NOTE

EFFECT OF AGE AND THYROCALCITONIN ON MYOCARDIAL
CHANGES INDUCED BY SODIUM SULFAACETYLTHIAZOLE

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SYNOPSIS

Na-sulfaacetylthiazole, 0.5 g/kg body weight, was injected into immature
and adult rats to produce obstructive nephropathy. Necrotic changes in the
myocardium were found in all of the 9 adult rats of about 120 days of age,
whereas no such changes occurred in immature animals of about 40 days of age.
Thyrocalcitonin, 50 mMRC units a day injected subcutaneously for one week,
completely inhibited the occurrence of such myocardial lesion in adult animals,
as did parathyroidectomy performed one week previously. Serum calcium was
decreased from the normal adult level in thyrocalcitonin treated or parathyroi-
dectomized animals but not in untreated immature rats. Thyrocalcitonin appears
to have some effect on cardiovascular system in addition to the known effect
on the bone.

In view of the definite preventive effect of
parathyroidectomy on Na-sulfaacetylthiа-
zole-induced cardiovascular changes suggest-
ing the importance of calcium metabolism
(Lehr and Martin, 1956; Lehr, 1959), a study
on the effect of thyrocalcitonin on this well
developed experimental lesion appears to be of
interest.

MATERIALS AND METHODS

Male rats of Imamichi strain at ages of about
40 days (immature rats) and 120 days (adult rats)
maintained on Oriental Rat Chow (Calcium
content 1.85%) were given Na-sulfaacetylthia-
zole, 0.5 g per kg body weight as 5% aqueous
solution, in a single intraperitoneal injection.
Some animals were parathyroidectomized by
cautery 1 week prior to the injection and 10 to
50 mMRC units of thyrocalcitonin dissolved in
physiological saline was injected in some others
subcutaneously in 2 equally divided doses daily
for 7 days before the injection of Na-sulfaacetyl-
thiazole and 7 to 10 days after the injection.
At the end of this period the animals were
sacrificed and blood samples were obtained into
heparinized test tubes for the determination of
plasma calcium by the method of Copp et al.
(1963). Histological examinations were carried
out on the formalin fixed, paraffin embedded
heart and kidney specimens stained with Hematoxylin-Eosin. Several parallel sections 2–3 mm apart were made vertical to the long axis of the heart for a comprehensive review of the distribution of myocardial changes. Changes in the heart and kidney were classified into ++++, ++, +, and – according to the severity.

Thyrocalcitonin was prepared from porcine thyroid tissue homogenate through extraction with acid buffer pH 4.0 for 24 hrs., TEAE cellulose treatment, CM cellulose chromatography using acetate buffer pH 4.5 precipitation with 70% acetone and gel filtration with Sephadex G-10. The purified extract contained 0.33 MRC units per mg (0.458–0.225) in an assay conducted according to Kumar et al. (1965).

RESULTS

In adult rats about 120 days after birth weighing 300–400 g, single injection of Na-sulfaacetylthiazole caused necrotic changes

<table>
<thead>
<tr>
<th>Rats (Number of Rats)</th>
<th>Treatment</th>
<th>Renal change</th>
<th>Cardiac change</th>
<th>Cardiac Change/Renal change %</th>
<th>Plasma Ca±S.E. mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature</td>
<td>None</td>
<td>++</td>
<td>–</td>
<td>0</td>
<td>9.9±0.2</td>
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<tr>
<td>(40 days old) (5)</td>
<td></td>
<td>+</td>
<td>–</td>
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<td></td>
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<td></td>
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<td>+</td>
<td>–</td>
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<tr>
<td>Adult</td>
<td>None</td>
<td>+++</td>
<td>+</td>
<td>100</td>
<td>10.1±0.1</td>
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<td>++</td>
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<tr>
<td>Adult</td>
<td>Thyrocalcitonin 10 mMRC u/day</td>
<td>+</td>
<td>–</td>
<td>60</td>
<td>8.9±0.2*</td>
</tr>
<tr>
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<td>++</td>
<td>+</td>
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<td></td>
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<td>++</td>
<td>–</td>
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<tr>
<td>Adult</td>
<td>Thyrocalcitonin 50 mMRC u/day</td>
<td>+</td>
<td>–</td>
<td>14</td>
<td>8.4±0.2*</td>
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<td>(120 days old) (7)</td>
<td></td>
<td>++</td>
<td>–</td>
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<td></td>
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<td></td>
<td></td>
<td>++</td>
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<tr>
<td>Adult</td>
<td>Parathyroidectomy</td>
<td>+</td>
<td>–</td>
<td>0</td>
<td>8.20±0.1*</td>
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<td>(120 days old) (5)</td>
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* Significantly different from adult animals with no treatment (p<0.01).
in the renal tubules, while the heart showed pictures of myocardial necrosis and basophilic changes accompanied by infiltration of monocytes and histiocytes in all of the 9 animals. In immature rats about 40 days after birth weighing 80-100 g, injection of the same dose per kg body weight caused similar changes in the kidney but failed to show corresponding changes in the heart (Table 1). Administration of 10 mMRC units/day of thyrocalcitonin inhibited the myocardial changes in 2 of 5 adult rats, while 50 mMRC units/day inhibited it in 6 of 7 (Table 1). Serum calcium was not significantly decreased in immature rats as compared with adult animals, but was definitely decreased in parathyroidectomized and thyrocalcitonin-treated animals (Table 1).

DISCUSSION

Besides lowering serum Ca in various species (Hirsch et al., 1964; Munson and Hirsch, 1966), thyrocalcitonin is known to act on the bone inhibiting resorption (Raisz and Au, 1967; Aliapoulios et al., 1966). However, the action of thyrocalcitonin on other tissues has not yet been studied in detail, except for the possible action on the calcium content of the kidney and cutaneous calcinosis (Selye et al. 1967). No evidence of 45Ca uptake by soft tissues was obtained during thyrocalcitonin hypocalcemia (Chausmer et al., 1965).

While the necrosis of the myocardium and other smooth muscle in response to Na-sulfathiazole injection was initially ascribed to autointoxication by parathyroid hormone, subsequent investigation also emphasized the importance of electrolyte metabolism. Effect of thyrocalcitonin administration in preventing such changes appears to be as complete as that of parathyroidectomy, although only myocardial change was used as the criteria in the present report on account of the excellent reproductibility. In view of the hypocalcemia of similar degree produced by these two procedures, serum Ca as regulated by the balance in the parathyroid-thyrocalcitonin system appears to be one of the important factors in the development of the myocardial lesion. Hypocalcemia produced by the relative or absolute parathyroid hormone deficiency or thyrocalcitonin excess apparently prevented such change. Although the immature animals used in the present experiment were normocalcemic, secretion of more thyrocalcitonin in younger than in older rats in response to hypercalcemia or superior sensitivity of younger rats than that of older rats (Orimo, 1967) might provide one explanation for the distinct difference in the susceptibility to myocardial necrosis between immature and adult rats, although participation of other factors cannot be ruled out.

REFERENCES


