

# Ontogeny of Circadian Clock

Resetting of pups' clock by maternal deprivation

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The biological clock is the machinery by which organisms optimize their functions in face of day-night and seasonal environmental changes.



## 1. Circadian rhythms and the clock in the Suprachiasmatic Nucleus

- a. Histological structure of the SCN
- b. Single neuronal rhythm of the SCN

## 2. Molecular Circadian Clock

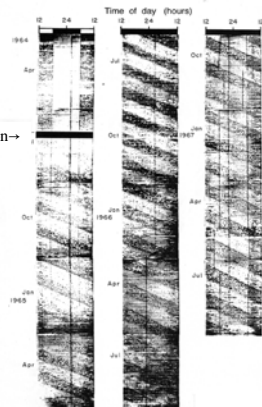
- a. Clock genes and molecular feedback loop for rhythm generation
- b. Monitoring clock gene expression

## 3. Maternal phase-setting of pups' circadian rhythms



Three year record of the locomotor activity rhythm from a squirrel monkey

Eye enucleation →



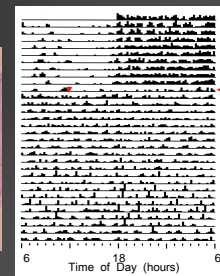
In mammals, a master clock is located in the hypothalamic **suprachiasmatic nucleus (SCN)**, which conducts and coordinates the peripheral clocks in each organ and tissue

Behavioral rhythm of an SCN lesioned rat

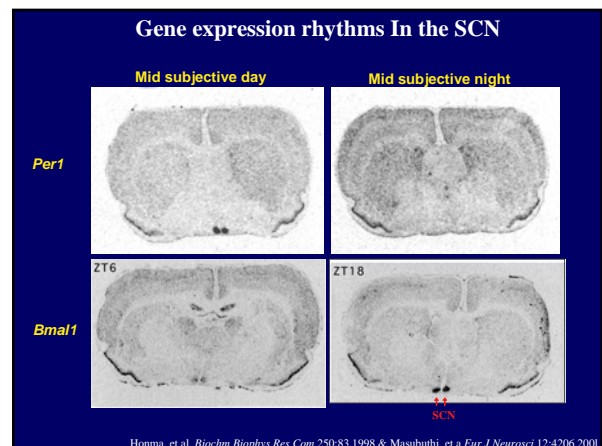
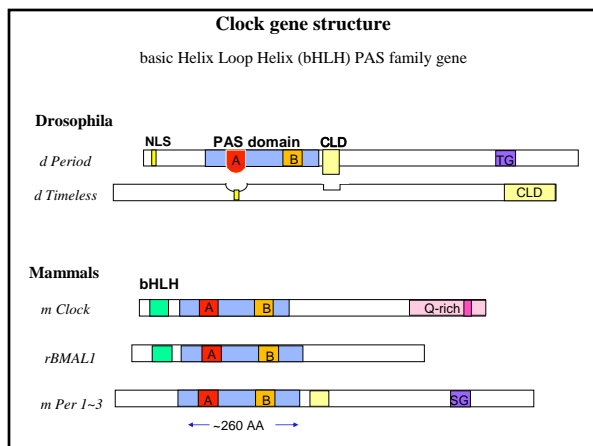
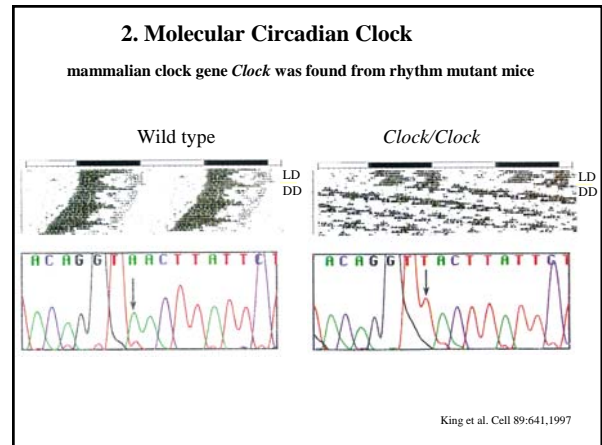
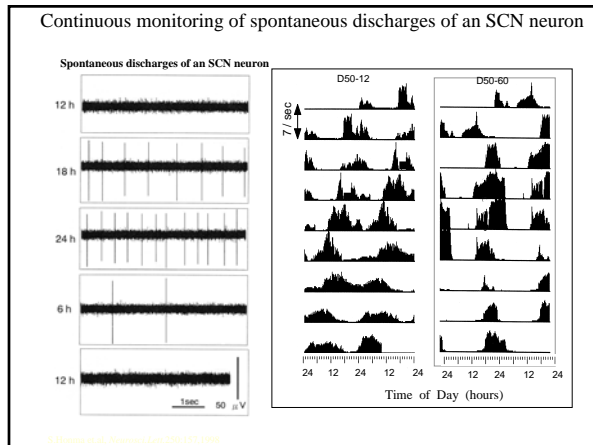
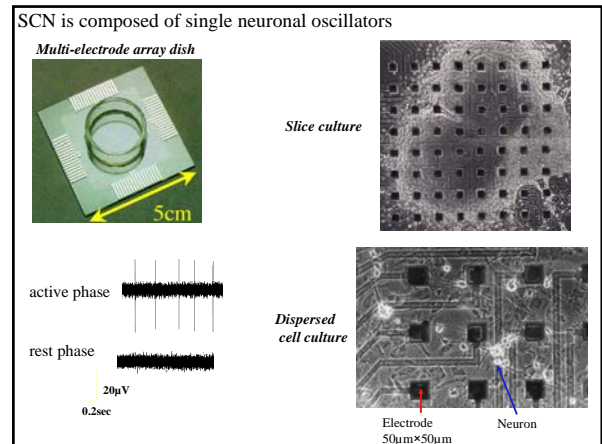
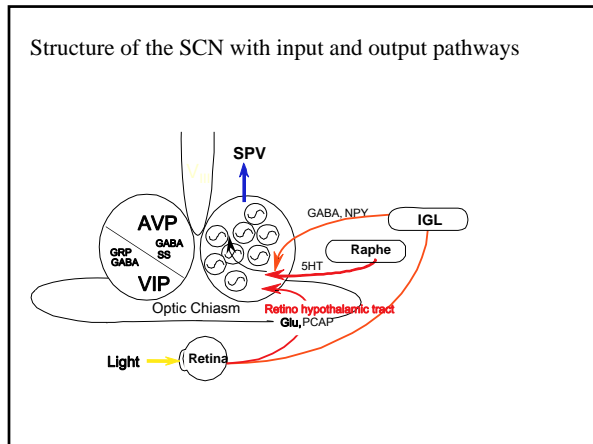
Coronal section of rat brain



Suprachiasmatic nucleus (SCN)



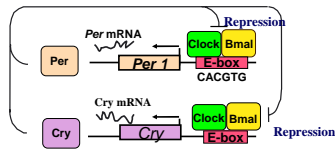
SCN lesion



## Networks of transcription-translation autofeedback loops

### Rhythmic *Per* transcription

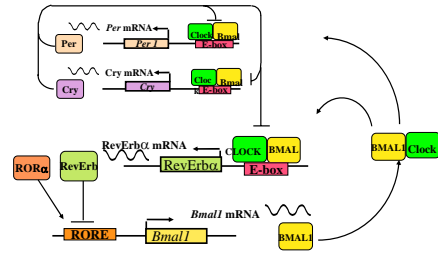
Positive elements: *Clock*, *Bmal1* (bHLH-PAS transcription factor)  
 Negative elements: *Per1*, *Per2*, *Cry1*, *Cry2*



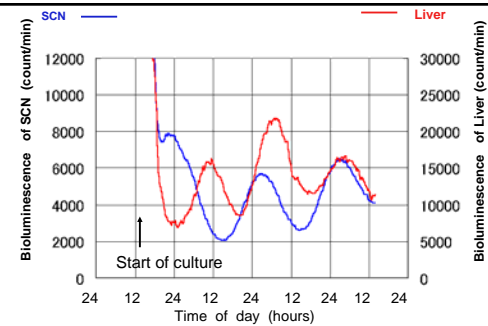
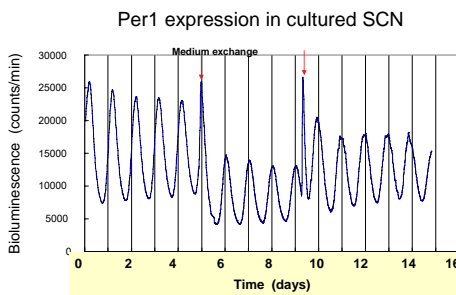
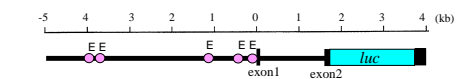
### Rhythmic *Bmal1* transcription

Positive elements: *ROR*, *Per2*

Negative elements: *RebErb a* binding to *RevErb/ROR* response element



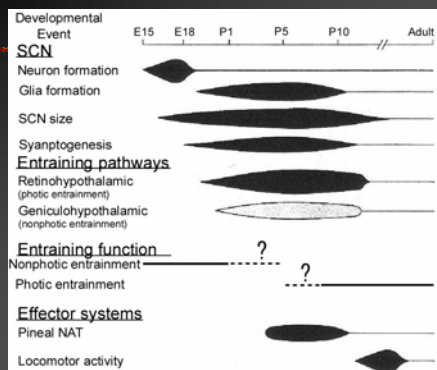
### Real-time monitoring of clock gene expression by luciferase reporter



Peak <i>Bmal1</i> activity rhythm (day2)	Circadian period
SCN $1.7 \pm 1.5$ h	$23.4 \pm 1.5$ hours
Liver $5.5 \pm 1.6$ h	$20.5 \pm 2.4$ hours

Mean  $\pm$ SD (n=11)

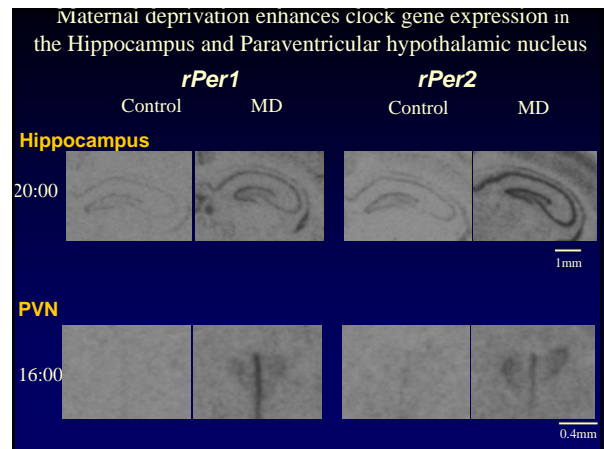
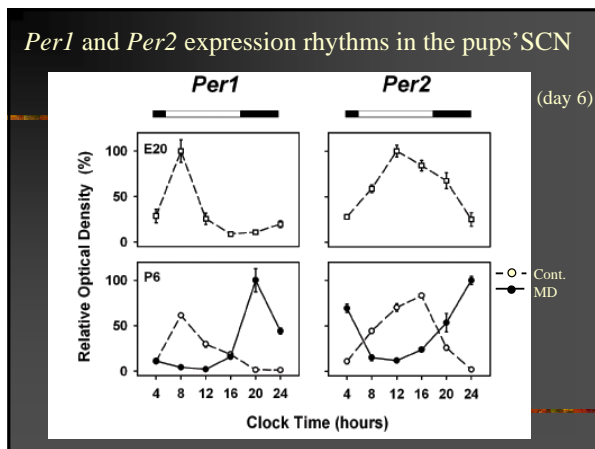
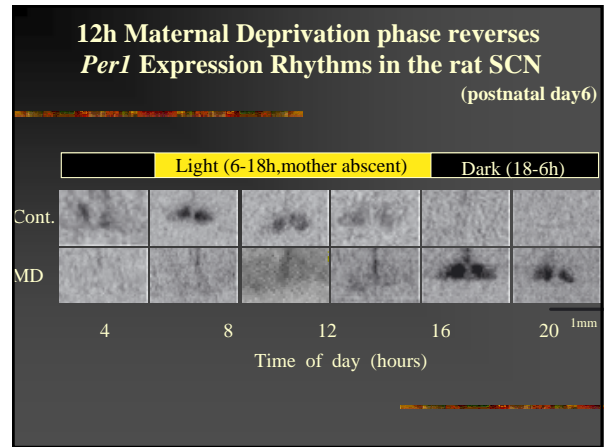
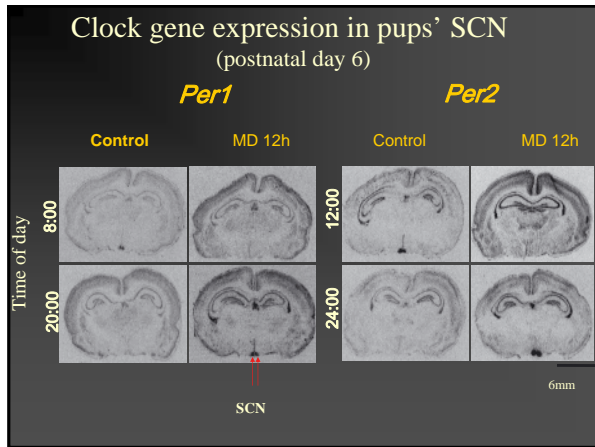
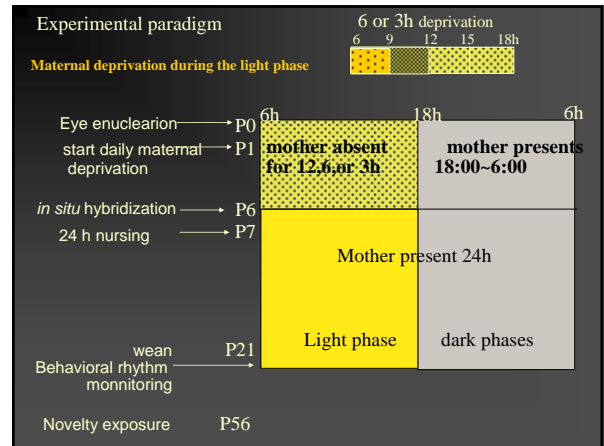
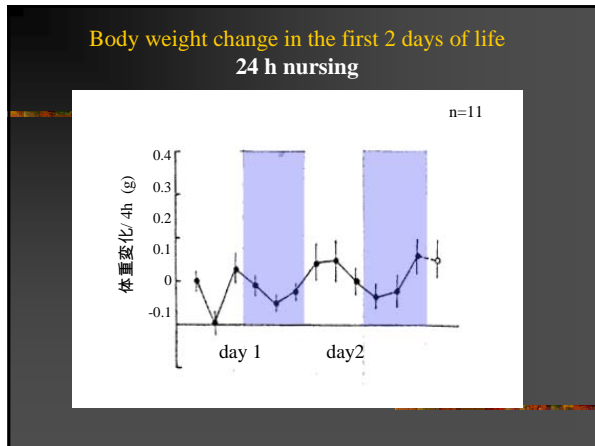
## 3. Ontogeny of rat circadian system

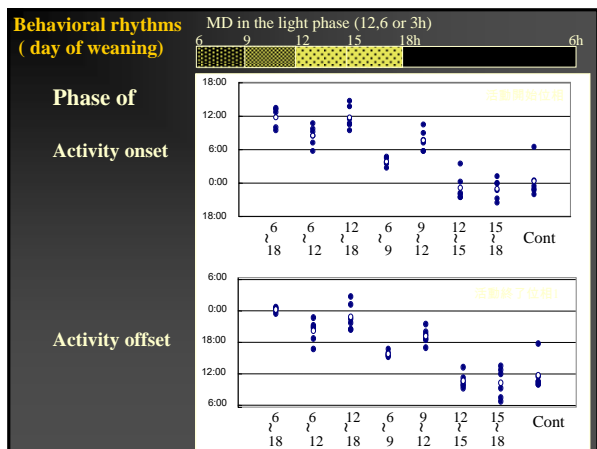
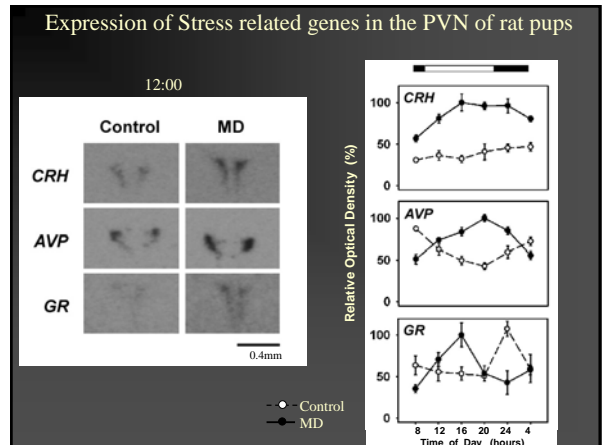
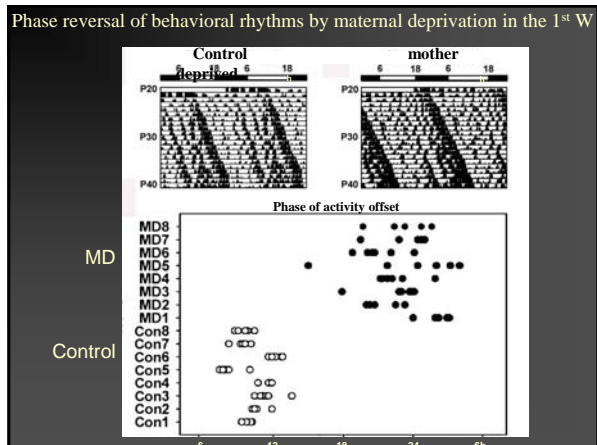
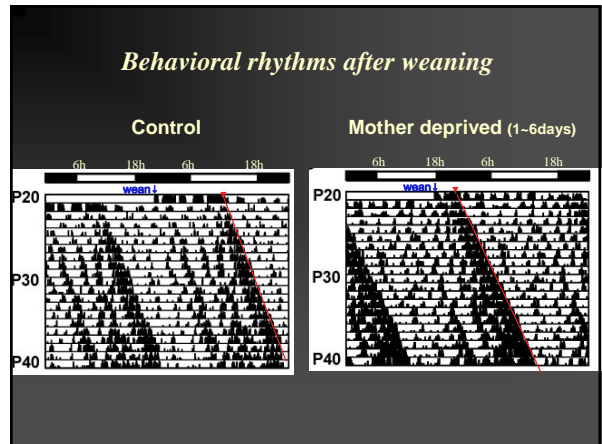
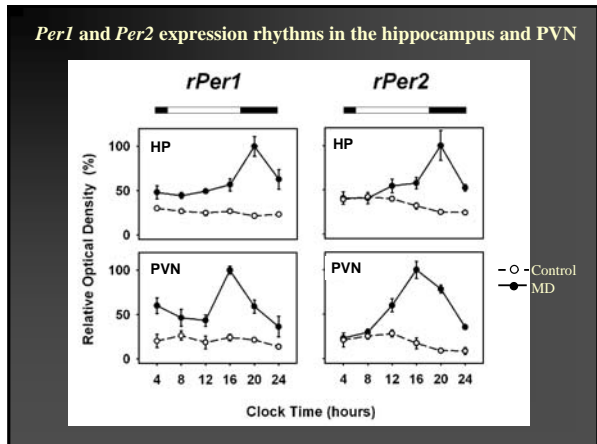


## Mother-Pup Interaction

Maternal cares are believed to have long-term effects on pups physiology and behavior

Growth  
 HPA Axis  
 Biological Clock





- Results**
- 12 h Maternal deprivation in the light phase from Postnatal day1 to day6
  1. phase reversed the circadian *Per1*, *Per2* expression rhythms in the SCN
  2. Phase reversed the circadian *AVP* and *GR* expression rhythms in the PVN
  3. Enhanced the rhythmic *CRH* expression in the PVN
  4. Phase reversed the circadian behavioral rhythms after weaning
  5. 24 h maternal nursing in postnatal day did not affect the pups' clock
  6. Even 3 h of maternal deprivation in the early light phase shifted the pups' clock

## Time cues of MD

### Milk/Nutrition

specific substance in the milk  
metabolic state  
hunger (starvation)  
thirst

### Coldness

Maternal care (grooming)

Physical stimulation

Stress / Crisis sensation

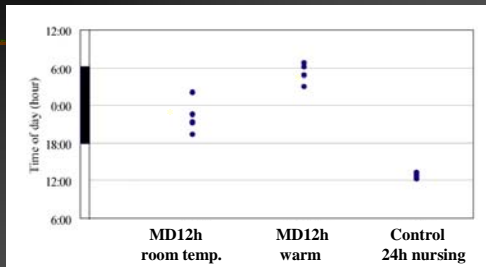
## Body weights of pups subjected to different MD conditions

MD conditions	Body weight (g) (mean±SE)		
	P7	P21	10W
MD12	10.63±0.33**	40.76±1.23**	419.82±14.45*
MD12 (Warm)	12.34±0.50**##	48.03±1.18**##	436.82±14.33
MD3 (9-12h)	16.91±0.51**	52.99±1.09	451.39±13.75
MD3 (9-12hWarm)	17.26±0.69*	51.35±1.36	457.78± 9.29
MD3 (15-18h)	18.67±0.51	57.39±2.09	476.15±21.25
Control	19.10±0.48	54.42±1.55	461.24±12.99

\*, p<0.05 \*\*\*, p<0.01 as compared with the control

##, p<0.01 as compared with the same MD length but with a different temperature.

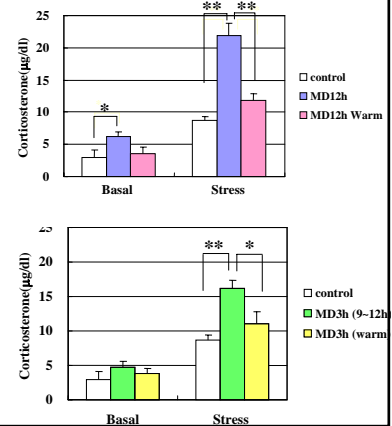
## Circadian phases of the activity end in spontaneous locomotor rhythm (MD in warm and humid condition)



.vs control \* p<0.01

Warming of pups during MD almost restored pups growth, but effects on clock was not cancelled

## Effects of Warming During MD on Stress Sensitivity

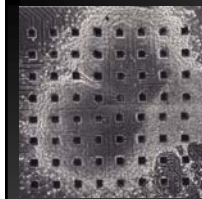


\*\*, \*\* P<0.05, 0.01

MD increased the basal plasma corticosterone level and stress reaction (mild novelty exposure).

### Warming of pups during MD

- cancelled the stress response by MD
- restored pups' growth slightly at weaning and completely at 10 W
- did not cancelled the effects on the circadian clock



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