A Possible Role for Endogenous Prostaglandins in the Electrophysiological Effects of Acetylstrophanthidin on Isolated Canine Ventricular Tissues

Margaret P. Moffat, Gregory R. Ferrier, and Morris Karmazyn
From the Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada

SUMMARY. A possible role for endogenous prostaglandins in the toxic electrophysiological effects of the aglycone acetylstrophanthidin was studied in isolated canine Purkinje fiber papillary muscle preparations by standard microelectrode techniques. Acetylstrophanthidin (5 x 10^-4 g/ml) caused a significant increase in 6-keto-prostaglandin F1 alpha release from these preparations. A significant loss of membrane potential and the development of oscillatory afterpotentials was observed, as well. Administration of either of two nonsteroidal antiinflammatory agents, indomethacin (3 x 10^-5 g/ml) or aspirin (5 x 10^-5 g/ml), in the presence of acetylstrophanthidin, abolished the stimulation of 6-keto-prostaglandin F1 alpha release and delayed and attenuated the loss of membrane potential and the development of oscillatory afterpotentials. In addition, indomethacin and aspirin appeared to preserve the electrogenic pumping capacity of Purkinje fiber cells exposed to acetylstrophanthidin. Exposure of Purkinje tissues to acetylstrophanthidin inhibited post-pacing hyperpolarization normally exhibited by these tissues. Both indomethacin and aspirin decreased this inhibition. Addition of prostacyclin (1 ng/ml) after 30 minutes of exposure to acetylstrophanthidin to preparations in which endogenous prostaglandin synthesis had been inhibited, resulted in a significant increase in the amplitude of oscillatory afterpotentials within 2 minutes. These results suggest that the presence of endogenous prostaglandins may play a role in the development of the toxic electrophysiological effects associated with acetylstrophanthidin. (Circ Res 58: 486-494, 1986)

VENTRICULAR arrhythmias are a major toxic effect of cardiac glycosides. These arrhythmias may occur as a result of induction of automaticity within the specialized conducting system of the ventricles or through changes in conduction of the normal impulse. In earlier studies, we demonstrated that toxic concentrations of the aglycone, acetylstrophanthidin, induced oscillatory afterpotentials (OAP) (also called delayed afterdepolarizations) in isolated canine Purkinje tissues (Ferrier et al., 1973). That study demonstrated that OAP could reach threshold, and that they represented a mechanism of abnormal automaticity. Cardiac glycosides also have been shown to induce OAP in isolated Purkinje fibers (Rosen et al., 1973a) and to do so at a concentration corresponding to that which induces arrhythmias in the anesthetized dog (Rosen et al., 1973b). The cellular mechanism by which digitalis agents induce OAP is not completely understood. However, an increase in intracellular calcium following exposure to cardiac glycosides, widely believed to result from the inhibition of Na^+,K^+-adenosine triphosphatase (ATPase) (Akera and Brody, 1978), is probably involved in both the therapeutic and toxic effects of these drugs. A transient inward current (TI) which occurs in the presence of strophanthidin has been identified (Kass et al., 1978b). The current is believed to be activated by oscillatory release of calcium from intracellular stores (Kass et al., 1978a). This oscillatory release may be responsible both for OAP and for aftercontractions (Ferrier et al., 1973; Kass et al., 1978b).

There is some evidence that suggests prostaglandins (PG) may play a role in the effects of cardiac glycosides. Mest et al. (1981) have reported release of prostaglandins from canine hearts exposed to ouabain. Similarities also exist between the actions of glycosides and prostaglandins. Both groups of agents have been shown to inhibit Na^+,K^+-ATPase (Akera and Brody, 1978; Karmazyn et al., 1981), and both can exert a positive inotropic effect on the heart (Akera and Brody, 1978; Karmazyn and Dhalla, 1983). In addition, some prostaglandins have been demonstrated to induce arrhythmias (Karmazyn and Dhalla, 1980). The purpose of the current investigation was to determine whether the aglycone acetylstrophanthidin could stimulate prostaglandin synthesis in isolated canine tissues and whether such synthesis might be related to the development of OAP or other electrical changes normally associated with arrhythmogenic concentrations of the drug.

Methods

Mongrel dogs of either sex were anesthetized with sodium pentobarbital (Somnitol, 30 mg/kg, iv), and their
hearts were rapidly excised. Papillary muscle/false tendon preparations were dissected from both ventricles. The preparations were studied in a chamber perfused with modified Tyrode's solution with the following millimolar composition: NaCl, 137; KCl, 4.0; CaCl₂, 2.5; NaH₂PO₄, 0.9; NaHCO₃, 20.0; MgSO₄, 0.5; and dextrose, 5.5. The solution was gassed continuously with a mixture of 95% O₂/5% CO₂ and the temperature was maintained at 37°C. Bipolar stimuli were delivered to the surface of the papillary muscle through two silver wires insulated except at the tip. Rectangular pulses, 3 msec in duration at 1.5 times threshold, were initiated by an optically isolated digital pulse generator (Frederick Haer). Stimuli were delivered at a basic cycle length (BCL) of 500 msec in trains of 15 beats except as noted below. Trains were separated by 3-second pauses. Transmembrane potentials were recorded with glass microelectrodes filled with 2.7 M KCl (tip resistance 20–30 MΩ). Electrical recordings were displayed on a Tektronix 5110 oscilloscope and photographed with a Grass camera.

Preparations were equilibrated in normal Tyrode's solution containing acetylsalicylic acid (AS; 5 × 10⁻⁸ g/ml) for 60 minutes. Following a washout period of 1 hour with drug-free Tyrode's solution, either indomethacin (3 × 10⁻⁴ g/ml) or aspirin (5 × 10⁻⁸ g/ml) was added and superfusion was continued for 30 minutes. The same preparations were reexposed to AS (5 × 10⁻⁸ g/ml) in the presence of indomethacin or aspirin for an additional 40 minutes. The reverse order was not used, because the effects of both inhibitors of prostaglandin synthesis are not readily reversible. Also, in preliminary experiments, we found that two 40-minute exposures to AS alone, with an intervening washout period comparable to that used in the present study, resulted in essentially identical electrophysiological effects.

At 10-minute intervals during exposure to AS, the response of Purkinje tissue to changes in BCL (300–700 msec in 100-msec increments) was determined. Pulses were delivered in two consecutive trains of 15 beats separated by a 3-second pause for each BCL tested. Following this, we assessed sodium-potassium pump activity by determining the response of membrane potential to pacing. After the test periods, the preparations were again superfused with drug-free Tyrode's solution to achieve a final concentration of 3 × 10⁻⁸ g/ml. Vehicle controls demonstrated that the final concentration of alcohol had no detectable effects on our preparations.

As a measure of endogenous prostaglandin synthesis, we assayed 6-keto-PGF₁α, the hydrolysis product of prostacyclin. PG release was measured in samples of the superfusate by radioimmunoassay using a double antibody technique (Karmazyn et al., 1982). Release is considered to be indicative of de novo synthesis because prostaglandins are not stored in tissues. In experiments in which the effects of aspirin and indomethacin did not differ, results were pooled for analysis. Results were analyzed by a completely randomized analysis of variance. Minimum statistical significance was taken as P < 0.05.

**Results**

The effects of AS on release of 6-keto-PGF₁α from isolated canine false tendon/papillary muscle preparations is shown in Figure 1. Before exposure of the tissue to AS (time = 0), basal release of PG was 638 ± 76 pg/min. Release of PG increased to 1272 ± 254 pg/min after exposure to AS for 10 minutes. This increase persisted at 20, 30, and 40 minutes, and all values were significantly greater than basal release. These results demonstrate a substantial stimulation of prostacyclin production throughout 40 minutes of exposure to the aglycone. Prostaglandin levels remained elevated above basal values during the subsequent 60-minute wash with drug.

![Figure 1. The effects of acetylsalicylic acid (5 × 10⁻⁸ g/ml) on 6-keto-PGF₁α release from isolated false tendon/papillary muscle preparations. 0 min represents basal (pre-acetylsalicylic acid) release. Time indicates minutes after the addition of acetylsalicylic acid. *P < 0.05, **P < 0.01 = significantly greater than basal release (n = 7).](http://circres.ahajournals.org/Downloadable/1982/00487F1.jpg)
free Tyrode's solution. The addition of either indomethacin or aspirin to the Tyrode's solution at this time reduced 6-keto-PGF₁α release to basal (pre-AS) or lower values (INDO 360 ± 48, ASA 458 ± 62 pg/min). These values represent the release of 6-keto-PGF₁α in the presence of the inhibitor before exposure to AS. Subsequent exposure to AS did not significantly increase release of 6-keto-PGF₁α above these values. These effects are consistent with the known actions of both nonsteroidal antiinflammatory agents to inhibit cyclooxygenase and reduce prostaglandin biosynthesis (Flower, 1974). In preparations that had not been exposed previously to AS, both nonsteroidal antiinflammatory agents suppressed basal synthesis to below detectable limits (5 pg/ml, data not shown). However, because ASA is an irreversible inhibitor of PG biosynthesis and the effects of indomethacin on synthesis are slow to wash out, the experiments testing the effects of these agents on the response of Purkinje tissue to AS usually were performed subsequent to the control experiment.

Figure 2 illustrates the time course of development of OAP in a fiber exposed to AS, washed, and then reexposed to AS in the presence of indomethacin. After 10 minutes of exposure to AS, either in the absence (panel A) or in the presence (panel D) of indomethacin, no OAP were observed. After 20 minutes, the preparation displayed a small OAP coupled to the last driven beat of the train when no indomethacin was present (panel B). However, in the presence of the drug, the same preparation did not exhibit OAP (panel E). Similarly after 30 minutes in the presence of AS alone (panel C), a prominent OAP followed by a smaller one was observed. In the presence of indomethacin (panel F), no OAP was noted.

Figure 3 illustrates the effect of aspirin on the development of the arrhythmogenic effect of acetylstrophanthidin in canine Purkinje fibers. Panels A and D show the activity in Purkinje tissue before administration of AS either in the absence (panel A) or presence (panel D) of aspirin (5 × 10⁻⁵ g/ml). In this experiment, exposure to AS alone resulted in the development of OAP which reached threshold at 6 minutes and initiated ectopic activity. After 20 minutes of exposure to AS (panel B), ectopic activity was seen throughout the pause in stimulation. The coupling interval of this activity was slightly less than the preceding basic cycle length of 500 msec and resulted in the appearance of a trigeminal rhythm during driven activity. Each driven beat, indicated by the stimulus record, was followed by two spontaneous beats. By 40 minutes, the cycle length of the ectopic activity during the pause had
decreased and a stable bigeminal rhythm was observed during driven activity. In contrast, when the same tissue was exposed to AS for 20 minutes in the presence of aspirin (panel E), only a low amplitude OAP was noted. Oscillatory afterpotentials did not reach threshold until 36 minutes (panel F), at which time ectopic activity was observed during the pause. However, the coupling interval exceeded the basic cycle length of stimulation (500 msec), and spontaneous activity was not observed upon resumption of stimulation. These results show that indomethacin and aspirin, two nonsteroidal antiinflammatory agents, are able either to suppress or delay the development of OAP and ectopic activity in canine Purkinje fibres exposed to acetylstrophanthin.

Cardiac glycosides are known to decrease membrane potential; therefore, we studied the effects of AS on membrane potentials in the absence and presence of aspirin and indomethacin. Figure 4 shows the effect of AS on the resting membrane potential of canine Purkinje fibers under these conditions. AS caused a significant decrease in membrane potential when compared to control following 10 (P < 0.05), 20, 30, and 40 min (P < 0.01) of exposure. Washout with normal Tyrode’s solution for 60 minutes restored membrane potential to control values. Addition of either indomethacin or aspirin to the Tyrode’s solution after washout did not alter membrane potential (INDO 90.2 mV, ASA 90.7 mV). However, both drugs were able to delay and attenuate the decline in membrane potential observed upon addition of AS. Thus, the decline in membrane potential was significantly greater in preparations treated with AS alone than when the same preparations were exposed to the aglycone in the presence of indomethacin (n = 6) or aspirin (n = 3). Differences between control and treated groups were significant at 20 minutes and remained so until the end of the experiment (P < 0.05).

The time course of appearance of oscillatory afterpotentials (OAP) in preparations treated with AS in the absence and presence of indomethacin or aspirin is shown in Figure 5. In preparations treated with AS alone, OAP appeared in only one of nine Purkinje fibres after 10 minutes of exposure to drug. This incidence increased rapidly with time and eight of nine preparations displayed OAP by 20 minutes. From 25 minutes onward, all Purkinje fibers studied exhibited OAP. In one experiment, OAP reached threshold (see Fig. 3), and spontaneous activity continued for the duration of the exposure to AS. Sixty-minute superfusion with drug-free Tyrode’s solution abolished OAP in all preparations. The same preparations were then exposed to AS in the presence of either indomethacin (n = 6) or aspirin (n = 3). In these experiments, OAP were not detected in any preparation until 20 minutes (Fig. 5). At that time, four of nine preparations exhibited oscillations. The incidence increased steadily and eight of nine preparations displayed OAP by the end of the experiment (40 minutes). Since inhibition of PG synthesis by indomethacin or aspirin delayed the onset of OAP, we studied the effect of these agents on the amplitude of OAP.

Both inhibitors of PG synthesis not only delayed the onset of OAP (Fig. 5), but also decreased the amplitude of the afterpotentials throughout the experimental period. Figure 6 illustrates the influence of indomethacin and aspirin on the increase in amplitude of acetylstrophanthin-induced OAP with
time at two different cycle lengths. At both longer (700 msec) and shorter (300-msec) cycle lengths, the amplitude of OAP increased with time in both groups. Nevertheless, from 20–40 minutes, in the presence of indomethacin or aspirin, AS elicited OAP of significantly smaller amplitude, compared to the values obtained when the same preparations were exposed to AS alone. Data collected at two cycle lengths are shown; however, a wide range of cycle lengths were tested and the results did not differ from those shown in Figure 6.

Figure 7 illustrates the amplitude of the most prominent OAP following driven action potentials at different cycle lengths of stimulation in both groups after 30 minutes of exposure to AS. The amplitude was less at all cycle lengths in preparations exposed to AS in the presence of prostaglandin synthesis inhibitors than in those exposed to AS alone. However, the change in OAP amplitude with cycle length for both groups was essentially parallel. The coupling interval of OAP also varies with cycle length of stimulation. OAP are coupled to the previous driven beat at an interval approximately equal to the cycle length of the stimulation (Ferrier, 1977). We found that inhibitors of prostaglandin synthesis did not alter the coupling intervals of OAP.

The effects of PG inhibition on postpacing hyperpolarization were studied in six preparations exposed to AS. The results of this study are shown in Figure 8. Preparations were stimulated continuously for 60 seconds at a BCL of 1000 msec, 90 seconds at a BCL of 300 msec, and a final period of 60 seconds at a BCL of 1000 msec. Before administration of AS, inhibitors of PG synthesis did not affect post-pacing hyperpolarization. In control preparations rapid pacing resulted in a loss of membrane potential from —91 mV to —87 mV. Restoration of the slow stimulation rate caused an increase in membrane potential which reached a maximum of —94 mV (Fig. 8A). In preparations exposed to indomethacin or aspirin, rapid pacing decreased membrane potential from —90 mV to —88 mV, and return to a basic cycle length of 1000 msec resulted in an increase in membrane potential to —92 mV (Fig. 8B). The time to achieve maximum membrane potential following the period of rapid pacing was variable. However, by 60 seconds, under control conditions, the membrane potential had returned to the values observed prior to rapid drive in both groups. Following 20 minutes of exposure to AS, the mean membrane potential in the control group was —87 mV. Rapid pacing resulted in a further loss of membrane potential to —83 mV. When stimulation at a basic cycle length of 1000 msec was reinstated, the mem-
brane potential increased to the initial values but did not exceed them as observed under control conditions. In contrast, after 20 minutes of exposure to AS, in the presence of prostaglandin synthesis inhibitors, membrane potential declined less (2 mV vs. 4 mV) in response to AS, and rapid drive caused a smaller depolarization (2 mV vs. 4 mV). Also, return to initial conditions again resulted in an increase in membrane potential to a maximum of −90 mV which exceeded the pre-rapid pacing value of −89 mV for this group.

By 40 minutes, membrane potential had declined to −85 mV in preparations treated with AS alone. Rapid drive further decreased membrane potential by 4 mV, and restoration of the basic cycle length to 1000 msec resulted in an increase of membrane potential only to pre-rapid drive values. In the presence of prostaglandin synthesis inhibitors, 40 minutes of exposure to AS resulted in a much smaller decline in membrane potential (2 mV vs. 6 mV) and attenuated the further depolarization caused by rapid pacing (3 mV vs. 4 mV). Restoration of the BCL to 1000 msec resulted in restoration of membrane potential. However, by this time, the pre-rapid pacing values were no longer exceeded. It appears, therefore, that inhibition of prostaglandin synthesis during exposure to AS may help to preserve the electrogenic pumping capacity of Purkinje cells.

If release of endogenous prostaglandins contributes to the induction of OAP by AS, adding exogenous prostaglandin to preparations exposed to AS but in which prostaglandin synthesis has been inhibited, should promote or potentiate the appearance of OAP. This hypothesis was tested in eight experiments. Figure 9 illustrates the typical response of Purkinje tissue to addition of exogenous PGI2 (1 ng/ml). In these experiments, endogenous PG synthesis was inhibited by exposing the tissues to indomethacin for 30 minutes before adding the AS. In the experiment illustrated in Figure 9, the tissue displayed a small OAP (4.1 mV, panel A) after exposure to AS for 30 minutes. Panel B was recorded from the same tissue 2 minutes after the addition of PGI2. The OAP had increased in amplitude to 7.8 mV. This increase persisted at 5 minutes (panel C). In six of six experiments in which small OAP could be elicited in the presence of indomethacin, the mean amplitude of OAP increased from 3.4 ± 1.0 mV to 6.2 ± 1.4 mV within 2 minutes of prostacyclin addition. In two additional experiments, 30 minutes of exposure to AS failed to elicit any OAP, and addition of PGI2 did not result in the appearance of OAP.

Discussion

This study demonstrates that prostaglandins may have a role in the development of OAP in canine Purkinje fibers exposed to acetylstrophanthidin. Exposure of isolated false tendon/papillary muscle preparations to the aglycone resulted in a significant stimulation of prostaglandin synthesis. This result is in agreement with the observation of Mest et al. (1981), who reported that administration of ouabain to dogs in vivo caused an increase in prostaglandin release into coronary sinus blood. That study involved the measurement of PGE and PGF2α, whereas, in the present investigation, we found an increase of 6-keto-PGF1α, the hydrolysis product of PGI2. Thus, the stimulation of prostaglandin synthesis by cardiac glycosides and aglycones is probably of a general nature. We chose to measure PGI2 as an index of prostaglandin synthesis, principally because it is the major arachidonic acid metabolite produced by either the whole heart or isolated car-
FIGURE 9. Effect of prostacyclin (1 \times 10^{-6} g/ml) on the transmembrane activity of Purkinje fibers which had previously been exposed to acetylstrophanthidin (5 \times 10^{-5} g/ml) for 30 minutes in the presence of indomethacin (3 \times 10^{-5} g/ml) (panel A). Panels B and C illustrate this activity 2 and 5 minutes after the addition of prostacyclin to the superfusate. Traces show trains of 15 driven responses at a BCL of 500 msec.

Circulation Research/Vol. 58, No. 4, April 1986

Arrhythmias both in vivo (Goldenberg and Rothberger, 1931) and in vitro (Dudel and Trautwein, 1958; Vassalle et al., 1962). Both aglycones (Ferrier et al., 1973) and glycosides (Rosen et al., 1973) cause the development of oscillations in transmembrane potential. If OAP are of sufficient amplitude, they may initiate ectopic activity (Ferrier et al., 1973). The OAP appearing in specialized conducting tissue of the ventricle are believed to be related to the arrhythmias seen in whole heart (Zipes et al., 1974).

Our results demonstrate a time-related loss in membrane potential in Purkinje fibers exposed to acetylstronanthidin which can be blocked, at least in part, by inhibition of prostaglandin biosynthesis. The time to onset of OAP, as well as their amplitude, are known to be voltage-dependent (Ferrier, 1973; Wasserman and Ferrier, 1981) and, thus, it is possible that the ability of prostaglandin synthesis inhibitors to retard the development and decrease the amplitude of OAP, as shown in this study, may be related in part to maintenance of membrane potential. The glycoside-induced loss of membrane potential is believed to be a consequence of inhibition of Na\(^{+},K\(^{+}\)-ATPase, and both glycosides (Aker and Brody, 1978) and prostaglandins (Karmazyn et al., 1981) have been shown to inhibit the activity of this enzyme. Evidence suggesting the possible involvement of prostaglandins in Na\(^{+},K\(^{+}\)-ATPase inhibition by AS was demonstrated by testing the electrogenic pumping capacity of the preparations. We observed that inhibition of prostaglandin biosynthesis during exposure to AS decreased the loss of membrane potential caused by a 90-second period of overdrive. Indomethacin or aspirin also increased the length of time Purkinje fibers were able to exceed the maximum membrane potential which had been observed prior to rapid drive, upon return to the slower stimulation pattern. However, these results by no means prove that prostaglandins are involved in the inhibition of Na\(^{+},K\(^{+}\)-ATPase by cardiac glycosides, and direct effects of prostaglandins on sodium influx or on the transient inward current cannot be excluded.

The inotropic effects of cardiac glycosides are believed to be a consequence of Na\(^{+},K\(^{+}\)-ATPase inhibition (Aker and Brody, 1978), and it is possible the toxic electrical effects may also be related, at least in part, to this action. From the results described here, it is tempting to speculate that stimulation of prostaglandin synthesis by AS may contribute to inhibition of Na\(^{+},K\(^{+}\)-ATPase. This would provide one explanation for the effects of prostaglandin synthesis on changes in membrane potential and development of OAP in response to acetylstrophanthidin. Nevertheless, some loss of membrane potential and development of OAP can occur in the presence of indomethacin and aspirin, suggesting that Na\(^{+},K\(^{+}\)-ATPase is still inhibited to some extent in the absence of stimulation of prostaglandin synthesis.
In preparations intoxicated by AS, washout of AS resulted in restoration of membrane potential and disappearance of OAP at a time when prostaglandin levels were still elevated. Thus, it would appear that prostaglandins do not cause loss of membrane potential or OAP in the absence of AS. It would seem from these data that prostaglandins might play a synergistic rather than a direct role in the inhibition of Na⁺,K⁺-ATPase by glycosides. In this regard, Akera and Brody (1978) have suggested that a lesser degree of sodium pump inhibition is required for the positive inotropic response than is present at the time when toxic electrophysiological effects become manifest. Thus, it is possible that the maximum inhibition of the sodium pump produced by endogenously released PG’s is insufficient to cause overt electrophysiological changes by itself, but is sufficient to cause a measurable difference when this effect is exerted upon the sodium pump when it is already partially inhibited by glycoside or aglycone.

Preliminary results from our laboratory suggest that there may be a dissociation between the mechanical and electrical effects of AS. Prostaglandin synthesis inhibitors do not appear to prevent the inotropic response of Purkinje fibers to AS (Moffat et al., 1983). Since the mechanical response precedes the development of OAP under the conditions used in this study, the two events may have different mechanisms. Alternatively, as noted above, it may be that the inotropic response requires a lesser degree of Na⁺,K⁺-ATPase inhibition than that required for the appearance of electrical toxicity.

One may ask whether the ability of prostaglandin synthesis inhibitors to retard or suppress induction of OAP is specific for OAP induced by digitalis agents or extends to OAP generated in response to other conditions. In a recent study, we have shown that OAP plus marked depolarization occur in an isolated Purkinje tissue model of ischemia-reperfusion arrhythmias (Ferrier et al., 1985). We also have demonstrated that release of endogenous cardiac prostaglandins plays an important role in this reperfusion response. However, in this model of arrhythmic mechanisms, inhibition of prostaglandin synthesis abolished depolarization but did not eliminate OAP (Moffat et al., 1984). In preliminary experiments, we have also examined the induction of OAP in Purkinje tissue by elevated levels of calcium. In these experiments, induction of OAP was not inhibited by indomethacin (unpublished observation).

Thus, at the present time, the role of prostaglandins in the induction of OAP appears to be specific for digitalis (AS) intoxication. Whether other conditions known to elicit OAP (catecholamine, barium, etc.) involve a role for endogenous prostaglandins can only be determined by additional experiments.

In conclusion, we have demonstrated that isolated canine tissues exposed to AS release significantly elevated levels of 6-keto-PGF₁α, compared to basal values. The decrease in membrane potential, as well as the development of oscillations in transmembrane potential characteristic of AS intoxication, is delayed and attenuated in the presence of inhibitors of prostaglandin biosynthesis. Our results further suggest that prostaglandins might participate in the inhibitory effect of AS on Na⁺, K⁺-ATPase and that it is this action which might be affected by indomethacin and aspirin. Furthermore, in this study, the actions of prostaglandins on membrane electrical properties appear to be dependent on the simultaneous presence of AS.

We wish to thank Rita Bekkers and Claire Cayette for excellent technical assistance. Sodium ibuprofen was generously supplied by the Upjohn Company of Canada.

Supported by the Medical Research Council of Canada.

Dr. Moffat was a Postdoctoral Fellow of the Medical Research Council of Canada. Her present address is: Department of Pharmacology and Toxicology, University of Western Ontario, London, Ontario, Canada, N6A 5C1.

Address for reprints: Dr. Gregory R. Ferrier, Department of Pharmacology, Sir Charles Tupper Medical Building, Dalhousie University, Halifax, Nova Scotia, Canada, B3H 4H7. Received May 11, 1984; revised in revised form December 18, 1985; accepted for publication January 22, 1986.

References


de Deckere EAM, Nugteren DH, Ten Hoor F (1977) Prostacyclin is the major prostaglandin released from isolated perfused rabbit and rat heart. Nature (Lond) 268: 160-163


Kass RS, Tsien RW, Weingart R (1978b) Ionic basis of transient inward current induced by strophanthin in cardiac Purkinje...
fibres. J Physiol (Lond) 281: 209–226
Moffat MP, Ferrier GR, Karmazyn M (1983) Role of prostaglandins in the electrical and contractile effects of acetylstrophanthin in isolated cardiac tissues (abstr). Circulation 68: (suppl III): 219

INDEX TERMS: Acetylstrophanthidin • Arrhythmias • Prostaglandins • Oscillatory afterpotentials • Cardiac glycosides
A possible role for endogenous prostaglandins in the electrophysiological effects of acetylstrophanthidin on isolated canine ventricular tissues.
M P Moffat, G R Ferrier and M Karmazyn

Circ Res. 1986;58:486-494
doi: 10.1161/01.RES.58.4.486

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/58/4/486

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/