MATERNAL MELATONIN OR AGOMELATINE THERAPY REPROGRAMS THE DEVELOPMENT OF HYPERTENSION IN MALE RATS BORN BY MOTHER EXPOSED TO CONTINUOUS LIGHT

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OBJECTIVES

1. Hypertension can originate from early-life insults. Whether maternal continuous light exposure can induce programmed hypertension in adult offspring remains unclear.
2. We examined whether maternal melatonin or its analogue agomelatine therapy prevented maternal continuous light exposure-induced programmed hypertension in adult offspring and explored the melatonin signaling pathway in the kidneys.

METHODS

1. Female Sprague-Dawley pregnant rats randomly divided into four groups: controls, rats exposed to continuous light (Light), exposed to continuous light plus treated with agomelatine (50mg/day i.p.) (Light+A), and exposed to continuous light plus treated with 0.01 % melatonin in drinking water throughout pregnancy and lactation period (Light+M). Male offspring (n=10/group) were sacrificed at 12 weeks of age.
2. Blood pressure was measured in conscious rats by an indirect tail-cuff method.
3. kidney cortex samples (n = 3/group) were pooled for whole-genome RNA NGS analysis.
4. Components of the RAS, AMPK, clock genes, and sodium transporters were analyzed by qPCR.
5. Protein levels of melatonin receptor-1 (MT1R) and -2 (MT2R), and retinoid-related orphan receptor-α (RORα) were determined by Western blot.

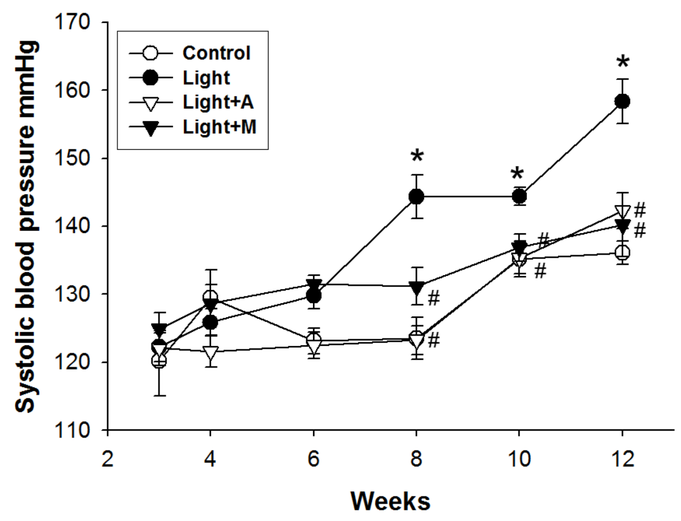
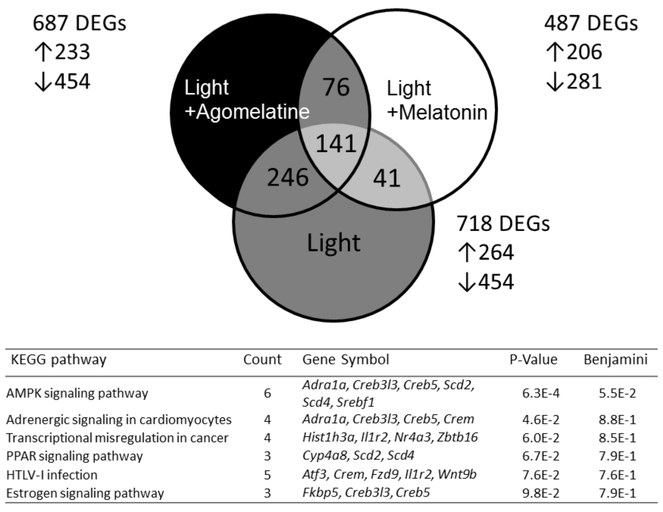


Fig. 1. Effect of maternal exposure to continuous light, agomelatine, and melatonin on systolic blood pressure in male offspring from 3 to 12 weeks of age. *P<0.05 vs control; #P<0.05 vs Light.



KEGG pathway	Count	Gene Symbol	P-Value	Benjamini
AMPK signaling pathway	6	*Adra1a, Creb3l3, Creb5, Scd2, Scd4, Srebf1*	6.3E-4	5.5E-2
Adrenergic signaling in cardiomyocytes	4	*Adra1a, Creb3l3, Creb5, Crem*	4.6E-2	8.8E-1
Transcriptional misregulation in cancer	4	*Hist1h3a, Il1r2, Nr4a3, Zbtb16*	6.0E-2	8.5E-1
PPAR signaling pathway	3	*Cyp4a8, Scd2, Scd4*	6.7E-2	7.9E-1
HTLV-I infection	5	*Atf3, Crem, Fzd9, Il1r2, Wnt9b*	7.6E-2	7.6E-1
Estrogen signaling pathway	3	*Fkbp5, Creb3l3, Creb5*	9.8E-2	7.9E-1

Fig. 2. Venn diagram depicting unique and shared (overlapping circles) sets of differential DEGs between maternal exposure to continuous light (Light, grey circle), maternal exposure to continuous light plus agomelatine (Light+ A, black circle), and maternal exposure to continuous light plus melatonin treatment (Light+ M, white circle). A total of 141 combined DEGs are analyzed and 6 significantly regulated KEGG pathways are listed in the lower panel.

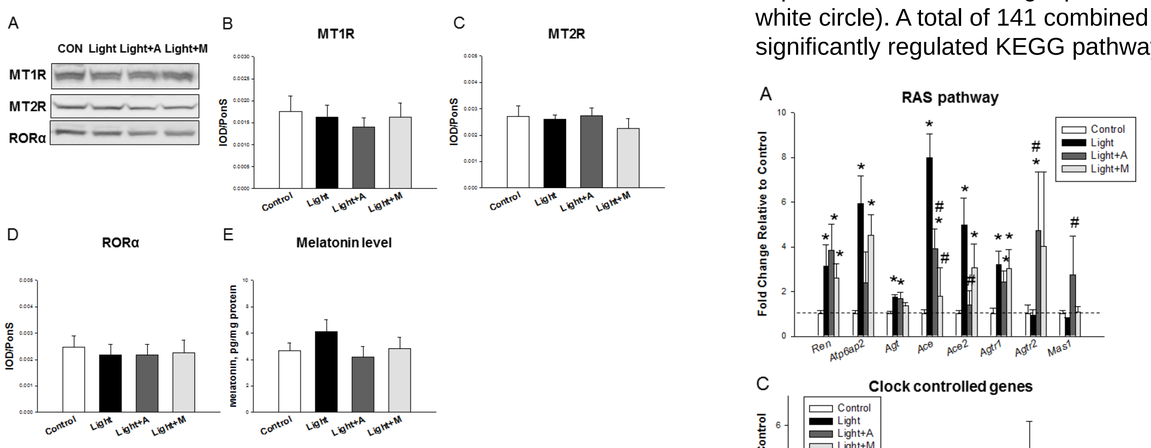


Fig. 3. A, Representative Western blots show MT1R (37 kDa), MT2R (40 kDa), and RORα (59 kDa) bands in offspring kidneys with maternal exposure to continuous light and/or treated with agomelatine or melatonin at 12 weeks of age. Relative abundance of renal B, MR1R, C, MT2R, and D, RORα were quantified. E, Renal melatonin level.

RESULTS

1. Exposure of the mother to continuous light induced programmed hypertension in adult offspring, which maternal agomelatine or melatonin therapy prevented (Figure 1)
2. Continuous light exposure in pregnancy caused 718 renal transcripts to be modified in the developing offspring kidney (Figure 2).
3. Continuous light exposure impaired melatonin synthesis and signaling in the developing kidney, but not persisted into adulthood (Figure 3).
4. Genes that belong to the RAS, sodium transporters, AMPK pathway, and circadian rhythm were potentially involved in the continuous light exposure induced programmed hypertension;

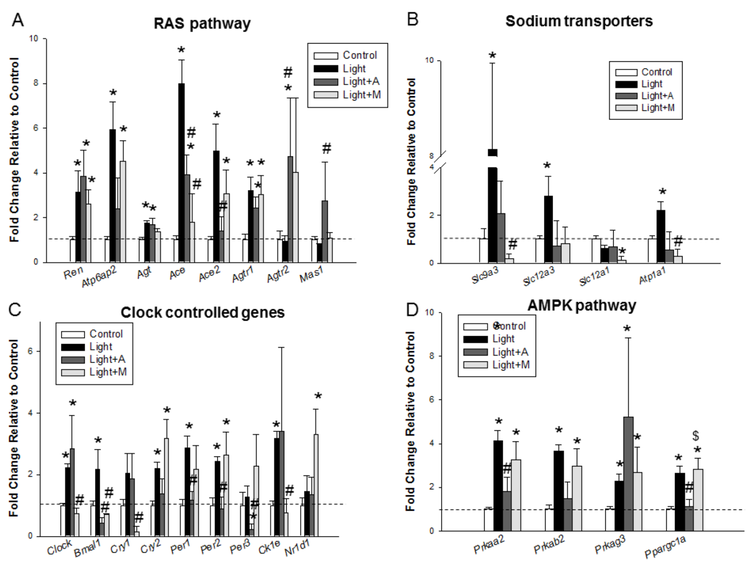


Fig. 4. Effect of maternal exposure to continuous light, agomelatine, and melatonin on gene expression of A, renin-angiotensin system components, B, sodium transporters, C, Clock controlled genes, and D, AMP-activated protein kinase pathway in offspring kidneys with maternal exposure to continuous light and/or treated with agomelatine or melatonin at 12 weeks of age. *P<0.05 vs control; #P<0.05 vs Light; $P<0.05 vs Light+A.

CONCLUSIONS

1. Early agomelatine or melatonin therapy provides protection against maternal exposure to continuous light-induced programmed hypertension.
2. Maternal agomelatine and melatonin therapy reprogram the RAS and sodium transporters differentially to prevent maternal exposure to continuous light-induced programmed hypertension.
3. Our NGS findings highlight that maternal exposure to continuous light can induce a large number of transcriptomic changes in the developing offspring kidney.

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