Cardiac effects of lead

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ABSTRACT

Symptoms consistent with cardiac disease have been noted as part of the syndrome of lead (Pb) intoxication. All types of cardiotoxicity noted in patients have been reproduced in experimental animals exposed acutely to high concentrations of Pb, or chronically exposed to lower levels. Types of cardiac effects observed include negative inotropism and electrocardiogram abnormalities, particularly conduction defects. Neonatal rats exposed to Pb via the milk of dams provided a drinking solution of lead acetate exhibit approximately four times the sensitivity to the arrhythmogenic effect of norepinephrine as adults compared with controls. Cardiotoxicity occurs after exposure as short as the first 10 postnatal days, but is not expressed until the rats are adult. Increased sensitivity to the arrhythmogenic effect of norepinephrine was seen in Pb-exposed animals in vivo and in isolated hearts from Pb-exposed animals in vitro. Norepinephrine arrhythmogenesis in vivo was attenuated by atropine or vagotomy, which indicates vagal nerve involvement. Possible mechanisms including interference with central γ-aminobutyric acid systems, alteration of adrenergic nerve development, and Pb-Ca interaction are discussed.—**Williams, B. J.; Hejtmancik, M. R., Jr.; Abreu, M.** Cardiac effects of lead. *Federation Proc.* 42: 2989–2993; 1983.

Clinical reports indicate that cardiotoxicity is a potentially lethal, although rarely recognized, complication of lead (Pb) intoxication. Relatively little experimental work, however, has examined the direct effects of Pb on the heart. This report will focus on the effects of experimental Pb exposure on the heart.

ACUTE Pb EXPOSURE

To explain sudden deaths of patients receiving Pb-contaminated i.v. solutions, Patel (26) exposed isolated frog hearts to lead nitrate, which caused a decrease in contractility. Negative inotropism in isolated rat hearts has been shown in response to perfusion with Pb (19). Pb caused an increase in the PR interval of the electrocardiogram (ECG) that was progressive with time and terminated in heart block in four of six hearts. The effect was concluded to occur at the level of the His-Purkinje system. In a later study perfusion of isolated rat hearts with a Pb-containing solution was shown to attenuate the increase in contractility caused by isoproterenol or calcium (Ca) (20). Pb also caused a decrease in the incorporation of ^{32}P into myosin light chain 2 (MLC_2), and reduced Ca-stimulated incorporation into tropomyosin, actin, tropomyosin-binding subunit of troponin, troponin inhibitory subunit, and MLC_2. The isoproterenol-stimulated increase in ^{32}P incorporation into troponin inhibitory subunit and MLC_2 was also reduced by Pb. These investigators suggest that Pb may interfere with transmembrane Ca transport either directly by interfering with Ca binding or indirectly by inhibiting phosphorylation of sarcolemmal proteins necessary for Ca translocation.

In this laboratory the effects on the heart of Pb administered i.v. to intact rats were compared with those seen when Pb was added to the perfusion fluid of isolated hearts. Administration of sufficient Pb in vivo to achieve blood levels of 10^{-5}–10^{-4} M caused only small decreases in heart rate and increases in the PR interval. In contrast, 10^{-5} M Pb in the perfusion fluid caused significant decreases in rate and contractility of isolated hearts. In addition, two to three times as much lead was accumulated in isolated hearts after a 20-min perfusion with Pb-containing solution than was accumulated by hearts in vivo in the 30–90 min after Pb injection. These data suggest the existence of some protective mechanism in the intact animal.

CHRONIC Pb EXPOSURE IN MATURE ANIMALS

Human Pb intoxication is probably best modeled by chronic experimental exposure because the majority of clinical cases result from long-term exposure. Studies of chronic Pb exposure have used a wide variety of exposure models, which makes direct comparisons among studies difficult. In addition to the obvious differences in experimental design, such as exposure time and level, differences in age of the experimental population can greatly influence the results. In the following studies Pb was administered chronically to mature animals.

Chronic administration of Pb to rabbits caused ECG abnormalities that correlated with myocardial histopathological changes found on necropsy (23). Ultrastructural changes in the myocardium were observed in rats allowed free access to water containing Pb (1 mg/liter) (25). More extensive ultrastructural damage was seen in the

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