Pathogenesis of "Electrolyte-Steroid-Cardiopathy"

By Mark Nickerson, Ph.D., M.D., Gerald W. Karr, B.Sc., and Peter E. Dresel, Ph.D.

In 1957, Selye and Renaud reported that the combined administration of 2a-methyl-9a-chlorocortisol and sodium phosphate could induce focal necrotic lesions of the myocardium. This report was followed by a large number of papers from the same laboratory in which it was reported that many, but not all, adrenal cortical steroids could act in the same way as 2α-methyl-9α-chlorocortisol and that the sodium salts of certain other anions could be substituted for phosphate in the production of the myocardial lesions. Administration of the steroid or of the electrolyte alone did not produce lesions. These observations led to the postulation of specific interactions between the ions and the steroid in the form of "sensitizing" or "conditioning" of the organism to the action of one agent by the other, and of specific interactions and antagonisms of the cellular (myocardial) "toxicities" of the various ions. Much of this material now has been summarized in book form.

The present studies were undertaken because of our interest in three factors associated with the production of "electrolyte-steroid" myocardial necrosis, which became apparent from a survey of the many scattered reports. (1) The most effective steroids are those which strongly influence electrolyte distribution and excretion. (2) Sodium phosphate and sodium sulfate administered orally are among the electrolytes most effective in inducing myocardial lesions, although they are poorly absorbed and are known to be effective cathartics. (3) The myocardial lesions can be prevented by the administration of potassium. It therefore appeared to us possible that the "electrolyte-steroid-cardiopathy" might be simply an expression of potassium deficiency caused by the simultaneous steroid-induced renal loss and saline cathartic-induced gastrointestinal loss of the ion.

Methods

Female Sprague-Dawley rats weighing 100 to 125 Gm. were employed in all experiments. The steroid used was 2α-methyl-9α-chlorocortisol acetate, which has a very potent effect on sodium and potassium balance and distribution, administered subeutaneously in a daily dose of 100 μg. suspended in 0.2 ml. of water. Chlorothiazide HCl, 15 to 50 mg./Kg. given subeutaneously twice daily, was substituted for the steroid in one experiment. Various groups of animals also received twice daily 0.2, 0.4, or 0.5 mM Na₂SO₄ in 0.5 to 1.25 ml. or 1.0 mM Na₂SO₄ in 5 ml. of water, 125 mg. of a carboxylic acid cation exchange resin (CTS-21, hydrogen cycle), 0.5 to 5.0 ml. of castor oil, or 0.25 to 0.5 ml. of 25 per cent croton oil in peanut oil by stomach tube. In some experiments, the animals were maintained on a low-potassium diet (2.0 or 6.4 mEq./Kg.) during the experimental period. Control animals were kept on the stock diet (Victor Fox Chow) in adjacent cages, and were sacrificed at intervals in parallel with animals in the treated groups. All animals which died during the experimental period, or were sacrificed, were autopsied as soon as possible after death and the heart carefully examined for gross lesions which were graded from 0 to 3 with respect to extent and severity. Portions of many of the hearts were fixed in 10 per cent neutralized formalin, and sections studied microscopically, using hematoxylin-eosin and fuchsin stains. Approximately one half of the heart and a piece of gastrocnemius muscle from each animal were blotted dry and weighed. The samples of cardiac and skeletal muscle (250 to 500 mg. of fresh tissue) were digested in 0.1 ml. of 10 per cent NaOH and the resulting solutions analyzed for potassium content with a Patwin flame photometer after neutralization and appropriate dilution. Preliminary experiments showed this method to be simpler than grinding in 0.1 N HNO₃, and...
Table 1
Alterations in Tissue Potassium Concentrations and Their Relation to the Induction of Focal Myocardial Necrosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration (days)</th>
<th>Tissue K⁺ concentration (mEq./Kg. wet wt.)</th>
<th>Myocardial necrosis (gross lesions)</th>
<th>Average severity</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>843.3 ± 1.7 (21)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Steroid</td>
<td>12 to 29</td>
<td>76.5 ± 1.1 (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Na₂SO₄ (p.o.)</td>
<td>12</td>
<td>109.7 ± 2.1 (8)</td>
<td>81.0 ± 1.6 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Steroid plus Na₂SO₄ (p.o.)</td>
<td>&lt;12</td>
<td>68.6 ± 0.6 (14)</td>
<td>62.7 ± 2.7 (14)</td>
<td>2.3</td>
<td>93</td>
</tr>
<tr>
<td>Steroid plus Na₂SO₄ (s.c.)</td>
<td>12 to 18</td>
<td>81.9 ± 1.7 (9)</td>
<td>75.7 ± 1.1 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low-K⁺ diet</td>
<td>18 and 22</td>
<td>73.7 ± 3.1 (16)</td>
<td>71.9 ± 1.7 (16)</td>
<td>0.06</td>
<td>6</td>
</tr>
<tr>
<td>Steroid plus croton oil</td>
<td>29</td>
<td>61.6 ± 2.1 (13)</td>
<td>65.7 ± 2.1 (14)</td>
<td>2.0</td>
<td>100</td>
</tr>
<tr>
<td>Low-K⁺ diet</td>
<td>29 and 37</td>
<td>79.4 ± 1.9 (11)</td>
<td>70.0 ± 0.8 (11)</td>
<td>0.27</td>
<td>27</td>
</tr>
<tr>
<td>Low-K⁺ diet (animals with gross lesions)</td>
<td>29 and 37</td>
<td>77.3 ± 3.2 (14)</td>
<td>72.0 ± 2.8 (15)</td>
<td>0.67</td>
<td>27</td>
</tr>
</tbody>
</table>

*All values are mean ± standard error.
†Figures in parentheses are the number of animals in each group.

Results
The incidence and severity of myocardial lesions and the myocardial and skeletal muscle potassium concentrations in various groups of animals are presented in Tables 1 and 2. Administration of 2α-methyl-9α-chlorocortisol alone caused a highly significant reduction in the myocardial potassium concentration ($P < 0.01$). This effect of the steroid appeared to reach a steady state within 12 days, and no further reduction was apparent in animals treated for up to 29 days. No gross or microscopic myocardial lesions were found in this group of animals.

Oral administration of Na₂SO₄ (1.0 mM twice daily) alone did not alter the tissue potassium levels significantly and induced no lesions. However, combined steroid and Na₂SO₄ administration caused a marked reduction in the tissue potassium levels to below those reached with the steroid alone ($P < 0.01$), and induced severe focal necrotic lesions of the myocardium. Seventy-two percent of the animals in this group died before the end of the 12-day period of treatment. The lesions induced by this combined treatment were, in all respects, the same as those previously reported by others.³

In contrast to the pronounced effect of Na₂SO₄ administered orally, subcutaneous administration of this salt in amounts equal to or greater than could be absorbed from the oral dose did not reduce the myocardial potassium concentration below the level expected from the concurrently administered steroid, and no myocardial lesions were induced even when the treatment was continued for a total of 18 days. No differences between the groups treated with 0.2, 0.4, and 0.5 mM of Na₂SO₄...
could be detected. None of the animals in these groups died prior to the end of the experimental period. The oral, but not the subcutaneous, administration of Na$_2$SO$_4$ induced a severe diarrhea which appeared after the first administration of the salt, and persisted throughout the experiment.

The apparent close correlation between the tissue potassium concentration and the induction of myocardial necrosis in animals treated with a steroid and Na$_2$SO$_4$ suggested the desirability of studying potassium depletion induced by other methods. One approach was to substitute a reduced potassium intake for the increased gastrointestinal loss induced by the orally administered Na$_2$SO$_4$. A combination of the steroid and a low-potassium diet caused reductions in myocardial potassium and induced lesions entirely comparable to those produced by the combination of steroid and orally administered Na$_2$SO$_4$. The data presented in table 1 are the combined results of two separate experiments. In the first, some of the animals were autopsied on the twelfth day and no myocardial lesions were found. However, continuation of the treatment to a total of 18 days induced severe lesions in all of the remaining animals. In the second experiment, only one small lesion was found among six animals sacrificed at 18 days, but relatively severe lesions were found in all of the remaining animals after 22 days. Analysis of the tissue potassium data indicated that the animals sacrificed at 12 and 18 days in the first experiment formed homogeneous populations with those sacrificed at 18 and 22 days, respectively, in the second experiment; consequently, the data are combined in table 1. The myocardial potassium concentrations in the two groups were significantly different ($P < 0.05$). Subsequent analysis of the "low-potassium" diets employed revealed that, although they had come from the same supplier (Nutritional Biochemicals, Cleveland, Ohio), they contained 2.0 and 6.4 mEq./Kg. of potassium. These observations further emphasize the close parallelism between potassium deficiency and the appearance of myocardial lesions.

### Table 2

Tissue Potassium Concentrations Following Procedures Ineffective in Inducing Focal Myocardial Necrosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration (days)</th>
<th>Skeletal muscle</th>
<th>Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>110.9 ± 2.1*</td>
<td>84.3 ± 1.7</td>
</tr>
<tr>
<td>Steroid plus ion exchange resin</td>
<td>12 to 18</td>
<td>83.4 ± 3.0</td>
<td>73.2 ± 1.4</td>
</tr>
<tr>
<td>Ion exchange resin plus low-K diet</td>
<td>12 to 14</td>
<td>91.0 ± 4.5</td>
<td>76.1 ± 1.7</td>
</tr>
<tr>
<td>Steroid plus castor oil</td>
<td>12</td>
<td>87.1 ± 4.5</td>
<td>82.5 ± 3.3</td>
</tr>
<tr>
<td>Chlorothiazide plus Na$_2$SO$_4$ (per os)</td>
<td>18 to 37</td>
<td>100.7 ± 2.5</td>
<td>75.0 ± 1.5</td>
</tr>
</tbody>
</table>

*All values are mean ± standard error.
†Figures in parentheses are the number of animals in each group.

An attempt also was made to study the effects of 2α-methyl-9α-chlorocortisol in combination with nonsaline cathartics. These experiments were hampered by the well-known resistance of rats to most cathartic agents. Doses of castor oil up to 5 ml. per rat twice daily and of phenolphthalein up to 100 mg. twice daily induced no detectable catharsis and failed to affect myocardial or skeletal muscle potassium concentrations or to induce myocardial lesions (table 2).

A moderate catharsis was obtained by the administration of 25 per cent croton oil in peanut oil. The diarrhea was never as severe as that induced by the oral Na$_2$SO$_4$, and the dose had to be increased progressively from 0.25 to 0.5 ml. twice daily in order to sustain the cathartic action. However, combined treatment with croton oil and steroid did decrease the tissue potassium significantly below the levels observed when only the steroid was administered ($P < 0.01$). The depletion was significantly less than that produced by the steroid plus Na$_2$SO$_4$ ($P < 0.02$), and correspondingly less severe lesions of the myocardium were produced. Relatively small, but
distinct, areas of myocardial necrosis were found in three of the 11 animals in this group on gross examination, and in addition, definite microscopic lesions were found in two of the four animals without gross pathology from which sections of the myocardium were obtained.

It was difficult to produce severe potassium deficiency in rats of the size employed in these experiments by the use of a low-potassium diet alone (6.4 mEq./Kg.). A considerable period on the diet was required to induce a marked deficiency, and the tissue levels reached were variable, probably depending to a considerable extent on the amount of cophagy. In most of the animals which received the low-potassium diet alone, tissue potassium did not reach the levels associated with myocardial lesions in the other groups. However, four animals were found to have relatively severe lesions, and their myocardial potassium concentrations had dropped to an average of 68.6 mEq./Kg.

A number of additional procedures designed to induce potassium depletion failed to produce any demonstrable myocardial lesions (table 2). In none of these groups of animals was the myocardial potassium reduced to the level associated with lesions produced by the successful combinations. Doses of cation exchange resin larger than 125 mg. per rat twice daily caused death from impaction and intestinal obstruction. Administration of large doses of chlorothiazide subcutaneously plus Na2SC>4 per os resulted in tissue potassium levels significantly lower (P < 0.05) than those obtained with oral Na2SO4 alone, but still well above the levels associated with gross myocardial lesions. These results were not altered when the animals were given 1.0 per cent NaCl solution to drink in place of tap water.

The appearance and severity of the gross lesions were generally, but not precisely, correlated with myocardial potassium concentrations in individual animals within the groups in which myocardial necrosis was induced. Sufficient variability was noted to suggest that other factors, such as duration of the depleted state, may have contributed to the production of lesions. However, when the average severity of the myocardial necrosis in the various groups was plotted against the average myocardial potassium concentration (fig. 1), it was apparent that the two were closely related below a threshold value of about 72 mEq./Kg.

In general, the skeletal muscle potassium concentrations appeared to follow the myocardial levels, but the correlation with the appearance of cardiac lesions was less exact. No gross skeletal muscle lesions were observed in any of the animals, although minimal microscopic lesions, qualitatively similar to those seen in the myocardium, were noted in skeletal muscle samples from a few of the animals which had been on the low-potassium diet for the longest period of time.

In the earlier experiments of this series, samples of cardiac and skeletal muscle were dried to constant weight in an oven at 100 C. to determine whether the changes in ionic composition were associated with alterations in total tissue water. The values obtained were very uniform: 77.4 ± 0.17 and 79.2 ± 0.18 per cent water in the skeletal muscle and myocardial samples, respectively. No differences were noted in any of the treated groups, irrespective of the presence or absence of lesions; consequently, the potassium values given on the basis of fresh tissue weight may be considered to be entirely parallel to the concentrations of potassium in total tissue water. A series of random plasma potassium determinations done on animals from the various depleted groups revealed no values less than 3.0 mEq./L., and the effect of changes in extracellular potassium would have been negligible.

The relatively poor absorption of sulfate anion from the gastrointestinal tract is recognized as the basis of the very effective cathartic action of Na2SO4. It is generally accepted that not over one-third to one-half of orally administered sulfate appears in the urine. To obtain additional information under our experimental conditions, the urinary excretion of sulfate was measured in five rats restrained in holders to prevent any mixing of urine and feces. Each animal was given a single standard
dose of Na$_2$SO$_4$ (1.0 mM in 5 ml.) by stomach tube and the total 24-hour increase in urinary sulfate above the control values determined by the benzidine method. Recovery was 36 ± 5 per cent of the administered sulfate, a value very similar to that reported in dogs. These results indicate that the subcutaneous administration of 0.5 mM Na$_2$SO$_4$ would contribute considerably more systemic sulfate than the standard oral dose of 1.0 mM.

Gross myocardial lesions had essentially the same appearance and distribution in all of the affected groups. They appeared as slightly raised, yellowish areas which occurred most commonly in the wall of the right ventricle, but which were found also at the apex, and less commonly, elsewhere in the left ventricle in the more severely affected hearts. In all groups, the lesions were most severe in the subendocardial area and many lesions were limited to this region. The lesions in all affected groups were qualitatively indistinguishable on microscopic examination. They characteristically showed variable fragmentation of muscle cells associated with mononuclear- and some polymorphonuclear-cell infiltration. In some of the more advanced lesions, the muscle bundles had largely disappeared and were being replaced by fibrous tissue. In minimal lesions, the muscle cells stained poorly, cross striations were indistinct, and mononuclear-cell infiltration was limited.

Varying degrees of fuchsinophilia of the myocardial fibers also were observed in the hearts of animals from all of the experimental groups developing myocardial necrosis. Fuchsinophilic fibers frequently made up 30 to 50 per cent of the myocardium and usually were scattered in irregular groups with no clear relation to the areas with other abnormal microscopic findings, although fuchsinophilic fibers usually were present in or at the periphery of such areas.

**Discussion**

It has been known for many years that potassium depletion can cause morphological lesions of the myocardium.

Such lesions form an important and characteristic part of the deficiency pattern, usually observed in growing animals on a potassium-deficient diet. Published descriptions and our own observations on the myocardial lesions of "electrolyte-steroid-cardiopathy" reveal no anatomical basis for distinguishing these from the classical lesions of potassium depletion.

We believe that all the results of the present study can be interpreted on the assumption that the "electrolyte-steroid" myocardial necrosis is due to a simple intracellular potassium deficiency* and its sequelae, and that the roles of the various procedures reported herein are merely to induce potassium depletion by various mechanisms. Any "specific interaction" between the steroid and the sodium or sulfate ions in the production of lesions is ruled out by the failure of Na$_2$SO$_4$ to act after subcutaneous administration, even when given for considerably longer periods of time than are required to produce lesions when the salt is administered orally and in larger doses than could have been absorbed from the gastrointestinal tract under the conditions of the experiment.

*While this manuscript was in preparation, a paper from the Selye laboratory appeared reporting that under conditions similar to our own, 2a-methyl-9a-chlorocortisol, neither alone nor combined with oral administration of the cathartic salt NaH$_2$PO$_4$, caused any reduction in myocardial potassium concentrations (du Ruisseau and Mori). We can offer no clear explanation for the major discrepancy between their results and our own, but would like to point out the following features of their data which we feel question the correctness of this observation. (a) The potassium content of skeletal muscle was unaltered by the cathartic alone and was progressively decreased by the steroid and the steroid plus cathartic, as in our experiments, without any change in the myocardial potassium, although changes in the ionic composition of the two tissues have been found to be roughly parallel in many previous studies. (b) Myocardial sodium was markedly increased, in parallel with the skeletal muscle sodium, without the concomitant change in potassium characteristic of myocardial electrolyte alterations induced by steroids and most other procedures. (c) Serum potassium was markedly decreased although hypokalemia usually occurs only in the presence of significant depletion of potassium in various tissues, including the myocardium.
Relation of myocardial potassium concentration to the appearance and severity of acute necrotic lesions of the myocardium. Each point represents the averages for all animals in one of the groups listed in tables 1 and 2.

and histology of the myocardial lesions, induced by the various combinations of agents, suggest a common etiology and indicate that the specific mechanisms of depletion are relatively unimportant. Decreased intake, increased intestinal loss due to saline or irritant cathartics, and increased renal loss due to an adrenal cortical steroid appear to be interchangeable as long as the necessary degree of tissue potassium depletion is attained. A prolonged inadequate intake, particularly in growing animals, appears to be the only single mechanism of depletion adequate to induce morphological lesions consistently, but various combinations of two mechanisms readily produce the requisite depletion. Thus, the "sensitizing" or "conditioning" by cathartic electrolytes or by steroids to the effects of the other may properly be considered to be merely an additive effect of two mechanisms, neither of which alone causes a sufficient depletion of potassium to induce morphological lesions.

From the present results, it appears that the development of anatomical lesions begins at a rather critical myocardial potassium level of about 72 mEq./Kg. wet weight. However, the lack of a precise correlation between the severity of the lesions and the potassium levels in individual animals suggests that factors such as the rate of depletion may alter this relationship. Involvement of a time factor is suggested also by the fact that the more slowly developing lesions induced by the low-potassium diet alone appear to be associated with slightly higher tissue potassium levels.

In the above discussion, it has been assumed that the myocardial lesions are the result of, rather than the cause of, the potassium depletion. This relationship is indicated strongly by three observations. (1) Among the various treated groups, varying degrees of tissue potassium depletion were noted, but only when the values had reached a level of approximately 72 mEq./Kg. of fresh myocardial tissue did lesions appear. (2) Within a given group of hearts with gross lesions, the degree of potassium depletion and the extent of the lesions were not precisely correlated. Some hearts with very low potassium levels had relatively restricted areas of necrosis. This observation argues strongly against the low values resulting simply from the loss of potassium from necrotic cells. (3) Skeletal muscle potassium was reduced in parallel to myocardial potassium, although no macroscopically visible necrosis developed in this tissue.

Potassium depletion undoubtedly can induce focal myocardial necrosis in man, but such lesions have been reported infrequently. Histological changes apparently identical to those observed in the present experiments have been described as a feature of potassium depletion due to severe diabetic acidosis17 and to prolonged diarrhea,18 and in the hearts of patients with Addison's disease who died after treatment with desoxycorticosterone (DOC).19 Such cases should be relatively easy to identify as these lesions are only one manifestation of a generalized deficiency syndrome. Most types of heart disease in man clearly do not involve generalized potassium depletion, and therefore, cannot be compared to the lesions induced by electrolyte-steroid administration.

It obviously is impossible to discuss the specific relations of the present findings to all of the multiple permutations and combinations of procedures which have been reported...
to induce "electrolyte-steroid-cardiopathy."" (See reference 2 for summary.) Among the many steroids studied, it is clear that only those which significantly alter electrolyte metabolism effectively contribute to the production of myocardial necrosis. In line with its very potent effect on electrolyte metabolism, 2α-methyl-9α-chloro cortisol, employed in the present experiments, is the most effective of the steroids tested. Cortisone is considerably less active, prednisone and prednisolone have only minimal activity, and triamcinolone and methylprednisolone are reported to be entirely inactive in this regard. However, it should be remembered that clinical experience indicates that all of the active adrenal cortical steroids have some ability to alter potassium metabolism.

It has been suggested that DOC is less effective in producing myocardial necrosis than might be expected from its considerable effect on renal electrolyte excretion, and that its deleterious effect is enhanced by the concurrent administration of triamcinolone. However, others have reported that prolonged administration of DOC can produce characteristic myocardial lesions even without the concomitant use of other potassium-depleting procedures, and that it accentuates the lesions induced by a low-potassium diet or by the administration of a sympathomimetic. The significance of apparent quantitative exceptions to the general correlation between effects on sodium and potassium metabolism and production of myocardial necrosis can be evaluated only when the effects of the agents and procedures in question on myocardial potassium levels have been determined directly.

Many reports by the Montreal group have pointed out that in the presence of electrolyte-steroid (potassium-depletion) treatment adequate to produce only minimal myocardial changes, "stress" of various kinds can markedly increase the necrotic lesions. It appears possible to analyze these effects in more exact terms than the rather nebulous catch-all of "stress." Although other factors may be involved in some of the innumerable permutations and minor variations reported, the evidence for implicating increased myocardial work in the production of the lesions under consideration is substantial. The procedures involved increase considerably sympathetic nervous system activity and/or the work of the heart—struggling during prolonged forceful restraint, cold, injection of sympathomimetics, injection of large doses of vasopressin, etc. Severe myocardial stimulation by sympathomimetics has been shown to produce myocardial lesions even in the hearts of otherwise normal animals, and these lesions are markedly accentuated by DOC, but not by triamcinolone.

It is of interest to note that steroid pretreatment, which causes a considerable decrease in myocardial potassium (table 1), promotes the production of lesions by epinephrine and norepinephrine, whereas cathartic-electrolyte treatment, which does not alter myocardial potassium significantly, does not. Increased myocardial work might accentuate the lesions at a given myocardial potassium level or cause further potassium depletion. Heart and skeletal muscle are known to lose potassium during activity, and with exertion to fatigue, this loss is of sufficient magnitude to make a major contribution to the depletion necessary to induce morphological changes. Exercise-induced loss can occur from tissues which are already potassium depleted, and it is quite possible that even a small additional loss of potassium might precipitate the development of anatomical lesions in hearts with pre-existing borderline depletion.

The reported beneficial effects of magnesium salts also are entirely compatible with the assumption that the "electrolyte-steroid-cardiopathy" is due primarily to potassium depletion. Interaction of the two ions has been observed in several quite diverse situations. Of particular interest are the observations that during magnesium deprivation, skeletal muscle magnesium and potassium are depleted in parallel, and that infusion of magnesium causes a rapid fall in plasma potassium levels, the potassium presumably being shifted to an intracellular locus.

It appears unlikely that magnesium defi-
iciency is the primary defect in the production of myocardial lesions by the procedures described herein. Early studies on potassium and combined potassium-magnesium deficiencies in rats demonstrated the production of lesions entirely comparable to those noted in the present study. However, fatal magnesium deficiency alone did not produce detectable myocardial lesions in this study. Heart lesions have been reported to occur in magnesium deficiency in rats but these appear to involve primarily the loose mesenchymal tissue around capillaries and precapillaries rather than myocardial cells, do not differ significantly from similar lesions distributed rather uniformly throughout the body, and apparently do not progress to massive areas of necrosis such as are seen in dietary potassium deficiency and in several groups of animals in the present study. In addition, the gross appearance and behavior of the animals in experiments leading to the production of myocardial lesions was similar to that produced by potassium deprivation. The hyperirritability, convulsions, and early skin lesions characteristic of magnesium deficiency were never observed in our experiments. However, the possibility that magnesium depletion may have contributed to the development of "electrolyte-steroid-cardiopathy" cannot be excluded. The procedures which induce potassium deficiency and myocardial lesions, particularly the cathartic action of sulfate and phosphate salts, also may lead to a loss of magnesium.

Previous attempts to explain the production of "electrolyte-steroid-cardiopathy" have relied on a considerable variety of entirely hypothetical and poorly defined mechanisms, largely inaccessible to direct measurement. For example, the activity of sodium salts such as Na₂SO₄ and Na₂HPO₄ and the inactivity of NaCl, have been attributed to "activation" of the sodium ion by the effective anions and to a diminution of sodium ion "activity" by chloride. The failure of NaKHPO₄ to produce "electrolyte-steroid-cardiopathy" as does Na₂HPO₄ has been attributed to an "intra-molecular antagonism" between sodium and potassium.

We feel that sufficient data now are available to justify the hypothesis that the lesions of "electrolyte-steroid-cardiopathy" result primarily from cellular potassium depletion and its sequelae, with or without some involvement of magnesium, and that other contributing factors act either by accentuating the depletion or by increasing cardiac work. It is quite possible that this formulation is too simple to explain the roles of all factors which may possibly affect this condition. However, it is amenable to direct testing in any situations in which its applicability may be questioned.

Summary

The production of acute necrotic lesions of the myocardium and concomitant changes in myocardial and skeletal muscle potassium concentrations were investigated in rats. Lesions were induced by the administration of 2α-methyl-9α-chlorocortisol plus oral Na₂SO₄ (which caused a profuse catharsis), steroid plus an irritant cathartic (croton oil), steroid plus low-potassium diet, and low-potassium diet alone. Lesions in the various groups were grossly and microscopically indistinguishable. Their incidence and severity were well correlated with the degree of myocardial potassium depletion below a threshold value of approximately 72 mEq./Kg. wet weight. Skeletal muscle potassium was decreased roughly parallel to that of the myocardium, but somewhat more variably. Other treatments, including steroid or oral Na₂SO₄ alone and steroid plus subcutaneous Na₂SO₄, which failed to produce comparable reductions in myocardial potassium, failed to induce morphological lesions. Any specific interaction between steroid and electrolyte in the production of the myocardial lesions appears to be ruled out by the ineffectiveness of Na₂SO₄ administered subcutaneously. It is concluded that the "electrolyte-steroid-cardiopathy" 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.
ELECTROLYTE-STEROID-CARDIOPATHY

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