Dopamine D3 receptor knockout mice mimic aging-related changes in hypertension and cardiac fibrosis

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Background: Restless legs syndrome (RLS) is often associated with a concomitant increase in blood pressure, and dysfunction of the dopamine D3 receptor system has been implicated in the pathogenesis of hypertension.

Objective: To evaluate the role of the D3 receptor in aging-related hypertension and to compare it with the changes in the D3KO animal model of RLS, we assessed cardiac structure and function in differently aged (2 mo, 1 yr, 2 yr) wild type (WT) and young (2 mo) D3 receptor knockout mice (D3KO). In WT, systolic and diastolic blood pressures and rate-pressure product (RPP) significantly increased with age, while heart rate significantly decreased.

Results: Blood pressure values, heart rate and RPP of young D3KO were significantly elevated over age-matched WT, but similar to those of the 2 yr old WT. Echocardiography revealed that the functional measurements of ejection fraction and fractional shortening decreased significantly with age in WT and that they were significantly smaller in D3KO compared to young WT. Despite this functional change however, cardiac morphology remained similar between the age-matched WT and D3KO. Additional morphometric analyses confirmed an aging-related increase in left ventricle (LV) and myocyte cross-sectional areas in WT, but found no difference between age-matched young WT and D3KO. In contrast, interstitial fibrosis, which increased with age in WT, was significantly elevated in the D3KO over age-matched WT, and similar to 2 yr old WT. Western analyses of myocardial homogenates revealed significantly increased levels of pro- and mature collagen type I in young D3KO. Column zymography revealed that activities of myocardial MMP-2 and MMP-9 increased with age in WTs, but in D3KO, only MMP-9 activity was significantly increased over age-matched WTs.

Conclusion: Our data provide evidence that a dysfunction of the D3 receptor system not only has a critical role in the emergence of the sensorimotor deficiencies in RLS, but that it may also be involved in aging-related cardiac fibrosis, remodeling, dysfunction, and a decrease in life span.