ABSTRACT

EFFECTS OF β- ADRENERGIC ANTAGONIST THERAPY IN MICE LACKING α_{2A}/α_{2C} ADRENERGIC RECEPTORS

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We have recently reported that disruption for both α_{2A} and α_{2C} adrenergic receptor subtypes in mice (KO) leads to sympathetic hyperactivity with evidence of heart failure (HF) by the age of 7 months. These mice provide a model system for evaluating the efficiency among different â- adrenergic antagonists (BB) for HF therapy. In the present study, we evaluate the effect of three different BB in a cohort of a wild type (n=22) control group (WT) and a cohort of congenic KO (n=94) from five to seven mo of age. Mice from both groups were randomly assigned to receive by gavage (seven days/wk) either saline (S), propranolol (P), metoprolol (M), or carvedilol (C). Exercise capacity was measured using a graded treadmill protocol. Blood pressure (BP) and heart rate (HR) were determined by tail cuff and LV function by echocardiography. The cardiomyocyte width (CW) and cardiac collagen content (CC) were evaluated by light microscopy. At seven mo of age, when cardiac dysfunction is severe, KO treated with S displayed exercise intolerance and 30% decrease in fractional shortening (FS) when compared with WT. In addition, CW (13%) was increased. All BB were efficient in reducing baseline HR of KO mice towards WT levels, however P was less tolerated. Again, all BB similarly restored FS, and reduced CW, but only M reduced CW towards WT levels. Only M significantly decreased CC. M and C decreased mortality rate

of KO mice (31 %), while P did decrease it in only 24%. Collectively these data provide direct evidence for beneficial effect of M and C in restoring cardiac function. Further investigation is need to better understand the pharmacodynamics of M on cardiac remodeling.

Key words: heart failure, sympathetic hyperactivity, â- adrenergic antagonists, genetic modified mice.