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Molecular Analysis of Mice with Salt-Sensitive Hypertension Due to Lack of Biological Clock

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Summary

Background: Cry-deficient (Cry KO) mice are known to have high aldosterone levels which present salt-sensitive hypertension. We aimed to investigate our hypothesis that we could prevent the organ damage by restoring the circadian rhythm using Cry-deficient mice that present salt-sensitive hypertension due to increased endogenous aldosterone.

Methods: We used 8-12 week Cry-deficient mice and wild type littermates. Lymphatic capillary density and macropharge number in the skin were measured by immnostaining using LYVE-1 and F4/80 antibodies, respectively. Telemetry system was used to monitor blood pressure, heart rate, and activity for 24 hours continuously. Histological analysis was performed using heart samples to observe the cardiac fibrosis. Real-time PCR analysis for TGF-β and CTGF was done by using RNA prepared from heart samples.

Results: Both wild-type and Cry-KO mice showed increased lymphatic capillary density and macrophage number. Telemetry analysis revealed that wild-type mice showed clear circadian variation in blood pressure, heart rates, and activities. Diurnal variations of blood pressure, heart rates and activities in Cry KO mice were not observed in constant darkness condition. However, when Cry KO mice were kept in 12-our light-dark cycles, weak but statistically significant circadian rhythm in blood pressure was observed. Histological analysis showed that apparent cardiac fibrosis was noted in Cry KO mice. Interestingly, cardiac fibrosis in constant darkness condition is more severe as compared with that in light-dark cycle. These results suggest that circadian rhythm induced by the light in Cry KO mice is beneficial for preventing the cardiac damages.

Conclusion: Our results suggest that restoring the circadian rhythm by light could prevent the cardiac damage, and that it may provide novel therapeutic approach for human pathology.