Lack of G\(\alpha_{i2}\) leads to dilative cardiomyopathy and increased mortality in \(\beta_1\)-adrenoceptor overexpressing mice.

Inhibitory G (Gi) proteins have been proposed to be cardioprotective. We investigated effects of G\(\alpha_{i2}\) knockout on cardiac function and survival in a murine heart failure model of cardiac \(\beta_1\)-adrenoceptor overexpression. \(\beta_1\)-transgenic mice lacking G\(\alpha_{i2}\) (\(\beta_1\)-tg/G\(\alpha_{i2}\) (-/-)) were compared with wild-type mice and littermates either overexpressing cardiac \(\beta_1\)-adrenoceptors (\(\beta_1\)-tg) or lacking G\(\alpha_{i2}\) (G\(\alpha_{i2}\) (-/-)). At 300 days, mortality of mice only lacking G\(\alpha_{i2}\) was already higher compared with wild-type or \(\beta_1\)-tg, but similar to \(\beta_1\)-tg/G\(\alpha_{i2}\) (-/-), mice. Beyond 300 days, mortality of \(\beta_1\)-tg/G\(\alpha_{i2}\) (-/-) mice was enhanced compared with all other genotypes (mean survival time: 363 ± 21 days). At 300 days of age, echocardiography revealed similar cardiac function of wild-type, \(\beta_1\)-tg, and G\(\alpha_{i2}\) (-/-) mice, but significant impairment for \(\beta_1\)-tg/G\(\alpha_{i2}\) (-/-) mice (e.g. ejection fraction 14 ± 2 vs. 40 ± 4% in wild-type mice). Significantly increased ventricle-to-body weight ratio (0.71 ± 0.06 vs. 0.48 ± 0.02% in wild-type mice), left ventricular size (length 0.82 ± 0.04 vs. 0.66 ± 0.03 cm in wild types), and atrial natriuretic peptide and brain natriuretic peptide expression (mRNA: 2819 and 495% of wild-type mice, respectively) indicated
hypertrophy. G?i3 was significantly up-regulated in G?i2 knockout mice (protein compared with wild type: 340 ± 90% in G?i2 (-/-) and 394 ± 80% in ?1-tg/G?i2 (-/-), respectively). G?i2 deficiency combined with cardiac ?1-adrenoceptor overexpression strongly impaired survival and cardiac function. At 300 days of age, ?1-adrenoceptor overexpression alone had not induced cardiac hypertrophy or dysfunction while there was overt cardiomyopathy in mice additionally lacking G?i2. We propose an enhanced effect of increased ?1-adrenergic drive by the lack of protection via G?i2. G?i3 up-regulation was not sufficient to compensate for G?i2 deficiency, suggesting an isoform-specific or a concentration-dependent mechanism.

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