Cardioprotection by Oxyfedrine in Hereditary Cardiomyopathic Hamsters

Vorbeugende Wirkung von Oxyfedrin bei der erblichen Kardiomyopathie des Hamsters

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With 1 figure and 3 tables

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Summary

A defect of the myocardial plasma membrane, resulting in increased transmembrane calcium conductivity with consecutive myocardial calcium accumulation and exhaustion of high energy phosphates is considered the determinant factor for cardiac degeneration in the dystrophic cardiomyopathy of Syrian hamsters from strain BIO 8262. Since oxyfedrine (L-3-[[β-hydroxy-α-methyl-phenethylamino]-3'-methoxy-propiophenone hydrochloride), a drug against coronary heart disease, is described as a partial β-adrenoceptor agonist inducing moderate stimulation of β-adrenoceptors and simultaneously exerting an unspecific quinidine-like membrane effect on cardiac and smooth muscle, it was of interest to investigate the action of this substance on the development of the hereditary hamster cardiomyopathy.

Although during the prenecrotic stage of the disease only a very high acute dose of oxyfedrine (60 mg/kg s.c.) was able to distinctly counteract myocardial calcium accumulation induced by isoproterenol (1 mg/kg s.c.), chronic administration of low doses of oxyfedrine (twice daily 0.3 mg/kg s.c.) – as applied in humans – were able to considerably suppress spontaneous myocardial calcium accumulation. By chronic subcutaneous injection of 30 mg/kg oxyfedrine twice daily it was possible to avoid spontaneous myocardial calcium accumulation as well as to nearly prevent degeneration of the myocardium.

These findings suggest that oxyfedrine exerts cardioprotection by its calcium antagonistic properties.

The aminoketone derivative oxyfedrine (L-3-[[β-hydroxy-α-methyl-phenethylamino]-3'-methoxy-propiophenone hydrochloride) is clinically used as a drug against coronary heart disease (42, 39, 36, 15, 44, 13, 27). Pharmacologically it is described as a partial β-adrenoceptor agonist inducing simultaneous stimulation of β-adrenoceptors and blockade of catecholamines at adequate concentrations and a quinidine-like effect on cardiac and smooth muscle at higher concentrations (14, 2, 38, 28, 11). Its β-adrenoceptor stimulatory effect, however, is about ten times lower than that of adrenaline (11).
Since Plamenac and Stern (1970) have reported on an antinecrotizing effect of oxyfedrine in corticoid-treated stressed rats, we were interested in seeing whether oxyfedrine would be able to prevent spontaneous cardiac degeneration in the hereditary dystrophic cardiomyopathy of the Syrian hamster. A beneficial effect in this respect was observed by long-term treatment with the calcium-antagonistic substance verapamil (21, 22, 10, 25, 26). As a defect of the myocardial plasma membrane resulting in increased transmembrane calcium conductivity and myocardial calcium accumulation is considered the determinant factor for cardiac degeneration in these animals (25, 26), the results of our experiments with oxyfedrine should shed more light on the myocardial metabolic effects of this substance.

By simultaneous injection of oxyfedrine with isoproterenol into prenecrotic cardiomyopathic hamsters we intended to ascertain whether oxyfedrine can counteract isoproterenol as well as interfere with the disturbed myocardial calcium metabolism of these animals, which has been recently reported (26). Chronical application of oxyfedrine was employed in order to investigate the influence of this substance on spontaneous myocardial calcium accumulation and myocardial degeneration of the hamsters. Correlation of the results gained should answer the question of whether oxyfedrine possesses cardioprotective properties and by which pharmacological means it possibly exerts its beneficial effect.

Materials and Methods

I.a. Animals

Genetically cardiomyopathic hamsters of both sexes from the BIO 8262 inbred strain were used. Details about the genetic background of the animals as well as the morphologic appearance of the heart and of biochemical and functional features are extensively reported elsewhere (30, 29, 19, 22, 23, 41, 24, 25, 26). Thirty-day-old cardiomyopathic hamsters do not yet show any histopathologic signs of cardiomyopathy, thus being in the prenecrotic phase of the disease (29). Their myocardial electrolyte content (Ca, Mg, Na, K) does not differ from that of healthy control animals of the same age (23). However, it turned out that cardiomyopathic hearts differ from healthy control hearts with respect to their radiocalcium uptake as well as total myocardial calcium accumulation after isoproterenol (22). Hence, a latent disturbance of the myocardial calcium metabolism already existing during the prenecrotic phase of the heart disease has been shown (26). About the 40th day of life spontaneous and progressive myocardial necrotization in parallel with giant cell formation and increasing calcification—especially of these giant cells—is occurring, followed by resorptive changes and fibrosis (29). Biochemical analysis showed a tremendous increase in myocardial calcium content with increasing age of the animals (23).

The animals were housed in air-conditioned rooms with artificial light in a 12 hour day-and-night-circle. Normal laboratory diet (Ssniff-H hamster chow) and tap water were provided ad libitum.

I.b. Substances

Isoproterenol: commercially available 1% Aludrin®-solution (1-[3, 4-dihydroxyphenyl]-2-isopropylamino-ethanol-sulfate; Boehringer, Ingelheim) was used as isoproterenol. The original Aludrin®-solution was diluted 1:60 with aqua bidest., which was brought up to pH 3.5 with n/10 hydrochloric acid. Depending on body