ciba), 0.5 mg, was dissolved in 2 ml of 0.1 m acetic acid to yield a solution containing 250 mg/liter. Each morning prior to the experiment, a fresh solution was prepared by diluting this angiotensin II 1:50 in 5% glucose. The final concentration of angiotensin II was 5 mg/liter. Lysine-vasopressin (Vasopressin R; Sandoz) containing 10 IU/ml was diluted 1:4 by adding 5% glucose to yield a final concentration of 2.5 IU/ml. All stock solutions were stored at −30°C and thawed immediately prior to the experiment.

Experimental Protocol

In each rat, following stabilization of blood pressure, dose-response curves to angiotensin II, vasopressin, and norepinephrine were determined. The doses used for angiotensin II were 5, 10, and 20 ng, for norepinephrine 50, 100, and 200 ng, and for vasopressin 2.5, 5, and 10 mlU (which corresponds to 9.3, 18.5, and 37 ng). In addition, angiotensin I was injected at doses of 16 and 32 ng. First the smallest dose of each hormone was injected and then the doses were increased using a fixed sequence of the hormones. Between injections, blood pressure was allowed to return to baseline for at least 5–10 minutes. Following this first part of the experiment, all animals received an intraperitoneal injection of 1 ml containing, as outlined above, in group 1, 5% glucose and, in groups 2 and 3, captopril, 100 mg/kg. Forty minutes later, the dose-response curves to angiotensin II, vasopressin, and norepinephrine and injections of angiotensin I were repeated in identical fashion.

Statistics

The linear regression line for each dose-response curve of every pressor hormone was calculated in individual rats by the least squares method. In the figures, the mean regression lines for each hormone and group of animals are depicted before and after intraperitoneal injection. The slopes and the various points obtained with the same hormone were compared among the groups pre- and post-intraperitoneal injection using an analysis of variance (F-test) followed by Student's t-test for unpaired data (Freund, 1971).

Results

On the final day, i.e., after 2 weeks of gavage and following surgery, group 1 had a mean arterial pres-
sure of 118.2 ± 1.1 mm Hg (mean ± SEM) and group 2, 118 ± 2 mm Hg (see Table 2). The baseline blood pressure of group 3 was significantly lower than that of groups 1 and 2 (P < 0.001) at 80.2 ± 2.9 mm Hg. For comparison, blood pressures measured in awake animals (groups 1' and 3'), which had been treated similarly to groups 1 and 3, respectively, also are shown in Table 2. With the doses of pentobarbital used, the anesthetized rats exhibited blood pressures which did not differ from those observed in the corresponding non-anesthetized animals (P > 0.1). Intraperitoneal administration of glucose (group 1) did not change blood pressure, whereas the intraperitoneal injection of captopril significantly reduced mean arterial pressure of groups 2 (P < 0.001) and 3 (P < 0.001). The weights of rats in the three groups were not significantly different. Two doses of angiotensin I, i.e., 16 and 32 ng, were injected to evaluate the degree of converting enzyme blockade caused by the administration of captopril (Fig. 1). In group 1, intraperitoneal administration of glucose did not reduce the response to angiotensin I. In contrast, intraperitoneal injection of captopril in group 2 markedly blunted the response to angiotensin I. Group 3 already exhibited a weak response to angiotensin I prior to intraperitoneal injection as a result of the chronic gavage with captopril. Subsequent intraperitoneal administration of another dose of captopril had no further influence on the response to angiotensin I. Following intraperitoneal injection, the responses to both doses of angiotensin I were significantly reduced in group 2 (P < 0.001) as well as in group 3 (P < 0.001) when compared to those of group 1. The percent inhibition of converting enzyme will be calculated below following quantification of the angiotensin II response.

Figure 2 depicts the dose-response curves to angiotensin II. Prior to intraperitoneal injection, groups 1 and 2 exhibited similar responses to angiotensin II. The slope of the dose-response curve of group 3 was also similar, albeit slightly steeper (P > 0.1). However, it was significantly shifted to the left. Following the intraperitoneal injection, the response of group 2 was also shifted to the left in parallel fashion and approached that of group 3 though the slope of the latter now was significantly steeper than that of group 1 (P < 0.005). Thus, acute as well as chronic administration of the converting enzyme inhibitor markedly increased the sensitivity to angiotensin II.

Based on the findings shown in Figures 1 and 2, it is possible to calculate the percent blockade of converting enzyme induced by captopril administration. To do this, one has to take into account the increased sensitivity to angiotensin II following con-

**TABLE 2** Weight, Mean Arterial Pressure, and Pentobarbital Doses

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Wt (g)</th>
<th>MAP before i.p. injection (mm Hg)</th>
<th>MAP after i.p. injection (mm Hg)</th>
<th>Pentobarbital (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>7</td>
<td>190.9 ± 2.4</td>
<td>118.2 ± 1.1</td>
<td>115.1 ± 2.1</td>
<td>75</td>
</tr>
<tr>
<td>Group 2</td>
<td>7</td>
<td>191.1 ± 1.3</td>
<td>118 ± 2</td>
<td>73.1 ± 2.8*</td>
<td>75</td>
</tr>
<tr>
<td>Group 3</td>
<td>7</td>
<td>186.8 ± 3.7</td>
<td>80.2 ± 2.9*</td>
<td>57.6 ± 4.7*</td>
<td>50</td>
</tr>
<tr>
<td>Group 1' awake</td>
<td>7</td>
<td></td>
<td>116.6 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3' awake</td>
<td>7</td>
<td></td>
<td>84.8 ± 2.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAP: mean arterial pressure.
* P < 0.001 vs. group 1.
RESPONSE TO 3 PRESSOR HORMONES FOLLOWING CAPTOPRIL/Spertini et al. 615

RESPONSE TO ANGIOTENSIN II

Gavage Intraperitoneal injection

\[ \Delta \text{Mean Arterial Pressure} \]

mmHg

<table>
<thead>
<tr>
<th>Dose Angiotensin II ng</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
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</tbody>
</table>

**FIGURE 2** Dose-response curves to angiotensin II obtained before and after intraperitoneal injection of 5% dextrose (D5W) (group 1) or of captopril (CEI) (groups 2 and 3). Mean ± SEM; n = 7 in each group. *P < 0.05, **P < 0.01, and ***P < 0.001 vs. group 1. °°P < 0.01 vs. group 3.

When converting enzyme blockade (Thurston and Laragh, 1975). Thus, the response to a certain dose of angiotensin I before blockade is related to that obtained with a given dose of angiotensin II. Knowing the response to the same dose of angiotensin II obtained following converting enzyme blockade, one can then calculate by how much the response to angiotensin I would be increased if it were still converted to angiotensin II. One then can relate the observed blood pressure response to angiotensin II to that theoretical value. With this approach, the percent blockade was calculated for the group 2 animals based on the response to 32 ng of angiotensin I and found to be 78%.

**FIGURE 3** Dose-response curves to lysine-vasopressin obtained before and after intraperitoneal injection of 5% dextrose (D5W) (group 1) or of captopril (CEI) (groups 2 and 3). Mean ± SEM; n = 7 in each group. * * *P < 0.001 vs. group 1. °°P < 0.01 and °°°P < 0.001 vs. group 3.

Figure 3 depicts the dose-response curves to lysine-vasopressin. Prior to the intraperitoneal injection, only group 3 showed a net and significant increase in sensitivity to lysine-vasopressin accompanied by a steepening of the response-curve (P < 0.001). Similar to the findings with angiotensin II, following the intraperitoneal injection, group 2 animals also showed an increased sensitivity to lysine-vasopressin. The dose-response curve remained parallel to that of group 1. Again the slope of the group 3 response remained steeper (P < 0.001).

Finally, Figure 4 summarizes the responses to norepinephrine. Groups 1 and 2 had again very similar responses to norepinephrine prior to the intraperitoneal injection. In contrast, rats of group 3 with chronic blockade of converting enzyme exhibited a dose-response curve with a significantly flatter slope (P < 0.001). This blunted response persisted following intraperitoneal injection of captopril (P < 0.001). However, in group 2 animals after acute blockade, there was a slightly increased sensitivity, with a slope that was not different from that of group 1 animals. Thus, unlike the responses to angiotensin II and vasopressin, the response pattern to norepinephrine differed diametrically, depending on whether blockade of converting enzyme was only acute or had lasted for a prolonged period of time.

**Discussion**

We recently have reported that hypertensive patients treated chronically with converting enzyme blockade have normal plasma-converting enzyme activity 12 hours after the previous administration of the inhibitor. Notwithstanding, their blood pressure remained low (Waeber et al., 1980). Based on these findings, it was speculated that chronic blockade of converting enzyme, and thus chronic reduction of circulating angiotensin II levels, may reduce pressor responsiveness to angiotensin II. The present experiments were carried out to test this hypothesis. Chronic converting enzyme blockade did not reduce pressor responsiveness to angiotensin II: group 3 animals also exhibited an enhanced sensitivity to angiotensin II, as did group 2 animals following acute blockade of converting enzyme. In-
interestingly, the dose-response curves to vasopressin were similar to that obtained with angiotensin II following converting enzyme blockade. Thus, captopril administered acutely or chronically always enhanced the response to vasopressin. Contrasting with this increased sensitivity to both angiotensin II and vasopressin, the pressor response to exogenous norepinephrine was blunted significantly following chronic blockade of converting enzyme, although the norepinephrine response also was enhanced by acute captopril administration.

Before attempting to interpret the physiological meaning of these findings, we feel that it is appropriate to discuss the validity of the approach used in the present experiments. Inherent to the design of a study using whole animals is the problem that baseline blood pressure, on which the dose-response curves were constructed, varied among the groups both before and after intraperitoneal injections (Table 2). At least theoretically, pressor responsiveness might depend partially on the level of baseline blood pressure. That this was not the case in the present experiments is suggested by the dose-response curves observed in group 3, which hardly changed following the acute administration of captopril despite a blood pressure drop from 80.2 ± 2.9 to 57.9 ± 4.7 mm Hg (P < 0.001). Furthermore, it is most likely that a possible influence of blood pressure per se on responsiveness to pressor hormones would be non-specific and therefore should affect equally the sensitivity to angiotensin II, vasopressin, and norepinephrine. This has not been observed, and it is precisely the hormone-related specificity of the changes that seems to render the present observations most meaningful.

It should be pointed out that several authors have observed much smaller or no blood pressure changes following administration of captopril to normal animals (Bengis et al., 1978; Harris et al., 1978; Nishiyama et al., 1979), though others have had results similar to ours (Phelan and Clark, 1979). These differences may be due to differences in rat strains used in the study. More likely, however, the surprising blood pressure response of our rats was attributed to the relatively low sodium intake of about 1 mEq/day (average of several balance studies), which is clearly lower than that reported by Bengis and his coworkers (1978).

The increase in pressor responsiveness to angiotensin II following acute blockade of converting enzyme in group 2 confirms earlier findings using the nonapeptide teprotide to block the enzyme (Thurston and Laragh, 1975; Jaeger et al., 1978). This increased sensitivity to exogenous angiotensin II has been thought to be related to the decrease in circulating angiotensin II which may result in greater availability of vascular receptor sites to exogenous angiotensin II (Thurston and Laragh, 1975). The results obtained in group 3 extend this observation by demonstrating that there is no change in this phenomenon with time; prior to intraperitoneal captopril injection; the group 3 animals exhibited an increase in angiotensin II sensitivity similar to that of group 2 following acute captopril administration, although the slope of the response curve was somewhat steeper.

It has been proposed that there is a close interrelation between the renin system and vasopressin (Malvin, 1971; Vander, 1968). However, the emphasis usually has been on the mutual influence of these two pressure systems on their secretion rates. The present findings point to an interaction between the two hormones, vasopressin and angiotensin II, at the target organ, since the pressor responsiveness to these two hormones was similar in all three groups before and after the acute intraperitoneal injections. Particularly, the increase in sensitivity to vasopressin following acute or chronic blockade of converting enzyme activity when angiotensin II levels are low is a surprising finding. It thus appears that when circulating angiotensin II levels are reduced the pressor response to vasopressin is increased.

Recently, several authors have suggested that vasopressin may play an important role in some forms of experimental and possibly clinical hypertension (Mohring et al., 1976, 1977, 1978; Padfield et al., 1976; Crofton et al., 1979). Most often a pathogenetic role for vasopressin has been suggested in types of hypertension that are accompanied by sodium retention and extremely low renin and angiotensin II levels (Mohring et al., 1978; Crofton et al., 1979). According to our results, this would represent a situation when responsiveness to vasopressin should be enhanced.

Administration of captopril has been suggested to elicit an increase in prostaglandin I2 levels, probably as a consequence of increased bradykinin and/or angiotensin I levels (Moncada et al., 1979; Mullan et al., 1980). Such an increase of this potent vasodilator hormone could of course blunt the pressor response to vasoactive hormones, but it seems difficult to imagine that prostacyclins would specifically reduce the pressor response to norepinephrine while that to vasopressin and angiotensin II was enhanced. The same is true for a possible change in baroreceptor reflex activation. If captopril inhibits reflex changes in vascular resistance, as suggested recently (Powell et al., 1980), one would expect similar changes in the response curves to the different agonists.

The present observations do not allow us to dissociate a possible non-specific effect of captopril from its inhibitory action on angiotensin-converting enzyme, since no other antagonist such as teprotide has been studied. There exists however a body of evidence that angiotensin II interacts with the sympathetic nervous system and with norepinephrine to potentiate its vasopressor effect. Angiotensin II has been shown to enhance the vasoconstrictor effect of
of norepinephrine in isolated perfused organs (Sakurai and Hashimoto, 1965; Khairallah et al., 1971). Similarly, the vasopressor effect of sympathetic nerve stimulation has been accentuated by the infusion of angiotensin II (Panisset and Bourdois, 1968). Recently, subpressor doses of angiotensin II as well as increased angiotensin II levels due to renal artery stenosis have been shown to enhance the pressor response to norepinephrine, and this change could be reversed by the infusion of an angiotensin II antagonist (Ichikawa et al., 1978). The potentiating effect of angiotensin II on the response of arterial smooth muscle cells to norepinephrine has been attributed to a decrease in reuptake of norepinephrine (Panisset and Bourdois, 1968; Khairallah et al., 1971) or to increased norepinephrine release from the terminal nerve ending (Zimmerman et al., 1972).

The present observations extend these earlier findings by suggesting that long-term reduction of presumably normal angiotensin II levels to subnormal levels by inhibiting angiotensin converting enzyme markedly blunts pressor responsiveness to norepinephrine. These observations underline the key position of angiotensin II as a blood pressure regulator, since it not only has a pressor effect of its own but also enhances the pressor effect of the sympathetic nervous system and of circulating norepinephrine. Conversely, the present findings add a new dimension to the observed and surprising efficacy of captopril as an antihypertensive agent. It now seems conceivable that chronic angiotensin converting enzyme blockade by reducing circulating angiotensin II levels not only decreases the direct pressor action of angiotensin II, but also simultaneously blunts the vasoconstrictor effect of the sympathetic nervous system. Accordingly, chronic pharmacological reduction of circulating angiotensin II levels seems to provide an ideal approach to treat hypertensive diseases.

References


SUMMARY The inward current ("oscillatory current") which may be present after the end of a depolarizing clamp was studied in sheep cardiac Purkinje fibers by means of a voltage-clamp method. The following results were obtained. In order to appear, the oscillatory current (Io) requires a previous depolarization to -20 mV or beyond and a repolarization to -40 mV or to more negative potentials. The Io requires a minimum duration of the depolarizing clamp and becomes larger with longer clamps. With repolarization to more negative potentials (< 90 mV), Io becomes smaller and may disappear. Also, Io can be triggered twice if the potential is clamped to two different levels in succession. By several procedures which modify the other known currents (fast Na+ current, slow inward current, early outward current, plateau current Ixi, and pacemaker current), it can be demonstrated that Io is not due to their oscillatory behavior and can occur in the absence of any one of them. Interventions which increase the contractile force presumably by increasing intracellular calcium stores enhance the Io, or may make it appear. In fact, these interventions may extend the voltage range over which Io appears. These interventions include lowering potassium, increasing calcium, trains of depolarizing clamps, and administration of norepinephrine and of strophanthidin. It is concluded that Io is a physiological event which is enhanced by certain procedures, and it appears to be of much importance in drive-induced arrhythmias under different conditions. Circ Res 48: 618–631, 1981

IN spontaneously active Purkinje fibers, a fast drive usually is followed by a transient period of quiescence ("overdrive suppression," see Vassalle, 1977). However, there are situations (in the presence of norepinephrine) in which the fast drive may be followed by the induction or acceleration of spontaneous discharge ("overdrive excitation," Vassalle and Carpentier, 1972). Overdrive excitation can be shown to occur also in the ventricle of dogs with recently induced complete atrioventricular block (Vassalle et al., 1976a, 1977) and to be favored by sympathetic stimulation, norepinephrine administration, and calcium infusion (Vassalle et al., 1976b).

The mechanism of overdrive excitation is not clearly understood and it has been postulated that the induction of a fast rhythm in vivo may be due to the development of an oscillatory potential superimposed on diastolic depolarization (Vassalle et al., 1977). In fact, it is known that, in the presence of an increased extracellular calcium concentration, an oscillatory potential is present during diastole and becomes exaggerated with fast drive (Temte and Davis, 1987). Furthermore, overdrive can induce oscillatory potentials leading to triggered activity (Cranefield, 1975; Wit and Cranefield, 1977) in canine Purkinje fibers exposed to norepinephrine and calcium (Valenzuela and Vassalle, 1978).

An Oscillatory Current in Sheep Cardiac Purkinje Fibers

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