Myocardial cAMP Levels and Inotropic Responsiveness in Terminal Renal Failure

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Table 1. Half maximal stimulating concentrations (EC₅₀) of (-) noradrenaline and (±) dobutamine and maximum isometric tension of isolated ventricular strips in organ bath experiments with modified Krebs-Ringer solution

Basal tension was 3.8 ± 0.2 mN in controls and 3.5 ± 0.1 mN in uremics.

Sir,

Catecholamine-induced increases in myocardial contractility are mainly mediated by β -adrenoceptor activation of adenylate cyclase activity, which leads to cAMP formation [5]. Chronic exposure of the heart to catecholamines, however, decreases the number of β -adrenergic receptors with a concomitant reduction in maximum adenylate cyclase activation and contractile responses to catecholamines [6] as well as to interstitial myocardial fibrosis [12], similar to that observed in chronic renal insufficiency [10].

In animal experimental models of renal failure, a decrease in β -adrenoceptor concentration [8] as well as a lowered basal and isoproterenol-stimulated adenylate cyclase activity [11] has been observed. Others [14], however, found elevated cAMP levels in the heart, liver and plasma of uremic animals.

In our own studies, we investigated cAMP concentrations as well as the inotropic responsiveness of isolated continuously electrically stimulated (0.5 Hz, 10 ms, 10 V) left ventricular anterior wall muscle strips in sham-operated and 5/6 nephrectomized rats 7.5 weeks after surgery.

cAMP levels in left ventricular homogenates of sham-operated (serum urea 47 ± 8 mg%, n = 63, mean values $\pm$ SEM) and in uremic rats (serum urea 215 ± 11 mg%, n = 70, p < 0.05) were determined by a radioisotope dilution technique [4] using ³H-cAMP (spe-

EC₅₀, μ M

cific activity 25 Ci/mmol). cAMP concentration was significantly (p < 0.02) lower in uremic animals: 0.44 ± 0.04 pM/mg (n = 9) versus 0.72 ± 0.26 pM/mg (n = 9) when normalized to wet weight and 2.9 ± 0.26 pM/mg (n = 9) versus 4.5 ± 0.3 pM/mg (n = 9) (p < 0.02) when related to protein content determined by the method of Bradford [1]. However, as shown in table 1, the inotropic responsiveness to (-)noradrenaline as well as to the synthetic catecholaminergic agonist (±) dobutamine was not significantly altered

in uremia: neither maximum responses nor the agonist concentration for eliciting half maximal stimulation was significantly changed. The basal tension was not significantly different in both groups either: 3.8 ± 0.2 mN (n = 20) in controls and 3.5 ± 0.1 mN (n = 20) in uremic animals. All data are mean values $\pm$ SEM.

Maximal tension

mN

The markedly decreased cAMP levels are possibly a consequence of a reduced adenylate cyclase activity in uremia as reported by Mann et al. [11]. However, an influence on the

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Myocardial cAMP concentration

* $p < 0.02$

Fig. 1. cAMP levels in sham-operated ($\square$) and 5/6 nephrectomized (E3) rats. cAMP concentrations were normalized to milligram wet weight and to milligram protein. The water content was $76 \pm 0.2\%$ in uremia and $76 \pm 0.3\%$ in controls.

responsiveness of the heart to catecholamines could not be demonstrated by determining the concentration-effect relationship in organ bath experiments. This is in accordance with clinical investigations in which systolic function in uremic patients without ischemic heart disease was normal and the pharmacodynamic response to ($\pm$) dobutamine was preserved [7]. Similar observations have also been made in animal experiments [15] by other research workers. Thus, the biochemical alteration appears to have no physiological relevance with respect to the positive inotropic action of catecholamines. Myocardial membrane preparations are highly contaminated with endothelial cell membranes [13] in which a β_2 -adrenoceptor-activated adenylate cyclase system exists [3]. Although there is some evidence [2,9] that uremic serum factors might influence the β_2 - and α_2 -adrenoceptor adenylate cyclase system in other organs, in the heart the varying degree of endothelial cell membrane fragments as well as potential alterations in the β_2 -adrenoceptor-mediated adenylate cyclase activity have to be respected. These necessary precautions make the interpretation of all observed variations in the enzyme activity and cAMP levels in the heart very difficult.

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360

Lübbecke/Steudle/Schütterle

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