Role of Potassium in the Pathogenesis of the "Electrolyte-Steroid-Cardiopathy with Necrosis"

By P. Prioreschi, M.D., Ph.D.

The possible role of potassium in the pathogenesis of the "electrolyte-steroid-cardiopathy with necrosis" (ESCN) has been suggested since the early experiments when it was shown that lesions were produced only after treatment with corticoids (such as 9a-fluorocortisol or 2α-methyl-9α-chlorocortisol), which strongly influence potassium metabolism, and that cardiac necroses were prevented by the administration of potassium salts.1 Recently, Nickerson et al.2-4 arrived at the conclusion that the ESCN "results from a simple intracellular potassium deficiency and its sequelae, and that the roles of the steroid, cathartic electrolyte, and other agents and procedures are to induce potassium depletion by various mechanisms."3 This conclusion was supported by Nickerson's observations that the sensitizing sodium salt (in that case Na₂SO₄), given per os, produces profuse catharsis and consequent loss of potassium, and that the necrotic hearts showed an important diminution of the K-concentration in comparison with the control animals treated with the steroid or the sodium salt alone.

On the other hand, the assumption that potassium is the center of the pathogenic problem of the ESCN seems to be in conflict with other observations: we never succeeded in producing the syndrome using desoxycorticosterone as sensitizing corticoid, in spite of the considerable effect of this electrolyte on potassium metabolism, and, furthermore, the ESCN is prevented not only by K-salts but also by different chlorides (of Rb, NH₄, Mg, Ca) including NaCl.1

Let us point out in connection with Nickerson's experiments that any necrosis of the myocardium, even if produced by ligature of the coronary vessels, is followed by a decrease of intracellular potassium.5-9 On the other hand, we never observed any diarrhea after gavages with Na₂SO₄ with the doses used for the production of the ESCN in the rat.1,10 In addition, this syndrome can be elicited by parenteral administration of noncathartic Na-salts, as confirmed by Nickerson himself.4 For these reasons, we think that the role of potassium in the ESCN is still poorly understood, and the experiments described in this paper were performed in an attempt to contribute to its clarification.

Methods

Female Sprague-Dawley rats, with a mean initial body weight of 200 Gm. (190 to 209 Gm.), were divided into groups and treated as described in table 1. 9α-Fluorocortisol (F-COL), 1.5 mg. as a microcrystal suspension in 0.2 ml. of water, was administered subcutaneously, once daily. The electrolytes were given separately in 2 ml. of water, by stomach tube, twice daily in the following doses: Na₂HPO₄, 1.5 mM; MgCl₂, 2 mM; NH₄Cl, 1 mM.

The sodium and potassium in the blood and myocardium were measured after 4, 8, and 11 days of treatment, respectively. The animals of each group, maintained on Purina Laboratory Chow and tap water, were divided into three subgroups, and the sodium and potassium in the blood and myocardium were measured after 4, 8, and 11 days of treatment, respectively. The blood was taken under ether anesthesia from the abdominal aorta 17 hours after the last electrolyte gavage. The hearts were first examined for gross lesions, placed on a small piece of ashless filter paper, and dried at 100 C. to constant weight, and subsequently reduced to ash at a temperature of 400 to 420 C. Sodium and potassium were measured with a flame spectrophotometer. The means of the determination are listed with the standard errors on table 1: the values are expressed in mEq. per 100 Gm. dry weight for the heart ventricles, and in mEq. per liter for the serum. By the end of the experiment, about one-third of the animals of group 3 showed gross...
### TABLE 1

Concentration of Na and K in Serum and Heart Ventricles During the Development of ESCN after Four, Eight, and Eleven Days of Treatment*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Na</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th day</td>
<td>146.56 ± 0.74</td>
<td>147.95 ± 0.96</td>
<td>146.01 ± 1.06</td>
<td>143.2 ± 1.35</td>
<td>145.97 ± 2.02</td>
</tr>
<tr>
<td>8th day</td>
<td>144.91 ± 1.00</td>
<td>147.54 ± 1.08</td>
<td>147.55 ± 1.04</td>
<td>147.50 ± 0.87</td>
<td>145.07 ± 1.39</td>
</tr>
<tr>
<td>11th day</td>
<td>146.41 ± 0.83</td>
<td>149.3 ± 1.84</td>
<td>146.72 ± 0.91</td>
<td>147.4 ± 1.24</td>
<td>146.69 ± 1.10</td>
</tr>
<tr>
<td><strong>K</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th day</td>
<td>5.06 ± 0.08</td>
<td>4.83 ± 0.08</td>
<td>4.59 ± 0.20</td>
<td>3.82 ± 0.09</td>
<td>3.68 ± 0.09</td>
</tr>
<tr>
<td>8th day</td>
<td>4.81 ± 0.09</td>
<td>4.08 ± 0.10</td>
<td>3.95 ± 0.10</td>
<td>4.00 ± 0.05</td>
<td>3.95 ± 0.14</td>
</tr>
<tr>
<td>11th day</td>
<td>4.06 ± 0.28</td>
<td>14.74 ± 0.58</td>
<td>14.55 ± 0.56</td>
<td>13.58 ± 0.56</td>
<td>13.58 ± 0.31</td>
</tr>
<tr>
<td>8th day</td>
<td>14.31 ± 0.32</td>
<td>15.43 ± 0.84</td>
<td>15.03 ± 0.44</td>
<td>14.80 ± 0.44</td>
<td>14.78 ± 0.62</td>
</tr>
<tr>
<td>11th day</td>
<td>14.02 ± 0.47</td>
<td>15.35 ± 0.27</td>
<td>14.96 ± 0.40</td>
<td>14.28 ± 0.32</td>
<td>14.65 ± 0.23</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th day</td>
<td>35.67 ± 0.89</td>
<td>34.57 ± 0.86</td>
<td>34.57 ± 0.86</td>
<td>34.54 ± 0.52</td>
<td>32.41 ± 0.72</td>
</tr>
<tr>
<td>8th day</td>
<td>35.89 ± 0.33</td>
<td>32.26 ± 0.77</td>
<td>32.26 ± 0.77</td>
<td>33.80 ± 0.52</td>
<td>31.90 ± 0.77</td>
</tr>
<tr>
<td>11th day</td>
<td>36.53 ± 0.55</td>
<td>34.57 ± 0.86</td>
<td>34.57 ± 0.86</td>
<td>34.54 ± 0.52</td>
<td>32.41 ± 0.72</td>
</tr>
</tbody>
</table>

*In parentheses is the number of animals used for each determination. The values in italics are statistically significant in comparison with the controls (P < 0.025).
myocardial necrosis; those hearts were eliminated, and the measurement of their electrolyte content was not included in the table.

**Results**

As mentioned before, myocardial necroses developed only in some animals of group 3 because of the protective action of the MgCl₂ and NH₄Cl in the rats of groups 4 and 5. The decrease of serum potassium was evident after four days of treatment in all groups, while the diminution of this electrolyte in the myocardium appeared to be significant only later, with the exception of the animals of group 2.

The sodium concentration in the serum and in the myocardium did not show any significant change in comparison with the controls.

The necrotic hearts (not listed in the table) of some animals from group 3 showed important variations in the concentration of both electrolytes. The mean values of the five most seriously affected hearts were the following: Na, 43.06 (± 6.0) mEq./100 Gm. dry weight; K, 28.17 (± 2.19) mEq./100 Gm. dry weight.

**Discussion**

The variations of potassium concentration in heart and serum of the animals on the verge of developing myocardial necroses (group 3) are similar to those observed in the other groups receiving a treatment which does not produce the lesions. On the other hand, there is no difference between the values on the eighth and the eleventh days of treatment, although on this latter date all the rats of group 3 must have been very near to developing the necrosis, as shown by the observation that in the last two or three days of the experiment about one-third of the animals of this group died with lesions. In addition, the protection observed after treatment with MgCl₂ and NH₄Cl is not related to any reverse of the electrolytic alteration.

In connection with the assumption that the ESCN is due to simple potassium depletion, it has been assumed that the beneficial effects of magnesium could be explained by a possible interaction between the two ions. Although these electrolytes seem to influence each other in certain situations, this hypothesis fails to explain why, among all Mg-salts tested, only MgCl₂ is able to prevent the development of the lesions. On the contrary, the fact that all the tested chlorides showed such beneficial effects strongly suggest the possibility of a different pathogenetic mechanism.

The observed variations of the sodium and potassium content in the hearts with necrosis are in agreement with the fact that any cellular damage is followed by similar changes which, for this reason, are to be considered as the results and not the causes of the lesions.

On the basis of our findings, we think that the diminution of potassium in the heart could conceivably favor the action of an unknown pathogenetic mechanism, but the hypothesis that ascribes the ESCN merely to potassium depletion cannot be accepted.

The production of cardiac necroses by potassium deficiency is only seemingly in contradiction with our view, since similar (or even identical) effects do not necessarily imply identical causes.

**Summary**

During the development of the "electrolyte-steroid-cardiopathy with necroses" (ESCN) in rats, there is a decrease of myocardial potassium in the group bound to develop the cardiac necroses. A similar variation was observed in the control animals treated with a noncardiotoxic association of steroid and electrolytes. Only after the necrosis had been established was an important increase of sodium and decrease of potassium observed. On the basis of these and other previously described facts, the author concludes that, although it is conceivable that the diminution of potassium in the heart could favor the development of the necroses, the hypothesis of the ESCN as a result of a simple potassium depletion cannot be accepted.

**References**

2. NIKERSON, M., KARR, G. W., AND DREBEL, P. E.: Pathogenesis of "electrolyte-steroid-cardiopathy," (American Society for Pharmacology and Experimental Therapeutics, Forty-
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