**Delayed onset and reduced severity of adrenal-compression hypertension in rats treated with digitoxin**

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**Summary**

1. Bilateral compression of adrenal glands combined with unilateral nephrectomy and followed by imposition of a high sodium chloride intake caused severe hypertension in all rats, accompanied by enlargement of the heart, kidneys and adrenal glands, atrophy of the thymus and severe nephrosclerosis.

2. Digitoxin treatment delayed the onset, reduced the incidence and ameliorated the magnitude of the hypertensive response in such rats; it also reduced the degree of cardiac hypertrophy, the severity of nephrosclerosis and completely prevented enlargement of the adrenals and kidneys or atrophy of the thymus.

Key words: cardiac glycosides, digitoxin, heart, hypertension, kidney, vascular disease.

**Introduction**

Digitalis and its derivatives are drugs of choice in the treatment of congestive heart failure, although their mode of action remains unclear.

Their effect on blood pressure is reported to depend on the integrity of reflexogenic areas of the cardiovascular system (Gillis, Quest & Standaert, 1969) and the presence or absence of heart disease (Braunwald, Mason & Ross, 1965). Therefore, in response to glycoside administration, blood pressure may increase (Ross, Waldhausen & Braunwald, 1960; Williams, Zohman & Ratner, 1958; Cotten & Stopp, 1958), decrease (Abarquez, 1967; Chai, Wang, Hoffman & Wang, 1967) or not change (Smith, Gershwin & Hurley, 1968).

Preliminary studies performed in this laboratory on spontaneously hypertensive rats of the Okamoto/Aoki strain indicate that cardiac glycosides may exert a hypotensive effect (unpublished observations). This encouraged us to explore the effect of digitoxin treatment on the course of hypertension induced by adrenal compression in rats (Hall, Ayachi & Hall, 1974a, b). The cause of this type of hypertension, like that of adrenal regeneration hypertension (Skelton, 1955), is uncertain, but hypertension is presumed to be due to an excessive secretion of one or more mineralocorticoids.

**Methods**

Thirty female Sprague–Dawley rats weighing 75–90 g were divided into three equal groups; all were nephrectomized on the right and given NaCl solution (10 g/l) to drink and laboratory Chow ad libitum. In addition, groups 1 and 2 underwent bilateral adrenal compression, and group 3 adrenal exploration.

From postoperative day 8, the earliest time at which hypertension could be expected to occur, until day 26, all rats were given 1 ml of NaCl solution (150 mmol/l)/100 g body weight daily by gavage. In group 2, each 1 ml contained 0.5 mg of digitoxin powder (Parke Davis & Co., Detroit, Mich., U.S.A.).

Weekly systolic blood pressure, electrocardiogram (ECG) and heart-rate recordings were obtained on unanaesthetized rats with a Narco-Biosystems PE-300 Programmed Electrophysmomanometer and a DMP-4B Physiograph (Narco-Biosystems Inc., Houston, Texas, U.S.A.). Pressures above 150 mmHg were regarded as hypertensive.

The rats were killed with an overdose of ether on day 27 and autopsied. Various organs were removed, examined for lesions and placed in neutral 10%
formalin. The organs were subsequently weighed on an analytical balance. Renal lesions were graded by modified established criteria (Crane & Ingle, 1965) as follows: 0, no abnormality; 1, few small nodules, hypertrophy; 2, moderately nodular with some mottling; 3, greater nodularity, mottled with red spots; 4, rough, mottled and flea-bitten appearance. The average severity of lesions was obtained by dividing the total score by the number of rats in the group.

The two-tailed Student's t-test was used to determine the significance of differences between group means.

Results

Blood pressure

Two rats in group 1 died during the first week: one of pneumonia, the other of hydronephrosis. Data on these are not reported here. In the survivors, systolic pressure rose rapidly so that by day 15, five of eight rats had pressures ranging from 157 to 197 mmHg. By day 25, all rats had readings in excess of 150 mmHg (164–230 mmHg). The averages were significantly different ($P < 0.03$) from control values on all occasions after the first week.

In group 2 (digitoxin-treated), only one rat showed moderate hypertension and two others had pressures slightly above 150 mmHg by day 15. By day 25, eight of ten rats were hypertensive (160–210 mmHg). One rat, which became hypertensive early, became severely so (210 mmHg). The averages for this group were higher than those of control rats, but not significantly so on any occasion ($P > 0.07$). No ECG abnormalities such as T-wave inversion or heart block occurred.

Three of the ten rats in group 3 developed salt hypertension (155–214 mmHg). The data appear in Table 1.

Body weight and organ weights

Rats treated with digitoxin showed a slightly depressed growth rate. Nevertheless, there was no difference in the final weight between adrenal-

<p>| Table 1. Pertinent findings in rats with compressed adrenals, with and without digitoxin treatment |
| Mean values ± SEM are shown. * Different from control group ($P &lt; 0.05$). |</p>
<table>
<thead>
<tr>
<th>Group 1 Compressed adrenals</th>
<th>Group 2 Compressed adrenals + digitoxin</th>
<th>Group 3 Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>84 ± 2</td>
<td>85 ± 1</td>
</tr>
<tr>
<td>Final</td>
<td>153 ± 9</td>
<td>153 ± 6</td>
</tr>
<tr>
<td>Incidence of hypertension (%)</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>123 ± 6</td>
<td>129 ± 3</td>
</tr>
<tr>
<td>Day 15</td>
<td>163 ± 9*</td>
<td>146 ± 4</td>
</tr>
<tr>
<td>Day 22</td>
<td>190 ± 10*</td>
<td>162 ± 8</td>
</tr>
<tr>
<td>Day 25</td>
<td>200 ± 16*</td>
<td>176 ± 8</td>
</tr>
<tr>
<td>Renal lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>86</td>
<td>20</td>
</tr>
<tr>
<td>Severity</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Organ weights (mg/100 g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>481 ± 28*</td>
<td>412 ± 16*</td>
</tr>
<tr>
<td>Kidney</td>
<td>893 ± 54*</td>
<td>719 ± 33</td>
</tr>
<tr>
<td>Thymus</td>
<td>81 ± 32*</td>
<td>154 ± 9</td>
</tr>
<tr>
<td>Adrenals</td>
<td>44 ± 4.6*</td>
<td>36 ± 0 ± 2.7</td>
</tr>
</tbody>
</table>
compressed rats receiving digoxin and those given NaCl solution, because the latter became ill from very severe hypertension. Neither group differed significantly from control rats (Table 1).

Untreated rats with compressed adrenals had greatly enlarged hearts, kidneys and adrenals, atrophic thymus glands and severe renal lesions (Table 1). In contrast, although there was slight cardiac hypertrophy in the digitoxin-treated group, kidney enlargement did not occur. Furthermore, except for two of the rats which developed moderately severe hypertension and nephrosclerosis, such organs from digitoxin-treated rats were indistinguishable from control rats and neither adrenal enlargement nor thymic atrophy occurred.

Discussion

Digitoxin treatment retarded, but did not entirely prevent, the development of hypertension and also ameliorated its severity and reduced lesion formation (as observed macroscopically) in the kidneys. Possibly digitoxin treatment would have abrogated hypertension more effectively if treatment were started immediately after surgery rather than being deferred until hypertension was expected to appear.

Digitoxin would presumably also be effective in other forms of adrenal injury hypertension (enucleation, puncture) and perhaps hypertension due to steroid overdosage.

The mechanism(s) by which digitoxin modulates the hypertensive process is (are) uncertain. The glycoside may influence baroreceptors (Quest & Gillis, 1974), causing them to respond 'effectively' in counteracting pressure elevations.

Another possibility is that, because of its structural similarities, digitoxin competes with a hypertensogenic steroid for mineralocorticoid receptors, thereby normalizing electrolyte balance. Selye, Krajny & Savoie (1969) have reported that spironolactone antagonizes digitoxin-induced arrhythmias and prevents myocardial lesion formation. Other substances may also antagonize digitoxin and other digitalis drugs. Toxic doses of ouabain kill rats within 40–50 min, but injection of adenosine triphosphate immediately after administration of ouabain not only protects the rat from death, but also from any disturbances of cardiac rhythm (Matesević, Vojvodić & Pavlović, 1971).

Glycosides may cause blood pressure elevation in anaesthetized (Ross et al., 1960; Cotten & Stopp, 1958) as well as conscious animals (Vatner, Higgins, Franklin & Braunwald, 1971), and in patients with (Mason & Braunwald, 1964) and without (Kumar, YankoPoulos & Abelmann, 1973) cardiovascular disease. On the other hand, there is an indication that they exert both a hypotensive (Abarquez, 1967; Chai et al., 1967) and other protective effects, thus reducing morbidity and mortality from cardiac failure due to aortic constriction (Braunwald et al., 1965) and shock (Cronin & Zsotér, 1965; Marano, Kline, Cestero & Kuhn, 1966).

Of particular significance is the finding that in addition to antagonizing cardiac (Braunwald et al., 1965) and renal (vide supra) hypertrophy, digitoxin inhibited lesion formation in these organs, in spite of the moderate hypertension observed. It also prevented thymus involution and adrenal enlargement, changes associated with the stress state evoked by severe hypertension.

Acknowledgments

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References


