Original Article

Chronic Hypertension Induced by Ouabain but Not Digoxin in the Rat: Antihypertensive Effect of Digoxin and Digitoxin

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Elevated circulating levels of an endogenous ouabain (EO) have been associated with essential hypertension. To investigate structure-activity relationships relevant to blood pressure, we infused either ouabain, ouabagenin, digoxin or digitoxin at 30 μg/kg/day in normal Sprague Dawley rats. After five weeks, the ouabain and ouabagenin infused rats were hypertensive, whereas blood pressures declined below their vehicle controls in rats infused with digoxin or digitoxin. In a second study, mean blood pressures were 118.5 ±1.7 mmHg in rats infused with ouabain (15 μg/kg/day) on day 35 vs. 98.3±1.8 and 100.3±1.1 mmHg in the digoxin (30 μg/kg/day) and vehicle infused groups (both p<0.005 vs. ouabain), respectively. Plasma and kidney levels of ouabain immunoreactivity were increased 4-8 fold in ouabain infused rats while blood pressure and plasma levels of ouabain returned to normal one week following discontinuation of the steroid infusion. In rats with ouabain-dependent hypertension, secondary infusions of digoxin or digitoxin (30 μg/kg/day) normalized blood pressure even though circulating ouabain remained elevated. In digoxin infused rats, neither blood pressure nor kidney digoxin immunoreactivity was raised whereas plasma digoxin was increased. Collectively, the results show that the hemodynamic effects of these sodium pump inhibitors differ dramatically during prolonged administration and that tissue rather than circulating levels of these agents appear to better explain their effects on blood pressure. These studies suggest that sodium pump inhibition is not the exclusive mediator of the hemodynamic effects of these cardiac glycosides and demonstrate the presence of structure-specific mechanisms that regulate their tissue levels and effects on long-term blood pressure. (Hypertens Res 2000; 23 Suppl: S77-S85)

Key Words: sodium pump, endogenous, blood pressure, cardiac glycosides, kidney

Introduction

Following the early documentation (1) of the therapeutic properties of the digitalis cardiac glycosides and their widespread use, the existence of a conserved receptor for the cardenolides and bufadienolides in mammals has fueled speculation regarding the existence of an endogenous mammalian counterpart. Much evidence suggests that endogenous sodium transport inhibitors circulate in amphibians and mammals and are present in elevated amounts in the blood of hypertensive animals (2, 3). Further, diminished sodium pump activity may be important in the etiology of hypertension (4-6). However, the significance of endogenous inhibitors of the sodium pump in hypertension has been controversial. One reason is that digitalis glycosides, while widely prescribed, have a short-term vasopressor action in humans (7) but fail to induce

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chronic hypertension among patients undergoing prolonged therapy. In addition, the short-term administration of ouabain and digitalis preparations in some other animal species does not evoke large sustained increases in blood pressure (8-12). Another problem is that some studies have used species such as dogs and sheep that are not thought to develop essential hypertension (8, 10). These species, while capable of secondary forms of high blood pressure, may lack some key mechanism that accounts for the relative ease with which essential hypertension appears among humans and rats.

Recently, an endogenous sodium pump inhibitor of probable adrenal origin has been isolated from human plasma and was identified as ouabain or a closely related isomer (13). Although ouabain and its endogenous counterpart (EO) share structural similarities with the digitalis glycosides, several characteristics differentiate them from the latter compounds. Ouabainlike compounds have been described in a many animal species, and elevated plasma concentrations of EO have been linked repeatedly with high blood pressure (14-18). Accordingly, we wondered whether ouabain- and digitalislike steroids might differ in their hemodynamic effects during prolonged administration. Therefore, we investigated the effects of infusing small quantities of these steroids on blood pressure and their plasma and tissue levels in normal rats. A preliminary account of similar experiments has been given in abstract form (19, 20).

Methods

Male Sprague-Dawley rats (7-8 weeks old) were obtained from Zivic Miller (Zelienople, PA, USA). They were maintained in an air-conditioned facility at constant temperature (23°C) on a normal rat chow diet (containing 0.5% w/w sodium and 1.1% w/w potassium) and water was available ad libitum. Rats were allowed to acclimatize to the facility for 1 week before use. Two separate studies using different sets of animals were performed.

In the first experiment, we administered either ouabain, ouabagenin, digoxin or digitoxin for 5 weeks at 30 μg/kg/day in a phosphate buffered saline vehicle using mini-osmotic pumps (ALZET 2002, ALZA Corp., Palo Alto, CA, USA) placed subcutaneously in the flank of the animal under anesthesia. Control animals received vehicle infusions only. The pumps were replaced every 14 days and routine inspection of the remaining infusate in the osmotic pumps during replacement or at sacrifice indicated that all pumps functioned normally. Towards the end of the fifth week, the rats were anesthetized and fitted with intraarterial catheters for recording of direct mean arterial pressures. Subsequently the rats were anesthetized and decapitated and trunk blood and tissues were removed for assay.

In a second study, rats were randomized to three groups. Two of the groups contained 8 rats each while the third group contained 32 rats. Group 1 received a vehicle (sterile phosphate buffered saline) infusion via osmotic pump for 35 days. Group 2 received a continuous infusion of digoxin at 30 μg/kg/day for 5 weeks. Each animal in group 3 received ouabain at 15 μg/kg/day for 5 weeks. At the end of the 5th week the rats in group 3 were randomized to 4 subgroups. The first, second and third subgroups continued with their primary infusions while and in addition received secondary osmotic pumps containing either vehicle, digoxin (30 μg/kg/day) or digitoxin (30 μg/kg/day), respectively. In the fourth subgroup, the osmotic pumps for the primary ouabain infusion were removed and replaced with a vehicle infusion to assess the reversibility of the hypertension. On day 42, cuff pressures were taken, the rats were anesthetized and trunk blood and tissues were collected.

Blood Pressure Measurements

Direct measurements of arterial pressure were made as indicated. Rats were anesthetized and fitted with femoral arterial catheters as previously described (21). Following a 48-72 h recovery period, direct mean arterial pressures were recorded from conscious unrestrained animals resting in their home cages. Blood pressure and heart rate were recorded on a Gould polygraph. Body weight in all the animals was measured weekly.

In the second experiment, indirect systolic (SBP) and mean blood pressure (MBP) were recorded weekly or as indicated by tail plethysmography using a commercial photoelectric system and a device that provided constant rates of cuff inflation and deflation (Model 29, IITC, Inc., Woodland Hills, CA, USA). In this procedure, conscious rats were restrained in acrylic animal holders for 5-10 min in a warm quiet room and conditioned to numerous cuff inflation/deflation cycles by a trained operator prior to data collection. Subsequently, a mean value for SBP, MBP and heart rates were obtained for each rat from four to six sequential cuff inflation/deflation cycles. The onset of oscillations during cuff deflation represents the systolic blood pressure while the maximal amplitude of the oscillations corresponds to the mean arterial pressure using this instrumentation (22). The variances of the indirect and simultaneous direct blood pressures correspond well ($r^2>0.9$) in our laboratory (Ashen and Hamlyn, unpublished data).

Sample Collection and Assay

At the end of each study, rats were fasted overnight, and the following morning they were anesthetized with halothane and killed by decapitation. Trunk blood, kidneys and the adrenal glands were collected. Tissues were rinsed quickly in saline, cleaned, weighed and stored at
-20°C until analysis. Ouabain, digoxin and digitoxin were extracted from 2 ml plasma acidified by addition of 2 ml H₂O containing 0.1% redistilled trifluoroacetic acid (TFA). Tissues were homogenized in 10 volumes of methanol and the methanolic high speed supernatant was obtained by centrifugation, dried by vacuum centrifugation and reconstituted in H₂O containing 0.1% TFA. Plasma and tissue extracts were passed over pre-washed 200 mg C-18 disposable Bound Elut columns (Analytichem International, Harbor City, CA, USA). Unbound materials were washed off the columns with 12 ml of water followed by a 4 ml wash with 2.5% acetonitrile. EO and ouabain were eluted with 4 ml 20% acetonitrile/80% water, and subsequently digoxin (or digitoxin) was eluted into separate tubes with 4 ml 45% acetonitrile/55% water. The eluates were dried with a vacuum centrifuge and reconstituted in the appropriate immunoassay buffer. Ouabain was measured by an immunoassay using a rabbit polyclonal ouabain antiserum (No. R7) of high titer (1:10⁶) similar to that previously described (23). The cross reactivity of the ouabain antiserum with digoxin and digitoxin was 5.7 and 24%, respectively although neither steroid would have been present in the ouabain assay due to the extraction method used. The ouabain antiserum has no significant crossreactivity (<0.01%) for a variety of adrenal, testicular and ovarian steroids. The inter- and intra-assay coefficients of variation for the ouabain immunoassay were 4.8 and 9.2% respectively, for these experiments. Digoxin and digitoxin were determined using commercial assay kits (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA, USA). Ambient plasma and tissue levels of immunoreactivity are expressed in terms of digoxin or digitoxin equivalents; i.e., assuming a level of crossreactivity equivalent to the native steroids. All experimental protocols involving animals were reviewed and approved by the Institutional Animal Care and Use Committee in accordance with the NIH guidelines.

**Statistical Analysis of Data**

All data are expressed as mean±SEM and statistical significance was determined using a two-tailed test comparing the means of independent sample groups. Analysis of variance was used for comparisons among groups, and repeated-measures of variance was used for within group comparisons. Tukey's multiple range test was used to determine the significance of the F ratio. The level of significance used was p<0.05; all statistics were computed using the Systat program (Evanston, IL, USA).

**Materials**

Ouabain, ouabagenin, digoxin and digitoxin were obtained (Sigma Chemical, St. Louis, MO, USA) as a crystalline octahydrate and an anhydrous powder, respectively. All other reagents were ACS grade or better.

**Results**

Figure 1 shows the effects of prolonged infusion of the various cardiotonic steroids used on direct mean arterial pressures and plasma aldosterone levels in normal rats. Relative to the vehicle controls, mean arterial blood pressure increased significantly in the rats infused with ouabain and ouabagenin. In contrast, blood pressures declined relative to vehicle controls in the rats that were infused with digoxin (p=0.07) and digitoxin and this effect was especially pronounced with the latter steroid. Figure 1 shows also that plasma aldosterone was raised 4–5 fold in each of the groups infused with cardiotonic steroids. Table 1 presents the plasma levels of the steroids infused...
and the weight of the excised adrenal glands and their content of EO. The plasma levels for each of the infused steroids were similar and typically 5-9 fold above the level of EO in the vehicle controls. Adrenal enlargement was observed in the steroid infused rats. The levels of EO in the kidney and adrenal glands were lower than the vehicle controls in the rats infused with digoxin or digitoxin.

Figure 2 shows the time course of the changes in mean blood pressure in normal rats given continuous subcutaneous infusions of ouabain and digoxin and the reversibility of ouabain-dependent hypertension. In rats infused with ouabain at 15 μg/kg/day, blood pressure rose progressively after the 7th infusion day and reached a plateau value around day 35, while the blood pressures in the vehicle or the digoxin groups did not change significantly. After day 35, mean blood pressure remained elevated in the vehicle subgroup that continued with their primary ouabain infusion. In contrast, blood pressures fell dramatically in two subgroups that continued with their primary ouabain infusions and received an additional secondary infusion of either digoxin or digitoxin from day 35. By day 42, the blood pressures in these two subgroups were similar to rats never infused with ouabain. Similarly, in another subgroup in which the primary ouabain infusion was stopped on day 35 by removal of the osmotic pumps, mean blood pressure fell progressively to 102±4 mmHg on day 42 and kidney ouabain was 2.3 ± 0.4 ng/kg (not shown).

Figure 4 shows that the plasma concentrations of digoxin were elevated in rats that received infusions of this steroid (3.4±0.31 nmol/l, p<0.005 vs. control). However, kidney digoxin levels were not significantly elevated in the digoxin-infused rats relative to the vehicle infused controls. A small amount of digoxin immunoreactivity was noted in the plasma (~0.06 nmol digoxin eq/l) and kidneys (~0.12 ng digoxin eq/g) of the vehicle infused animals. Throughout the various experiments, the growth rates and final body weights of the animals in the different groups were not significantly different: vehicle controls, 467±8 g; ouabain infused, 459±11 g; digoxin infused, 472±8 g, digitoxin infused 477±6 g. All animals appeared to be very healthy and no differences in behavior were observed. The heart rates of the rats in each of the groups were similar throughout the study; values at

Table 1. Plasma and Tissue Parameters in Rats Infused with Cardiotonic Steroids

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Ouabain</th>
<th>Ouabagenin</th>
<th>Digoxin</th>
<th>Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma steroid levels (nmol/l)</td>
<td>0.66±0.12</td>
<td>5.2±0.39</td>
<td>3.9±0.55</td>
<td>3.3±0.32</td>
<td>5.9±0.44</td>
</tr>
<tr>
<td>Adrenal wet weight (mg/kg body weight)</td>
<td>63.6±3.9</td>
<td>75.1±3.2*</td>
<td>77.5±2.4*</td>
<td>75.3±2.2*</td>
<td>75.1±3.8*</td>
</tr>
<tr>
<td>Adrenal EO (ng/g body weight)</td>
<td>26.2±2.7</td>
<td>24.5±3.3</td>
<td>16.9±2.8*</td>
<td>12.7±4.3**</td>
<td>10.8±2.9**</td>
</tr>
<tr>
<td>Kidney EO (ng/g body weight)</td>
<td>0.53±0.06</td>
<td>20.6±2.4**</td>
<td>25.8±3.7**</td>
<td>1.2±0.1*</td>
<td>1.4±0.2*</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.005 vs. vehicle. The plasma levels refer to EO specifically. The plasma levels reported for ouabain and ouabagenin are total immunoreactivity and include the EO component. The plasma levels for digoxin and digitoxin include the endogenous background immunoreactivity for their respective components. Typically, plasma digoxin and digitoxin immunoreactivity in vehicle infused rats was <0.08 nmol/l.
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day 42 in the vehicle, digoxin, digitoxin and ouabain-in fused groups were 341±7, 328±10, 333±4 and 358±9 beats/min, respectively.

Discussion

The major new results of the present study are several folds. First, the prolonged subcutaneous infusion of ouabain raises the plasma concentration and kidney content of this steroid and leads to the progressive development of hypertension in normal rats. Second, the aglycone, ouabagenin, was equally effective in raising blood pressure as ouabain itself. Thus, the sugar moiety does not appear to be critical to the ability of ouabain to raise blood pressure. Third, the chronic pressor effect is specific for ouabain and ouabainlike steroids because neither prolonged infusion of digoxin nor digitoxin raised blood pressure even though the latter sodium pump inhibitors circulated in elevated amounts. Fourth, during the infusion of digoxin and digitoxin, blood pressures fell to values below that of their vehicle controls. The effect with digitoxin was especially marked and suggests that digitalis glycosides may have antihypertensive activity. Fifth, interruption of the ouabain infusion showed that the hypertension was fully reversible with an approximate half time of 3 days. Sixth, both digoxin and digitoxin are strikingly effective antihypertensive agents in ouabain-dependent hypertension. The circulating levels of ouabain remained elevated during the infusion of digoxin and digitoxin even though the latter agents reduced the renal ouabain content. Thus, the antihypertensive effect of the digitalis compounds may reflect an ability to reduce the tissue burden of ouabain. Moreover, in contrast to ouabain and its genin, digitoxin itself was not accumulated by the kidney and this may be related to its apparent inability to raise blood pressure. Seventh, all the steroids infused here increased adrenal weight and the plasma levels of aldosterone irrespective of their effects on blood pressure.

In considering the striking structure-activity relationships raised by this study, the minimum steroidal structure common to each of the various agents infused is shown in Fig. 5. Table 2 presents the specific substitutions and their positions for the agents used. The key differences lie mainly in the area of the A and B rings. For example, both ouabain and ouabagenin are hydroxylated at positions 1, 5, 11 and 19 whereas digoxin and digitoxin
lack those substitutions. Therefore, it seems likely that the hypertensinogenic activity of ouabain and ouabagenin may depend upon substitutions in the steroid nucleus. The antihypertensive effects of digoxin and digitoxin indicate that the 12,βOH is not important because digitoxin lacks this substitution. Further studies will be needed to examine the role of the lactone ring and to pinpoint the specific structural features in ouabain and digoxin that account for their pressor and antihypertensive activities, respectively.

For the most part, the chronic pressor effect of cardiac glycosides in animals has been inconsistent. This may be explained by several factors. First, most studies administered cardiac glycosides for periods up to 1 week (8, 9, 12). As the rise in blood pressure developed following a prehypertensive period of 7-10 days in our hands, and did not reach a stable level until the fourth to fifth week (Fig. 2), many studies would have been of insufficient duration. Second, studies of the effects of prolonged administration typically employed orally active Digitalis preparations such as digoxin (10, 11). As indicated in Figs. 1 and 2, digoxin does not induce hypertension under conditions where ouabain is clearly effective in this regard. Third, in studies where ouabain was chronically administered to rats, toxic doses (1-5 mg/kg/day) were used (9). Indeed, Yuan et al. reported some toxicity in rats following administration of ouabain at ~30 µg/kg/day in the setting of reduced renal mass (24). The suggestion of even mild toxicity at this relatively modest dose is quite remarkable and is inconsistent with the pharmacological dogma that rats are globally resistant to cardiac glycosides. It is likely that the toxicity reflects the large transient increases in plasma ouabain concentrations shortly after injection and the combination of reduced kidney function in those studies (24). Nevertheless, the potential for toxicity with the much higher doses of ouabain used in other work is readily apparent.

The infusion rates used in this study were calculated to provide chronically elevated plasma levels in the range of 3-5 nmol/l. The latter values were chosen to be similar to the plasma levels following ouabain administration in man and the plasma levels of EO observed in essential hypertension (17, 25). For example, daily parenteral administration of 250 µg ouabain in normal humans (i.e., a dose/body weight ratio of ~3.33 µg/kg) resulted in a steady state plasma level of ~0.85 nM (25). Prolonged infusion of similar amounts of ouabain (3 µg/kg/day) achieved a circulating level of ~2 nmol/l in the normal rat (26). The half-time for the clearance of ouabain in normal humans is ~21 h (25). Therefore, comparison of the circulating levels suggests surprisingly that the half time for the clearance of ouabain from the rat circulation may be ~2 fold slower than in humans.

All of the steroids used here have quite similar potencies concerning their ability to bind and inhibit sodium pumps (27). Therefore, our results raise renewed interest concerning the role of sodium pump activity and, in particular, the hypothesis that inhibition of the enzyme is the key event that leads to a sustained rise in blood pressure (4, 5). The remarkable differences in the effects of the sodium pump inhibitors in this study raise three general possibilities. First, there may be novel receptors for ouabain. The binding of digoxin to such receptors might account for its activity as an antihypertensive (i.e., a ouabain antagonist) in the rat model. Second, if sodium pumps mediate the effects of these steroids exclusively, they must do so via hitherto unrecognized interactions with these agents. One possibility is that the binding of ouabain and digoxin to the sodium pump generate agent-specific signals that modulate cellular events independent of their ability to inhibit the enzyme. Third, the hemodynamic effects of digoxin and ouabain revealed here could reflect physicochemical properties of the inhibitors that allow differential access to sodium pumps or other cellular constituents. For example, digoxin and digitoxin are relatively lipophilic and cross cell membranes and the blood brain barrier more easily than ouabain. Therefore, tissue and/or intracellular levels of these agents may be important to their effects. One problem with this hypothesis is that ouabagenin is thought to cross plasma membranes fairly readily but it was effective in raising blood pressure. Another problem is that Table 1 and Figs. 3 and 4 show that ouabain was accumulated dramatically by the kidney whereas digoxin was not. Thus, there is clearly quite different tissue handling of these cardiac glycosides. Although ouabain and digoxin are filtered by the glomerulus, the renal clearance of digoxin is further augmented by active secretion by the kidney tubules (28).

### Table 2. Steroids Used and Their Substitutions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Steroid substitution</th>
<th>Sugar at C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouabain</td>
<td>OH</td>
<td>Rhamnose</td>
</tr>
<tr>
<td>Ouabagenin</td>
<td>OH</td>
<td>None</td>
</tr>
<tr>
<td>Digoxin</td>
<td>H</td>
<td>Digitoxose (3)</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>H</td>
<td>Digitoxose (3)</td>
</tr>
</tbody>
</table>

See Fig. 5 for the reference structure.
Moreover, polarized canine proximal tubule cells in culture transport digoxin but not ouabain from the basolateral to the apical side. The transport mechanisms in the canine cells are of interest because their sodium pumps exhibit high overall affinity to both steroids (29). In addition, sodium pumps cannot explain the differential renal accumulation of these agents in the rat kidney because they are highly insensitive to ouabain and digoxin (30). Thus, the renal accumulation of ouabain from the circulation and the ability of the renal epithelia to distinguish between digoxin and ouabain involve uncharacterized systems.

In ouabain infused rats, the renal levels of this steroid were reduced by administration of digoxin while the circulating levels of ouabain remained elevated (Fig. 3). Similarly, when the ouabain infusion was stopped, blood pressure and the kidney ouabain content fell to normal. Elevated circulating levels of EO and ouabain have been shown to correlate with blood pressure in human and rat studies (17, 18, 26). Moreover, the prolonged administration of ouabain raises renal vascular resistance and resets renal function significantly (31). It seems likely that the altered kidney function in these rats is critical to the maintenance of their hypertension. Therefore, when taken together, these results raise the possibility that the association between the tissue levels of ouabain and blood pressure may be causal and that the antihypertensive activity of digoxin specifically involves an ability to reduce the renal accumulation of ouabain. Other tissues may also be important. For example, increased sympathetic outflow from the central nervous system has been implicated in ouabain-dependent hypertension (32). The effect of digoxin on hypothalamic and/or brain stem ouabain levels and the relationship of those parameters to the ability of digoxin to augment sympathoinhibition and lower blood pressure are not known. However, the rat central nervous system (CNS) contains sodium pumps that are highly sensitive to digoxin and ouabain (33–35). It is well known that the CNS administration of ouabain augments renal sympathetic nerve activity and raises blood pressure and heart rate (32, 36–38). Similarly, the inhibition of sodium pumps in peripheral nerves by cardiac glycosides augments their excitability and secretory activity, diminishes transmitter reuptake, and increases forearm vascular tone via an α1 adrenoceptor-mediated process (39, 40). Nevertheless, the key difficulty remains that the CNS pumps appear to interact similarly with ouabain and digoxin (35) so that the significance of sodium pumps to the blood pressure responses we describe is presently unclear.

In view of the disparate effects of the ouabain and digoxin noted in this study, it was of interest that all the sodium pump inhibitors increased plasma aldosterone and adrenal mass to a similar extent (Fig. 1 and Table 1). This effect of low nanomolar concentrations of ouabain has been noted previously (26) and attributed to hypertrophy of the adrenal glomerulosa cell layer in the rat (41–43). The mechanism may be species-specific and result from a small rise in plasma K+ due to ouabain (44) and/or recruitment of the adrenal renin-angiotensin system (45). We have suggested that the intra adrenal concentrations of EO may provide some stimulus to aldosterone secretion in vivo (46). Nevertheless, the main observation is that plasma aldosterone was elevated in all steroid infused rats. Thus, the ability of ouabain to elevate blood pressure seems to be unrelated to its effect on plasma aldosterone.

During the infusion of exogenous ouabain, the adrenal content of EO remained unchanged in contrast to the kidney. Therefore, the adrenal gland does not sequester this steroid from the circulation in significant amounts under the circulating concentrations encountered in this study (26). However, the adrenal content of EO was significantly lower in the digoxin and digitoxin infused rats. This suggests either augmented adrenal secretion of EO, impaired clearance or inhibition of its biosynthesis. The first two possibilities seem more likely as the plasma levels of EO were elevated in the digoxin infused rats and this seems inconsistent with inhibition of biosynthesis. Impaired plasma clearance does not seem compatible with the fall in the EO content of the adrenal glands. Therefore, augmented secretion of EO seems more likely.

Finally, and perhaps most significantly, our results are compatible with the clinical reality that the prolonged administration of digoxin does not induce hypertension in humans. Moreover, they raise the possibility that the remarkable efficacy of digitoxin as an antihypertensive agent in some patients with essential hypertension (47) reflects the heightened dependence of their blood pressure on EO. They suggest also that the rat is an informative model in which to explore the key structure-activity relationships.

In summary, prolonged administration of ouabain and its aglycone induce a reversible form of hypertension in normal rats. In contrast, digoxalis glycosides lack hypertensinogenic activity but effectively lower blood pressure in ouabain-dependent hypertension. While the circulating levels of all the agents infused was raised, the impact of digoxin and digitoxin suggests that the net effect of these cardiac glycosides on long term blood pressure is linked in some way with mechanisms that govern their tissue levels. The novel structure-activity relationships suggested by our results may have physiological and therapeutic significance.

References


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