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Taurine Excretion Following Drug-Induced Muscle Necrosis and X-Irradiation.* (29298)

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Excretion of large amounts of taurine in the urine is a frequent, if not constant, sequel to necrosis of striated muscle(1,2). Skeletal muscle contains more than 75% of the total body taurine(3), but its precise role in the metabolism of the muscle cell is unknown.

In a previous paper(1), the taurinuria of muscle injury was attributed to an abnormal breakdown of taurine precursors. The occurrence of abnormal taurinuria following irradiation(3-6), and after administration of colchicine(7), suggests however that a generalized metabolic disturbance, rather than a specific disorder of muscle, may be implicated.

The purpose of this study was comparison of taurine excretion in the rat after administration of plasmocid and isoproterenol and after whole body irradiation. The quantity of taurine in certain muscles of normal rats and of rats given plasmocid was also compared.

Plasmocid (8-3-diethylaminopropylamino-6-methoxyquinoline) dihydroiodide induces a constant pattern of muscle necrosis in the rat. The diaphragm and heart are much more severely damaged than the limb muscles(2,8,9). The lesions of isoproterenol (1-(3,4-dihydroxyphenol-2-isopropylaminoethanol) dihydrochloride) are limited to the myocardium (10,11).

Materials and methods. White female rats of the Saint Louis University strain, weighing 150-250 g, were used. The animals were fasted during the 24-hour period of the experiment; water was not limited. Twelve rats each received a single intraperitoneal injection of plasmocid, 25 mg/kg: 6 were injected subcutaneously with isoproterenol, 85 mg/kg: 6 were radiated with 800 r: 18 animals served as controls.

The animals were kept in individual metabolic cages in which the urine, uncontaminated with feces, was collected in test tubes containing crystals of thymol. Collection was started at 9 A.M. immediately after injection of the drug or the radiation. The tubes were changed every 4 hours and the samples stored at 4°C until analyzed. Twenty-four hours later the animals were killed by exsanguination, the muscles quickly excised and aqueous extracts of heart, diaphragm, and quadriceps prepared by the method of Awapara(12). Portions of these muscles were also fixed in Zenker's solution for microscopic examination.

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TABLE I. A Comparison of Taurine in Urine from Controls and Following Drugs and Radiation. Taurine = μmol/100 g of rat per 24 hr.

Group	Taurine	Student "t" value (P = 0.005)	
1. Control (18 rats)	6.59 ± 3.39*(2.4–14.9)		
2. Plasmocid (12 rats)	28.32 ± 31.24 (4.3–94.0)	1 *vs* 2, t = + 2.95†	2 *vs* 3, t = +1.02
3. Isoproterenol (6 rats)	42.52 ± 18.62 (10.0–57.5)	1 *vs* 3, t = + 8.15†	3 *vs* 4, t = +1.33
4. Radiation (6 rats)	36.95 ± 5.06 (31.2–45.0)	1 *vs* 4, t = +16.79†	2 *vs* 4, t = − .66

* ± S.D.

† Statistically significant difference.

Taurine was measured according to the method of Pentz(13). The neutral and basic amino acids were removed by the acidic form of Dowex 50; the dinitrophenol derivative of taurine was prepared and its concentration measured with a Beckman Du spectrophotometer.

The plasmocid used in these experiments was synthesized by one of the authors (M.W.Y.) according to the method of Elderfield(14). Isoproterenol hydrochloride was obtained from Winthrop Laboratories, N. Y. X-radiation was given with a 250 K.V. constant potential machine operating at 15/mm. Filters used were 0.5 mm Cu. 1 mm Al., (half value layer 1.6 mm Cu.). The operating rate was 93 r per minute; target to skin distance was 50 cm.

Results. Excretion of taurine was significantly increased in the 24-hour periods following plasmocid, isoproterenol, and irradiation (Table I). The control animals showed a small diurnal variation in flow of urine whereas excretion of taurine remained fairly constant throughout the 24 hours (Fig. 1). The increased taurinuria which followed plasmocid was accompanied by a decreased volume of urine. Parallel increases of urine volume and taurine followed injection of isoproterenol. The taurine content of heart, diaphragm, and quadriceps, measured 24 hours after plasmocid, was not significantly different from normal (Table II). The plasmocid group of animals showed lesions of the diaphragm and heart similar to those previously described(1). Myocardial necrosis was observed in all of the rats given isoproterenol.

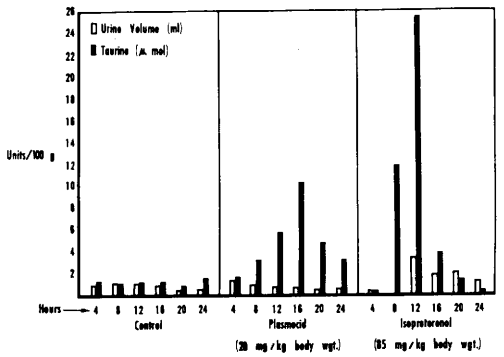

FIG. 1. Comparison of urine volume and taurine excretion from normal rats and following plasmocid and isoproterenol.

TABLE II. A Comparison of Taurine in Rat Muscle Following Plasmocid and in Controls. Taurine = μmol/g of wet tissue.

Muscle	Controls (18)*	After plasmocid (12)†	Student "t" value (P = .005)
Heart	26.27	25.67	t = + .25
Diaphragm	15.10	13.40	t = + .26
Quadriceps	13.60	14.77	t = −2.60

* Muscles from 18 rats pooled in 3 groups of 6 for analysis.

† Muscles from 12 rats analyzed singly.

Discussion. Excretion of taurine by the kidney is increased about 5 times following administration of myotoxic agents and radiation. The manner in which each of these agents produces its toxic effect is different. Plasmocid, like other 8-aminoquinolines, is thought to interfere with certain enzyme systems(15), whereas the myocardial necrosis produced by isoproterenol is probably secondary to hypoxia(10). X-irradiation does not, under these experimental conditions, produce discernible morphologic lesions.

Increased urinary taurine is not peculiar to the agents studied. Similar increases are reported in rats given colchicine(7), and in humans after steroid therapy(16). The only feature which is common to all of the examples cited is protein catabolism involved in breakdown of tissues.

The source of the excess taurine which appears in the urine in these several conditions

is unknown. There is no constant relationship between quantity of taurine excreted and volume of urine, which suggests that the abnormal aminoaciduria is probably not renal in origin. The compound is an end-product of the metabolism of the amino acids cystine, cysteine, and methionine, and it has been suggested that the taurinuria of radiation is the result of increased oxidation of sulfur-containing amino acids(6).

The apparently non-specific nature of taurinuria suggests a less complex mechanism, such as release from tissues which contain large amounts of pre-formed taurine. Although most tissues of the rat contain some free taurine(17) about 75% is found in muscle (3). Pathologic processes which produce muscle necrosis may therefore be expected to result in excessive taurinuria. Demonstration of the loss of taurine from injured tissue has, however, eluded direct analysis. Measurements of muscle taurine following radiation (3), after colchicine(7) and, in the present study after plasmocid, show no reduction of taurine content.

It is very difficult to alter the amount of taurine in muscles, either with sulfur-depleting diets or by injecting large amounts of taurine(18,19). Taurine is absorbed from the blood by striated muscle against a concentration gradient(19), and it is reasonable to suppose that the taurine which is released from injured cells is rapidly replaced by absorption from the blood. In the final analysis, therefore, it seems that the increased excretion of taurine which accompanies various catabolic disorders is dependent on the formation of new taurine derived from the oxidation of sulfur-containing amino acids.

Summary. Similar increases in urinary excretion of taurine follow drug-induced muscle necrosis and x-irradiation. The excess taurinuria appears to be unrelated to altered renal function but is probably a non-specific manifestation of increased tissue catabolism.

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