

# Circadian Regulation of IOP Rhythm by Dual Pathways of Glucocorticoids and the Sympathetic Nervous System

Ikegami K, Shigeyoshi Y, Masubuchi S

**PURPOSE:** Elevated IOP can cause the development of glaucoma. The circadian rhythm of IOP depends on the dynamics of the aqueous humor and is synchronized with the circadian rhythm pacemaker, that is, the suprachiasmatic nucleus. The suprachiasmatic nucleus resets peripheral clocks via sympathetic nerves or adrenal glucocorticoids. However, the detailed mechanisms underlying IOP rhythmicity remain unclear. The purpose of this study was to verify this regulatory pathway.

**METHODS:** Adrenalectomy and/or superior cervical ganglionectomy were performed in C57BL/6J mice. Their IOP rhythms were measured under light/dark cycle and constant dark conditions. Ocular administration of corticosterone or norepinephrine was also performed. Localization of adrenergic receptors, glucocorticoid receptors, and clock proteins *Bmal1* and *Per1* were analyzed using immunohistochemistry. *Period2::luciferase* rhythms in the cultured iris/ciliary bodies of adrenalectomized and/or superior cervical ganglionectomized mice were monitored to evaluate the effect of the procedures on the local clock. The IOP rhythm of retina and ciliary epithelium-specific *Bmal1* knockout mice were measured to determine the significance of the local clock.

**RESULTS:** Adrenalectomy and superior cervical ganglionectomy disrupted IOP rhythms and the circadian clock in the iris/ciliary body cultures. Instillation of corticosterone and norepinephrine restored the IOP rhythm.  $\beta$ -Adrenergic receptors, glucocorticoid receptors, and clock proteins were strongly expressed within the nonpigmented

**CONCLUSIONS:** These findings suggest direct driving of the IOP rhythm by the suprachiasmatic nucleus, via the dual corticosterone and norepinephrine pathway, but not the ciliary clock, which may be useful for chronotherapy of glaucoma.

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