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Chronobiology of micturition: putative role of the circadian clock

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Running head: Chronobiology and micturition rhythm

Key words: bladder, micturition, rhythm, diurnal, circadian

Abstract

Purpose: Mammals urinate less frequently during sleep period than during awake period, which is modulated by triad factors; decreased arousal level in the brain, decreased urine production rate from the kidneys, and increased functional bladder capacity during sleep. The circadian clock ('the clock') is genetic transcription-translation feedback machinery. The clock exists in most organs and cells, termed 'peripheral clock', which is orchestrated by the central clock in the suprachiasmatic nucleus of the brain. In this review we discuss the linkage between the day-and-night change in micturition frequency and the genetic rhythm maintained by the clock system, focusing on brain, kidney and bladder.

Material and Methods: We performed inclusive review of the literature on diurnal change in micturition frequency, urine volume, functional bladder capacity and urodynamics in humans and rodents, and related it with recent basic biological findings about the circadian clock.

Results: In humans, various behavioral studies demonstrated diurnal functional change in kidney and bladder, and conversely, patients with nocturnal enuresis and nocturia show impairment of these triad factors. Rats and mice, which are

nocturnal animals, also show rhythm in micturition frequency, decreased during daytime, which is sleep phase for them. Mice having genetically defective circadian clock system show impaired physiological rhythms in the triad factors. Existence of the circadian clock has been proven in brain, kidney and also in the bladder, in which exist thousands of circadian oscillating genes. In the kidney, they include genes involved in regulation of water and major electrolytes and in the bladder, a gene associated with regulation of bladder capacity, connexin 43.

Conclusion: Recent progress in molecular biology about the circadian clock provides an opportunity for investigating genetic basis of micturition rhythm, or impairment of the rhythm in nocturnal enuresis and nocturia. If this approach is to be translated clinically, one strategy is to analyze and treat the triad of micturition factors as separate parts of one problem. The other way could be, if possible, to cope with these triad problems simultaneously by treating the circadian physiological rhythm itself. Discoveries reviewed here point toward further investigation of micturition rhythm by basic and translational chronobiology.

Introduction

The day-night change in micturition frequency is essential for having a sound sleep for healthy humans. Studies on normal and abnormal micturition suggest that nocturnal micturition is prevented not only by sleep itself, but also by a decrease in urine production rate from the kidneys, and an increase in storage capacity of the urinary bladder (Figure 1).[1-3] Disturbance of such coordination typically occurs in nocturnal enuresis in children or nocturia in elderly people.[3] Nocturnal enuresis is seen in approximately 10% of 7-year-old children with a spontaneous cure rate of 15% a year, and has a significant effect on patients' self-esteem.[3,4] Nocturia is present in 60-90% of elderly people older than 60 years old, and significantly deteriorates their quality of life.[5] However, the treatment of these patients in clinics is often limited to palliation because the precise mechanism underlying enuresis and nocturia is unclear.

Chronobiology is an emerging new approach for investigating disorders related to biological rhythm. The discovery of the circadian clock, which is genetic machinery generating a circadian rhythm in systemic organs, was a revolutionary finding that enabled researchers to analyze circadian biological phenomena from the standpoint of genetics. There is increasing evidence that behavior, physiology and metabolism in mammals are under control of the circadian clock.[6-8] However, molecular

chronobiological analysis of micturition has not been reported until recently.[9,10]

This Review article describes how the notion of the circadian clock and chronobiology sheds new light on day-night changes in micturition frequency in mammals, interpreted as the circadian biological rhythm. This is a novel paradigm for investigating the pathophysiology of nocturnal enuresis as immaturity in development of the rhythm, and nocturia as loss of the rhythm.

Diurnal micturition rhythm

Humans

Urination in neonates involves reflex voiding, which gradually becomes regulated by upper central neurons with postnatal development, accompanied by enlargement of bladder capacity. Control of day and nighttime micturition is established by school age, but at least 10% of school children have nocturnal enuresis.[3] Studies have also shown that established diurnal micturition is gradually disturbed in many elderly people, which is known as nocturia.[1,2] Although the pathogeneses of these two conditions have been separately discussed, enuresis and nocturia share a similar triad of features: an impaired day-night rhythm of arousal level, urine production, and bladder storage.

Impaired arousal level during sleep is observed in enuresis and nocturia.

Studies with polysomnography have demonstrated that enuretic children are deep

sleepers just at the time of urine loss, but are light sleepers during the rest of the sleep

period.[11,12] Impaired sleep has also been documented in elderly people with nocturia.[5]

Nocturnal polyuria is another common feature of enuresis and nocturia.

Day-night variation in urine production is not simply caused by a change in oral intake

of food and liquid, but is maintained in subjects under a constant routine, when food

and drink are taken equally during 24 hours in constant dim light.[13] However, kidneys

of many enuretic children produce more urine when asleep than those of healthy

children, resulting in use of anti-diuretic hormone as standard treatment for such types

of cases.[3] Abnormal diurnal rhythms of plasma vasopressin have also been reported in

patients with enuresis.[14] Similarly, elderly people with refractory nocturia often show

excessive urine production and natriuresis during sleep.[15]

The same type of observation as impaired arousal level and urine production

rate during sleep in enuresis and nocturia is documented for day-night change in

functional bladder capacity. Normal healthy adults have a greater volume voided per

micturition during midnight to morning (Figure 2, left),[1,16,17] in parallel with a decrease

in maximal flow rate in uroflowmetry. In contrast, less voided volume and a higher

flow rate, representing greater detrusor tonus, are observed during afternoon to

evening.[16] These day-night changes in functional bladder capacity and maximal flow rate are interpreted as a "shift" of urinary bladder function between storage and elimination of urine within a day. Enuretic and healthy children have similar daytime holding-exercise volumes, but early-morning voiding volume in enuretic children is smaller than that in healthy children.[18] In only 28% of enuretic children, early-morning voided volume reaches maximal volume voided per micturition in a day, as opposed to 72% of healthy children. Such reduction in nocturnal functional bladder capacity is an important feature of refractory nocturnal enuresis.[3] This fact indicates that pathogenesis of enuresis may not be related to the structural bladder size itself, but to the regulatory mechanism of diurnal change in functional bladder capacity instead. In parallel with this suggestion, elderly people have a significantly decreased capacity for normal desire to void during night compared with middle-aged men,[17] and such a decrease in nighttime functional bladder capacity is also a hallmark of nocturia.

Rodents as models

Rodents are nocturnal animals, and therefore, the sleep-awake cycle is opposite from humans in the light-dark cycles. Early studies in rodents on the micturition cycle were performed using rats, mainly for technical reasons compared with mice. Studies showed

that the bladder capacity of rats is increased in the sleep phase and decreased in the active phase, as demonstrated by an electric balance system under free-moving conditions,[10,19] or by a cystometrogram without being affected by the urine production rate (Figure 2, middle).[20]

For studying genetic mechanisms of micturition, genetically-modified mice are a useful tool, but their bladder capacity is so minute that researchers employed a urine stain on filter paper as a surrogate of voided volume.[21,22] This principle was further developed for enabling diachronic measurement and was named automated voided stain on paper (aVSOP) method.[10,23] Micturition rhythm emerges with a urine production rhythm appearing at 3 to 4 weeks old, followed by maturation of a diurnal change in bladder capacity occurring around 5 weeks old.[23] This micturition rhythm, observed as that of humans and mice, is maintained in a constant dark condition (Figure 2, right), which indicates that mice have an internal control mechanism of micturition. Thus mice, young to adult, have become a model animal for studying micturition cycle.

The circadian clock system

The central master clock

Circadian rhythms of systemic activity are sustained even in the absence of

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environmental cues, and are often associated with an internal biological clock, i.e., the

circadian clock. The master circadian clock is located in the suprachiasmatic nucleus

(SCN) of the hypothalamus, and generates central circadian rhythm of the body. This

region has a self-sustained circadian expression of clock genes, and also synchronizes

the master clock to the environment, by receiving a light signal cycle from the retina.[6,8]

Transcriptional circuits

The molecular mechanism of the circadian clock in mammals was revealed with the

discovery of the mouse *Clock* in 1994 and the human and mouse *Period* in 1997. At the

molecular level, circadian clock oscillations are driven by transcription-translation

feedback loops consisting of PER and CRY as negative components, and CLOCK and

BMAL1 as positive components (Figure 3A). Rhythmic oscillations of these core loops

are followed by the clock-associated oscillations of *Dbp* and *Rev-erbα*, whose products

tune the core loops and also control oscillations of many genes through D-box and

RORE sites, respectively (Figure 3A). [6-8]

Peripheral clocks

Notably, this molecular clock system is present not only in the SCN, but also in most

peripheral tissues and organs, such as the brain, lungs, heart, liver, pancreas, gastrointestinal tract, adrenal glands, skeletal muscles, kidneys, and others.[24] Though the detailed interplay between SCN and peripheral clocks is not fully understood, peripheral clocks are tuned by signals from the SCN by three ways: 1) as neural signals via sympathetic/parasympathetic nerves; 2) as hormonal signals via the pineal body and adrenal glands; and 3) as indirect behavioral controls via feeding and sleep-awake cycles (Figure 3B).[8,24]

The clock and diseases

Emerging evidence indicates that disturbance of the circadian rhythm is linked to various pathological conditions in clinical and basic studies. For example, on the clinical side, polymorphisms of clock genes are associated with early or late chronotype, metabolic syndrome and cancer morbidity.[25,26] Epidemiological studies suggest that shift workers have a higher incidence of diabetes, obesity, cardiovascular diseases, psychological disorders, gastrointestinal dysfunction and cancer.[26,27] Basic studies have shown that dysfunction of the circadian clock is involved in salt-sensitive hypertension by dysregulated adrenal Hsd3b6,[8] and in diabetes mellitus by impaired insulin secretion from β-cells.[7]

The clock and micturition

As noted above, the frequency of micturition is deeply associated with three factors: arousal level in the brain, urine production rate in the kidneys, and functional capacity in the bladder (Figure 1). A relation between the circadian clock with two of the three factors (arousal level and urine production rate) has been reported relatively earlier.

With regard to arousal level of brain during sleep, clock gene mutant mice have several sleep abnormalities.[25] *Clock* mutant mice have reduced non-rapid eye movement (NREM) sleep and reduced total sleep time. *Bmal1* knockout mice have increased sleep fragmentation, but they have longer REM and NREM periods, while *Per1/Per2* double mutant mice show decreased REM and NREM sleep periods.

With regard to urine production in the kidneys, circadian excretion and reabsorption of water and major electrolytes in urine have been shown physiologically,[28] while rise in plasma vasopressin at late sleep phase is modulated by the central circadian clock[14] and circadian oscillation in transcription of the key molecules for these steps in the kidneys has also been shown genetically.[29,30] The examples of such genes are, Na^+/H^+ exchanger, aquaporin-2, 3 and 4, and type 2 vasopressin receptor that regulate water reabsorption, and many genes regulating

electrolyte movement, such as epithelial sodium channel (ENaC)-mediated sodium transport, chloride movement across the epithelia, and potassium excretion. *Clock* knockout mice have a significant reduction in renal and urinary content of 20-hydroxyeicosatetraenoic acid, a powerful endogenous regulator of renal sodium reabsorption and potassium secretion, and they have a reduction in renal vascular tone.[31] *Per1* regulates sodium transport genes, such as *αENaC* and *endothelin-1*,[32] and *Per1* and *Per2* double knockout mice lose the diurnal rhythm of urine volume.[9]

Circadian rhythm in the bladder

Discovery of the clock in the bladder

The circadian clock regulation for the third component of the triad, the functional capacity in the bladder, has not been investigated until recently.[10] The existence of a functional peripheral clock in the bladder was proven by three methods, as performed for other organs. The first method involved analyzing circadian expression of clock genes in the bladder *in vivo*, with and without modifications of clock genes. The urinary bladder has a strong oscillation rhythm in core clock genes, *Per2*, *Bmal1*, *Cry1/2* and *Clock*, and also in regulators, such as *Rev-erbα/β*, *Rorc*, *Dbp*, *Tef*, *Hlf*, *E4bp4* and *Dec1*. The second method is the *ex vivo* culture system using *Per2^{luciferase}* knock-in mice,

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carrying a PER2::LUC fusion protein, which was engineered to produce

bioluminescence in the presence of luciferin when the clock gene *Per2* is activated.

This system provides strong evidence that the peripheral clock in the bladder functions

without systemic cues.[10,33,34] Notably, the luminescence of extracted bladder can be

modulated by mechanical and/or chemical stimuli.[33] The period of the circadian rhythm

is different between organs as assessed by $Per2^{luciferase}$ mice as follows: in SCN it is

23.5 h, in pancreas islets 23.6 h, in the cornea 22.2 h, in the kidney 24.8 h, and in the

urinary bladder it is 24.9 h. In particular, this monitoring system has recently been

applied for animals *in vivo*, in a noninvasive and diachronic manner.[35] Use of this

system is expected to reveal the detailed relation between the central/peripheral clock

and the micturition rhythm, cross-linked to other genetic modified mice if possible. The

third method is the serum-shock method for synchronizing the circadian rhythm of

cultured cells *in vitro*. Primary cultured bladder smooth muscle cells show *in vitro*

genetic oscillation for *Per2*, *Bmal1*, *Rev-erbα*, and others.

Oscillating genes in the bladder

Genes having circadian expression vary between tissues and organs. For example,

expression levels of 8-10% of genes oscillate in a circadian manner in the heart and

liver, but only 0.3% of genes commonly oscillate in both organs.[36] Oscillatory genes are frequently associated with a crucial function in organs In the liver, oscillating genes encode key steps of metabolism as sterol regulatory element–binding protein (*SREBPs*), involved in the master pathway of hepatic lipid metabolism and *Nocturnin*, involved in lipogenesis and energy homeostasis.[7,37] In the urinary bladder also, thousands of genes oscillate.[10] When oscillatory genes in the urinary bladder are classified by the biological process in the third level of the Gene Ontology hierarchy,[38] most oscillatory genes are involved in "circadian rhythm", "regulation of biological process", "cellular and nitrogen compound metabolic process" and "response to stimulus". The bladder functions in a dynamic circadian manner with these biological processes. *Connexin 43*, a gap-junction protein in the urinary bladder and associated with sensitivity of bladder muscle,[39] is in both "regulation of biological process" and "response to stimulus" may have important role in circadian change in bladder function as reported.[10]

Clinical translation

The question can be asked: "Is the circadian clock system related to micturition disorder?" This should be the case, because *Cry*-null mice and *Per1*/*Per2* double knockout mice, which have a dysfunctional circadian clock, completely lose diurnal

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rhythm of micturition, urine production and functional bladder capacity.[10,34,39] These

findings correspond to dysfunction in the diurnal micturition rhythm observed in

patients with nocturnal enuresis and nocturia. Interestingly, a previous study reported a

correlation between enuresis in children and nocturia in their mothers.[40] A recent study

also showed that nocturnal enuresis is carried over as adult LUTS.[41] Studies from

Denmark suggest a strong genetic linkage of enuresis with identification of

chromosomal loci for responsible genes.[4] Taken together, these findings indicate that

disorders in the micturition cycle could be genetic events that encompass the whole life

of an individual, which may be "masked" during early adulthood after adolescence.

Such clinical findings suggest that applying a novel paradigm of chronobiology and the

notion of the circadian clock system could be a promising approach to elucidate the

genetic etiology of these diseases.

There are two strategies for treatment of enuresis and nocturia if the

chronobiological approach is to be applied for these micturition rhythm disorders. One

strategy is to analyze and treat each factor of this triad (the brain, kidney and bladder)

as separate parts of one problem. For nocturic elderly people with waking early in the

night and taking a time to return to sleep, using a rapid-acting hypnotic is a choice of

treatment. For altering the urine production rhythm in the kidneys, desmopressin is

available in market for enuresis and nocturia. Recipients of a denervated kidney in renal transplantation lose diurnal changes in urine production, which can be treated with daytime diuretics.[42] One could aim for inventing novel drugs to regain/suppress daytime/nighttime urine production based on circadian function of the kidney. For the bladder, one may investigate to develop a bladder-specific gap-junction inhibitor for treating patients with enuresis and nocturia. In addition, microarray data[10] also present a list of oscillating bladder genes that could be candidate targets for inventing drugs aimed at nighttime bladder problems. Dealing with the triad separately or by a combination of multiple drugs may be a natural extension of the studies done thus far.

The other strategy for treatment of micturition rhythm disorders could be to cope with these triad problems simultaneously by treating the circadian rhythm itself if the circadian clock system governs the triad. Indeed, the triad is intricately intertwined with each other.[5,43] If the major cause of enuresis and nocturia is dysfunction of the clock, targeting the clock itself could be a universal measure to treat these problems. If this is the case, it is important to identify a methodology or biomarker for measuring biological rhythm in each individual,[44] corresponding to the micturition rhythm to evaluate whether dysfunction of the clock is the etiology of enuresis and nocturia. Development process of such micturition rhythm in normal human infant is another

topic to be elucidated for further progress in this field, and we are currently working to devise a novel system for automatically recording infant micturition before toilet-training. It has been reported that nocturia is a significant risk factor for mortality,[5] indicating that disturbance of the micturition rhythm may represent a disturbance of systemic homeostasis itself. Disruption of circadian rhythms seriously affects life-span, as shown in mice with mutant clock genes.[45] Systemic diseases, such as diabetes, depression and hypertension, in which a link to the circadian clock has been documented, are often accompanied by each other and also with nocturia.[5] Aging, the most definite risk factor of nocturia, is also strongly associated with the weakness of circadian clock function in the SCN and peripheral organs.[45] Higher amplitude rhythms were restored and the life-span was extended when the fetal SCN was implanted in aged animals.[45] Weakness of the circadian amplitude in behavior was observed in mice lacking the large conductance Ca^{2+}-activated K^+ channel (BK),[46] whose expression was significantly decreased in smooth muscle during aging.[47] BK channel-null mice also showed overactive bladder and incontinence.[21] In this scenario, appropriate control of the circadian rhythm may restore general health, including bladder function. Melatonin and ramelteon, its agonist, not only facilitate sleep but also entrain the circadian system, increasing bladder capacity and reducing bother of nocturia.[48] An improvement in

life-style significantly affects the symptoms of nocturia.[49] Therefore, appropriate

entrainments by bright light, feeding, exercise, melatonin agonists and upcoming novel

medication acting on the products of clock-controlled genes or clock gene itself, could

be new candidates for treatment and prevention of enuresis and nocturia.

In summary, studying micturition as a biological rhythm may not only improve

the quality of life in children and elderly people, but may also uncover an unknown

regulatory mechanism of the human body by the clock, which affects daily life.

Currently, our research group is participating in a comprehensive and prospective

population-based cohort study aimed at systemic health status,[50] which includes a

genetic and behavioral survey of LUTS. Such an approach may determine the

implication of biological rhythm on LUTS and life in general.

Conclusion

The findings discussed in this Review article highlight a novel chronobiological

approach to micturition rhythm. Continued basic and clinical researches are required to

advance chronobiology of micturition, and this approach warrants further investigation

for disorders characterized as disorders of micturition rhythm: nocturnal enuresis and

nocturia.

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Author contributions

H. Negoro researched the data for the article and wrote the manuscript. A. Kanematsu planned and supervised the study, and prepared the manuscript. K. Yoshimura and O. Ogawa contributed to the discussions of content. All authors reviewed and edited the manuscript before submission.

Competing financial interests

The authors declare no competing financial interests.

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Legends

Figure 1 Diurnal change in triad of micturition: arousal state in the brain, urine production rate in the kidneys and functional bladder capacity.

Figure 2 Diurnal change in micturition in humans, rats and mice. Humans from Nakamura S *et al* (ref 1) modified. N, number of patients. NS, not significant. *P <0.05, **P <0.01, ***P <0.005 and ****P <0.001. Mean ± SD. Statistical significance between the 2 age groups was calculated with Student's *t*-test, and that between periods was calculated by paired *t*-test. Rats from Herrera GM *et al* (ref 20) modified. P <0.05 by 2-tailed, unpaired *t*-test. Mice from Negoro H *et al* (ref 10) modified. WT mice (n = 5), for 8 days under LD conditions and 5 days under DD conditions. Mean ± SEM.

Figure 3 The circadian clock system. (A) Transcription-translation feedback mechanism in the core loop (upper row) and other loops of the circadian clock (lower row). Clock-controlled elements on the promoter are shown as the E/E' box, D box and RORE, and positive transcription factors (green ovals) and negative transcription factors (magenta ovals) are indicated. Some of clock genes have more than one clock controlled elements. Clock genes also regulate clock-controlled genes (CCGs). (B) The

SCN tunes peripheral clocks via the hormonal system, autonomic nervous system and

behavioral controls as feeding and sleep-awake cycles. SCN, suprachiasmatic nucleus.
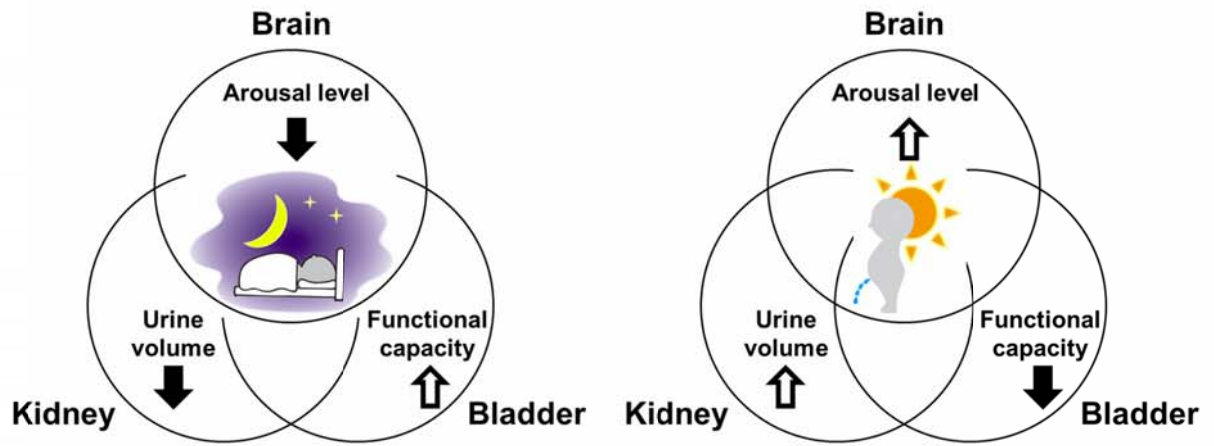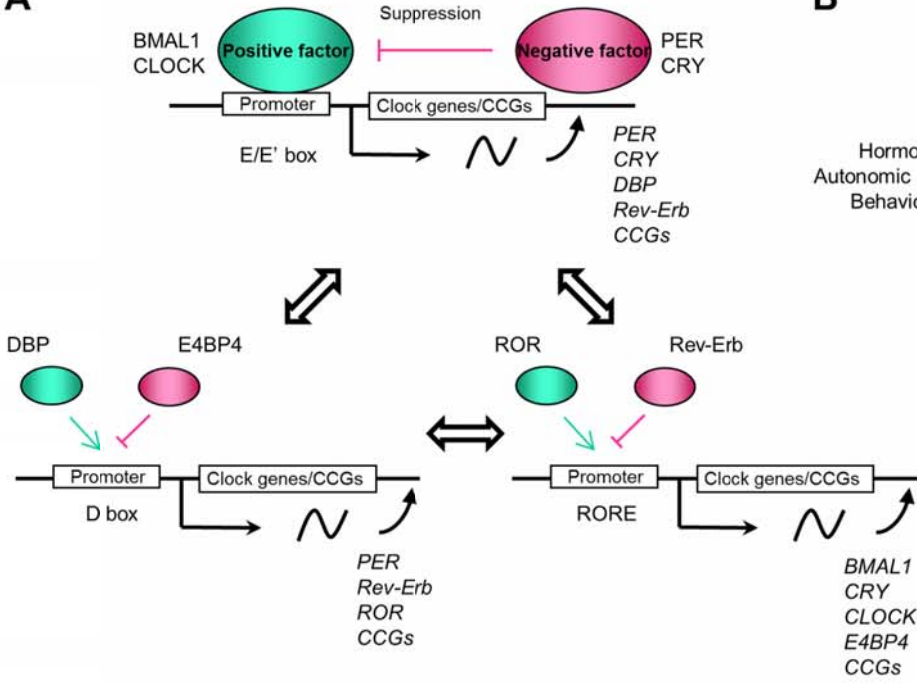
Figure 1 O.Ogawa *et al*

Figure 2 O.Ogawa *et al*

Humans

Rats

Mice

Figure 3 O.Ogawa *et al*