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Extension of PR Interval in Isolated Rat Heart by Cadmium (39102)

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The seriousness of cadmium as a toxic agent has been recognized for many years, but the nature of the toxicity has been obscure. As a divalent cation, cadmium has the potential for interaction with biochemical systems that normally interact with calcium, magnesium, and zinc. The symptoms of cadmiosis reflect such interactions. The testicular necrosis of cadmium poisoning suggests strongly that zinc metabolism in testicular tissue is disrupted (1, 2). The "itai-itai" disease which has been extensively investigated in Japan by Kobayashi (3) implicate cadmium interference with calcium metabolism. Unlike other divalent toxic agents such as cobalt or beryllium, cadmium is seldom the causative agent in acute poisoning (4). Cadmium is insidious in that long exposure to presumably "safe" amounts in the environment can lead to drastic and perhaps irreversible physiological consequences (5). The relative binding constants for cadmium by acetate, imidizole, amino, and sulfhydryl groups is some six to 10 times the constants for calcium, zinc, nickel, and cobalt (6). Such an affinity for biologically active groups leads to the problems of long-term cadmium exposure that have been documented by Schroeder and his coworkers (1). The influence of their work has focused attention on the possible association of cadmium with some form of hypertension. What is not clear is the immediate effect of cadmium on the cardiovascular system. Scattered data from several authors (7, 8, 9, 10) suggest that although hypertension may result ultimately, there is not a clear, direct development of hypertension as cadmium is accumulated. Among the most intriguing reports are those of an initial hypotension (7, 8) and electrocardiographic changes (9, 10) in cadmiosis.

Of particular interest is the report by Dotta and Fruscella (10), who found conduction time changes in rat heart following cadmium injection. Furthermore, histological studies revealed changes (vacuolization) specifically located in conductile tissue. A sequence of experiments was designed that would elucidate the effects of cadmium on conduction time in whole isolated mammalian heart.

Materials and methods. Albino, male, Sprague–Dawley rats (250–300 g) were sacrificed by cervical dislocation; the hearts were removed, and the aorta was cannulated for Langendorff perfusion. The rat hearts (n = 11) were perfused at constant temperature (34°) under 60–80 mm Hg pressure. The electrocardiogram was monitored from silver electrodes on the walls of a water-jacketed chamber with a Grass Model 5 polygraph using an EKG preamplifier. Perfusion pressure was monitored with a Statham P23 pressure transducer in the perfusion line near the cannula. The coronary overflow served as a volume conductor. A perfusion solution containing NaCl, 154 mEq; KCl, 5.4 mEq; MgCL, 2.1 mEq; CaCl, 1.8 mEq; dextrose, 5.6 mole; and 0.01 M Tris buffer, pH 7.4 (34°C), was used throughout the experiments with the exception of the cadmium containing perfusates which had cadmium sulfate ($3CdSO_4 \cdot 8H_2O$) added. The concentrations of cadmium used were 3×10^{-2} mM, 3×10^{-3} mM, 3×10^{-4} mM, and 3×10^{-5} mM. These doses bracket the ranges for cadmium found in human blood ($0.4–1.3 \times 10^{-4}$ mmoles/liter of blood) (1, 4).

In each experiment control electrocardiograms were made at 3-min intervals for 15–24 min by which time the hearts were stable with a rhythmic rate of 100–140 beats per min. After several control readings at a stable heart rate were obtained, the standard perfusate was replaced with a cadmium-containing one at the identical temperature

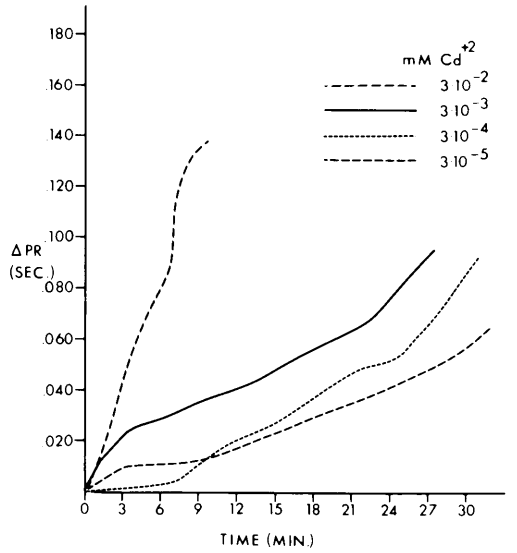

FIG. 1. Increases in PR interval during perfusion of rat hearts with varying doses of cadmium. Control PR duration for each point subtracted. Where $Y = bx + a$, for 3.1×10^{-2} M, $b = 0.0152$; for 3.1×10^{-3} M, $b = 0.0026$; for 3.1×10^{-4} M, $b = 0.0022$; for 3.1×10^{-5} M, $b = 0.0018$. p values comparing all slopes < 0.01.

and pressure. Special care was taken to avoid any changes in the geometry of the heart in the chamber. Cadmium perfusion was allowed to proceed until atrioventricular (A–V) blocking occurred, or for 30 min.

Results and discussion. A cadmium-induced bradycardia was noted for all levels of cadmium studied. Further electrocardiographic analysis for each dosage of cadmium showed a consistent pattern of increasing PR interval prolongation. Fig. 1 illustrates the increase over control in the duration of the PR interval per unit time. A dose-dependent relationship in extending the PR interval is clear. The progressive PR increase was accompanied by prolongation of the QS interval, followed by partial ventricular blocking and culminated in complete A–V blocking when the concentration of cadmium is greater than 3×10^{-3} mM. The duration of the QRS complex was increased by as much as 33% above controls over the experimental period. Atrial electrical events, characterized by the presence of a rhythmical P wave persisted after ventricular activity had stopped. Prolongation of the QS interval and ultimate cessation of QRS complex formation was indicative of prolonged ventricular depolarization time, possibly a result of depression of ventricular conduction. Measurements of T-wave duration in rat heart are uncertain because of the sliding wave form. Rats do not exhibit the long depolarized plateau characteristic of other mammalian hearts. Cadmium perfused hearts, however, did show anomalies such as T-wave inversion and inconsistent lengthening. When cadmium perfusion with the lower two doses was allowed to proceed for less than 10 min, the effects of the cadmium could be completely reversed by perfusing with the standard perfusate. If cadmium perfusion continued for longer than 20 min, the effects were never reversible.

The specificity exhibited by cadmium for PR interval prolongation suggests that its mode of action involves a strong affinity for the A–V node and/or common bundle of His causing a depression of this portion of the heart's conducting system. Cadmium is known to exhibit a strong affinity for sulfhydryl groups and is capable of displacing magnesium and calcium (6). The loss of reversibility of the cadmium effect with time suggests that cadmium's mode of action on the conduction system may be twofold: (i) an initial membrane effect prolonging conduction time by interfering with normal ion fluxes followed by (ii) an intracellular effect involving possible binding with proteins of functional significance, and possible uncoupling of oxidative phosphorylation (5). Experiments are currently in progress that correlate electrocardiographic changes with metabolic events in the myocardium in response to cadmium ions.

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