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Involvement of β3-Adrenoceptor in Altered β-Adrenergic Response in Senescent Heart: Role of Nitric Oxide Synthase 1–derived Nitric Oxide

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Résumé en anglais	Background: In senescent heart, β-adrenergic response is altered in parallel with β1- and β2-adrenoceptor down-regulation. A negative inotropic effect of β3-adrenoceptor could be involved. In this study, the authors tested the hypothesis that β3-adrenoceptor plays a role in β-adrenergic dysfunction in senescent heart.Methods: β-Adrenergic responses were investigated in vivo (echocardiography–dobutamine, electron paramagnetic resonance) and in vitro (isolated left ventricular papillary muscle, electron paramagnetic resonance) in young adult (3-month-old) and senescent (24-month-old) rats. Nitric oxide synthase (NOS) immunolabeling (confocal microscopy), nitric oxide production (electron paramagnetic resonance) and β-adrenoceptor Western blots were performed in vitro. Data are mean percentages of baseline ± SD. Results: An impaired positive inotropic effect (isoproterenol) was confirmed in senescent hearts in vivo (117 ± 23 vs. 162 ± 16%; P < 0.05) and in vitro (127 ± 10 vs. 179 ± 15%; P < 0.05). In the young adult group, the positive inotropic effect was not significantly modified by the nonselective NOS inhibitor NG-nitro-l-arginine methylester (l-NAME; 183 ± 19%), the selective NOS1 inhibitor vinyl-l-N-5(1-imino-3-butenyl)-l-ornithine (l-VNIO; 172 ± 13%), or the selective NOS2 inhibitor 1400W (183 ± 19%). In the senescent group, in parallel with β3-adrenoceptor up-regulation and increased nitric oxide production, the positive inotropic effect was partially restored by l-NAME (151 ± 8%; P < 0.05) and l-VNIO (149 ± 7%; P < 0.05) but not by 1400W (132 ± 11%; not significant). The positive inotropic effect induced by dibutyryl-cyclic adenosine monophosphate was decreased in the senescent group with the specific β3-adrenoceptor agonist BRL 37344 (167 ± 10 vs. 142 ± 10%; P < 0.05). NOS1 and NOS2 were significantly up-regulated in the senescent rat. Conclusions: In senescent cardiomyopathy, β3-adrenoceptor overexpression plays an important role in the altered β-adrenergic response via induction of NOS1-nitric oxide.
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Titre abrégé	Involvement of β3-Adrenoceptor in Altered β-Adrenergic Response in Senescent Heart

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