

## PINEAL STRUCTURES AND FUNCTIONS IN MAMMALIAN BODY MECHANISMS COPING WITH EXOGENOUS AND ENDOGENOUS CHANGES

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**Abstract** Various aspects of pineal structures and functions have been reviewed, mainly relating to our own observations and experiments. The pineal gland shows high amplitude circadian rhythms in cellular and metabolic activities, which are changeable under various circumstances. The pineal hormone appears to participate in the body's adaptive regulatory system mostly by cooperative and modulatory mechanisms, particularly in relation to environmental changes including stress/invasion, timing of physiological processes including reproductive activities, and possibly exogenous and endogenous pathological changes such as inflammatory disease and tumor. Pineal effects are variable due to the sensitivity/state of target mechanisms. For example, the pinealectomy effects on adreno-medullary adrenaline cells were more evident in comparison with the 'sham-pinealectomy' group than the normal group, and the pinealectomy effects on female reproductive activities were age-dependent. In any case, the pineal hormone retains physiological functions at least till middle age. Pineal actions are mainly inhibitory, but can be also stimulatory as shown in immune regulatory mechanisms. It has long been known that big differences in pineal structures and functions exist between mammals and submammals and that mammals show characteristic development of the brain, autonomic nervous system and unique style of reproduction including pregnancy and suckling. These and other related results seem to support a hypothetical view that the pineal hormone was involved in drastic reorganization of the regulatory system occurred in the evolutionary process from submammals to mammals and became participated in the system which regulates complex body mechanisms in mammals.

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**Key words:** chronobiology; stress; female reproductive activity; immune mechanism; pathology

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### Structural and functional bases of the pineal organ: evolutionary change

The pineal organ is a single, mid-line structure between the habenular and posterior commissures which composes the roof of third ventricle in the diencephalon<sup>1,2)</sup>. In most submammalian vertebrates, the pineal retains its contiguity with the brain and sends nerve tracts to other brain centers, principally in the epithalamus. However, with evolution, the centripetal neural link to the brain greatly diminishes, and the mammalian pineal newly

receives major innervation by postganglionic sympathetic fibers from the superior cervical ganglia (SCG)<sup>3-5)</sup>. Minor innervation by the trigeminal nerve and several centrifugal nerve fibers has also been reported<sup>6-8)</sup>.

Most of the pineal glands in vertebrates can synthesize melatonin (N-acetyl-5-methoxytryptamine), which is synthesized and secreted cyclically<sup>1,9,10)</sup>. Such cyclical circadian secretion is regulated by internal oscillator and photoreceptor cells, which exist in the pineal organ in lower vertebrates. In mammals, however, the circadian oscillator exists in the suprachiasmatic nucleus (SCN) of hypothalamus<sup>10-12)</sup>, which receives neural signals on environmental light from the retinal

photoreceptor<sup>13)</sup>. SCN is also important in the regulation of estrous cycle<sup>14)</sup>. Cyclic neural signals are transmitted from SCN to the pineal gland via the multisynaptic pathway including the paraventricular nucleus of hypothalamus (PVH), finally mainly by sympathetic nerve endings from SCG<sup>10,11)</sup>. Therefore, the pineal organ is considered to be sensory, or recepto-secretory, organ in submammalian vertebrates<sup>15)</sup> and neuro-endocrine transducer in mammals<sup>1)</sup>.

In addition to PVH, efferent fibers from SCN project to the neuroendocrine preoptic area, paraventricular thalamic nucleus (PVT), dorsomedial hypothalamic nucleus and midbrain periaqueductal gray region (PAG)<sup>16)</sup>. The complex central autonomic network is capable of regulating both autonomic and neuroendocrine functions and also provides connections to limbic and neocortical areas<sup>17,18)</sup>. It has been reported that melatonin exerts actions on, and melatonin receptors<sup>19)</sup> exist in, the nuclei including SCN and PVT in the network<sup>20-22)</sup>. Thus, big evolutionary changes occur in mammalian pineal structures and functions<sup>1,3,12,23)</sup>, and the mammalian pineal appears to be involved in complex information processing mechanisms. What unique roles does the pineal hormone play in mammalian body mechanisms and how?

### **Melatonin and functional morphology of the pineal gland**

The synthesis/secretion of melatonin increases in the daily dark phase and decreases during the light phase<sup>9,10,24)</sup>, and the former is suppressed by light, ganglionectomy or decentralization of SCG<sup>1,11)</sup>. The nocturnal increase in blood melatonin level mostly depends upon the pineal gland in humans and laboratory mammals<sup>25)</sup>. Melatonin, a lipophilic hormone, can be transferred from mother to embryos/fetuses through the placenta<sup>26)</sup>.

The pineal gland contains two types of parenchymal cells, pinealocytes and glial cells<sup>2,27)</sup>.

Pinealocytes contain both glycogen and lipid droplets in mice<sup>28,29,30)</sup> and only lipid droplets in rats<sup>9)</sup>, probably as the energy source. We reported that the glycogen level in mouse pinealocytes shows changes well-correlated with those of melatonin (Table 1).

High amplitude circadian rhythms in cellular and metabolic activities of the pineal gland have been established<sup>9,10)</sup>. Levels of melatonin, lipid and glycogen are also modified by the estrous cycle<sup>1,9,37)</sup>. In seasonal breeders, physiological effects of pineal hormone on seasonal behavioral changes have clearly been demonstrated in relation to the day-length changes<sup>49-52)</sup>. Melatonin serves as a signal to adjust the timing of reproductive and other functions to the external environment, playing an important role in synchronizing birth in spring and survival of pups and animals themselves. However, the whole picture of pineal functional significance is still enigmatic, particularly in non-seasonal breeders under constant environmental conditions.

### **Pineal effects on circadian rhythms**

We found in rats and golden hamsters that 24 h changes in many structural components of the adrenal medulla are generally maintained after pinealectomy (PX) with higher amplitudes in some components, although the patterns are slightly modified, and with suppressed changes in a few other components<sup>53-64)</sup>. Pineal effects on body's clock mechanisms and/or multioscillatory mechanisms have been investigated<sup>65-73)</sup>.

Many reports concerning the relationship between melatonin and sleep or jet lag have been published<sup>67,74,75)</sup>. However, recent works could not find evidence for the two concepts<sup>76-78)</sup>, i.e. melatonin is effective in treating secondary sleep disorders or those accompanying sleep restriction, such as jet lag and shiftwork disorder<sup>74)</sup>, and low melatonin production is an important factor in insomnia among the elderly<sup>79,80)</sup>.

**Table 1.** Results of our observation on pineal morphological changes under various conditions.

	Glycogen level	Pineal cell or organ size	Granular vesicle number	References
<Mouse>				
24 h rhythm	+	+	+	2,24,29,30
	(↑ Day; ↓ Night)	(↑ Early light phase; ↓ Early dark phase)	(↑ Mid-late light phase; ↓ Dark phase)	
Constant light (CL)*	↑↑ (for several days then decrease)	↓↓	(CL-1day: not decrease)	28 31,32
SCGX*, DC*	↑↑	↓↓		
Reserpine*	↑↑	↓↓		
	(* Rhythm: not seen)	(* Rhythm: not seen)		
Constant dark (CD)	(Rhythm: persist)	(Rhythm: not apparent)		33
Reversed LD cycle	(Rhythm: reversed within 7 d, and persists in CD)			
RWI stress	↑↑	↓↓		34,35
Winter (Severe, cold)	↑↑	↓↓		36
Estrous cycle	+			37,38
-related change				
Age-related change	+ (Marked)			39,40
~15 d	(Rhythm, CL-1day effect . Level, 5d: high; 15 d: ↓↓)			2,26,41,42,
21 d	(Rhythm, CL-1day effect +, then basically persisted)			43,44,45,
2~5 months	(Most prominent response)			46
1 year~	(Rhythm: persist till 1.5~2 years of age; Response: decrease in distal and mid portions where small cavities exist in part of animals.)			47
<Human>				
Tumor, Neurodegenerative disease (ALS, SCD)		↑↑, ↑~→		48,167
Diabetes mellitus, Hypotension		↑~→		61
Medico-legal Autopsy Cases†: († Aging-related changes were not seen in part of aged cases.)				
Seasonal change		+ (↓ Winter)		84,85,86
Death from cold		↓↓		

SCGX: superior cervical ganglionectomy; DC: decentralization of the ganglia; RWI: restraint, water-immersion

ALS: amyotrophic lateral sclerosis; SCD: spino-cerebellar degeneration

↑↑: very increased; ↑: increased; →: similar; ↓: decreased; ↓↓: very decreased, compared with normal size.

## Pineal roles in body mechanisms coping with exogenous stimuli

### 1. Different types of pineal stress responsiveness

The pineal activity has generally been considered to increase during winter<sup>25,50-52)</sup> or in response to various kinds of stressors<sup>2,81-83)</sup>, although apparent stress responses can be well induced with pretreatment, such as fasting or denervation<sup>83)</sup>. However, the pineal activity can be decreased also by special kinds of stress such as severe cold (Table 1).

### 2. Effects of sham-pinelectomy (SPX) and PX on the autonomic system, especially on the adrenal gland: pineal functions in the central mechanisms

It has well been known that the activities of adrenal cortex and medulla are increased under stressful situations. Although SPX is a kind of stress, the glucocorticoid secretion was suppressed in SPX animals<sup>87)</sup>, curiously. Effects of SPX were also reported in the milk yield<sup>88)</sup>, prolactin secretion<sup>89)</sup> and plasma insulin level<sup>90)</sup>.

We repeatedly reported unusual responses of the adrenal medulla induced in SPX rats and golden hamsters<sup>53-64,91-97)</sup>, also. Namely, SPX caused not only marked inhibitory effects on various components of adrenaline cells and nerve endings on them and their 24 h changes but also stimulatory effects on the enkephaline synthesis<sup>91,93,94)</sup>, both of which were reversed by PX. PX effects on the adrenal medulla were

more marked in the adrenaline/enkephaline-cell system than in the noradrenaline-cell system and in comparison with 'SPX effects'. Results relating to the inverse relationship between adrenaline and opioids have recently been confirmed<sup>98)</sup>. While the activities of adrenaline-synthesizing enzymes are stimulated by glucocorticoids<sup>99)</sup>, the glucocorticoid secretion appears to be stimulated by adrenaline<sup>100)</sup>. Melatonin has been reported to inhibit glucocorticoid synthesis/secretion directly<sup>101)</sup> and indirectly via the hypothalamo-pituitary-adrenal (HPA) axis<sup>102)</sup>. We also reported inverse effects of SPX and PX on the spinal sympathetic center, brain water content, and blood capillaries and neurons in the area postrema (AP)<sup>63,103,104)</sup>.

It seems to be important to note here that almost normal plasma melatonin rhythm, with larger dispersion of values, was seen in SPX rats, although several components in the pineal<sup>105-108)</sup> were affected by SPX. Therefore, it is likely that activities and circadian rhythms of the pineal and the HPA and sympatho-adrenomedullary systems are differentially regulated and that changes in the sensitivity/state of melatonin targets<sup>109-111)</sup> are crucial in 'SPX effects'. Inhibitory actions of melatonin on PGE<sub>2</sub><sup>61,112,113)</sup>, NO<sup>114-116)</sup>, calmodulin<sup>117,118)</sup> and NF-kappaB<sup>119)</sup> as well as the existence of melatonin receptors in the choroid plexus and brain arteries<sup>109,120,121)</sup> have been reported. These may be involved in the mechanism of pineal-dependent 'SPX effects' on brain defensive and circulatory responses.

According to recent investigations<sup>17,122)</sup>, the nucleus tractus solitarii (NTS) receives a variety of sensory inputs and other inputs from AP, and projects to a number of key nuclei in the lower brain stem that regulate the autonomic preganglionic neurons of the sympathetic and vagal systems as well as projecting to forebrain nuclei in the central autonomic network. The midbrain PAG contains high density of opioid receptors and has not only intimate relationships

to pain and analgesia but also afferent and efferent connections with NTS<sup>123,124)</sup>.

Melatonin receptors have been reported to exist in the spinal nucleus of trigeminal nerve and the parabrachial nucleus in addition to well-known regions such as SCN, PVT and AP<sup>20,21, 63,96,109,120,121)</sup>, and NTS can be influenced by the pineal hormone<sup>125)</sup>. Melatonin has also been shown to have stimulatory effects on GABAergic and serotonergic<sup>61)</sup> actions in the brain. Therefore, SPX quite probably influences the activity of trigeminal nerve system which conveys various information about the dura mater including intracranial pressure and elicits complex responses in the brain. One of such responses could be an inhibitory influence upon the sympathetic center via GABAergic neurons induced by the activation of vagal center<sup>17,122)</sup>. The pineal hormone has been shown to have effects on hypothalamo-pituitary neuroendocrine mechanisms, autonomic central networks, and/or central processing mechanisms of visceral information and relations to emotion<sup>63, 64,96,109,120,121)</sup>. But the exact mechanism of possible pineal-dependent SPX effects is unknown.

According to the Sydney group<sup>124,126-128)</sup>, PAG is an important integrating center for the autonomic and somatic elements of the defense reaction in addition to the hypothalamus. All animals react with distinct emotional coping strategies to different types of stress. Active coping strategies (e.g. confrontation, fight, escape) are evoked if the stressor is controllable or escapable. Passive coping strategies (e.g. quiescence, immobility, decreased responsiveness) are usually elicited if the stressor is inescapable, and help to facilitate recovery and healing.

Thus, the mammalian body seems to have much more complex stress-response mechanisms than ever thought before. As shown in pineal-dependent 'SPX-effects' and various types of stress responses in the pineal, the mammalian pineal hormone probably contributes to such versatile survival strategies, coping with

different stressful situations.

### 3. Pineal, melatonin and immune mechanisms

Accumulation of lymphocytes was found in the chicken pineal gland<sup>129)</sup>. Postnatal observation of lymphocyte accumulation in the mouse pineal region was performed by us<sup>130)</sup>. T lymphocytes<sup>131)</sup> and/or macrophage/microglia cells expressing class II MHC molecules<sup>132-134)</sup> have also been reported in rodent pineals.

The first firm evidence for the stimulatory effects of melatonin on immunity was provided by the studies of Maestroni and co-workers on mice<sup>135,136)</sup>. According to them, melatonin counteracts immuno-suppression and thymus atrophy induced by stress or corticosteroid treatment. Moreover, melatonin protects mice injected with encephalitogenic viruses, synergizes with interleukin-2 in cancer immunotherapy and rescues hematopoiesis from cancer chemotherapy toxicity<sup>137)</sup> (see also Lissoni<sup>138)</sup>). Lymphocytes appear to synthesize/secrete melatonin<sup>139,140)</sup> and have its receptors<sup>141-144)</sup>, and to be dually controlled by melatonin secreted in paracrine manner and hormonally from the pineal<sup>145)</sup>. On the other hand, cytokines such as interferon-gamma and interleukins have been shown to influence pineal indoleamine metabolism<sup>142,146,147)</sup>.

In addition, it has been reported that neonatal PX accelerates the development of autoimmune diabetes mellitus in mice while exogenous melatonin protects the animals<sup>137,148)</sup>. Since the nuclear melatonin receptor represses 5-lipoxygenase which is a key enzyme in the biosynthesis of leukotrienes from arachdonic acid, melatonin seems to be important in the regulation of inflammatory and immune processes<sup>149)</sup>. However, much remains to be done before a complete understanding of the mechanism underlying the immunological and hematopoietic action of melatonin<sup>136)</sup>. Pineal effects on CD4<sup>+</sup> CD25<sup>+</sup> (IL-2 receptor  $\alpha$ -chain-positive) regulatory T lymphocytes seem to be

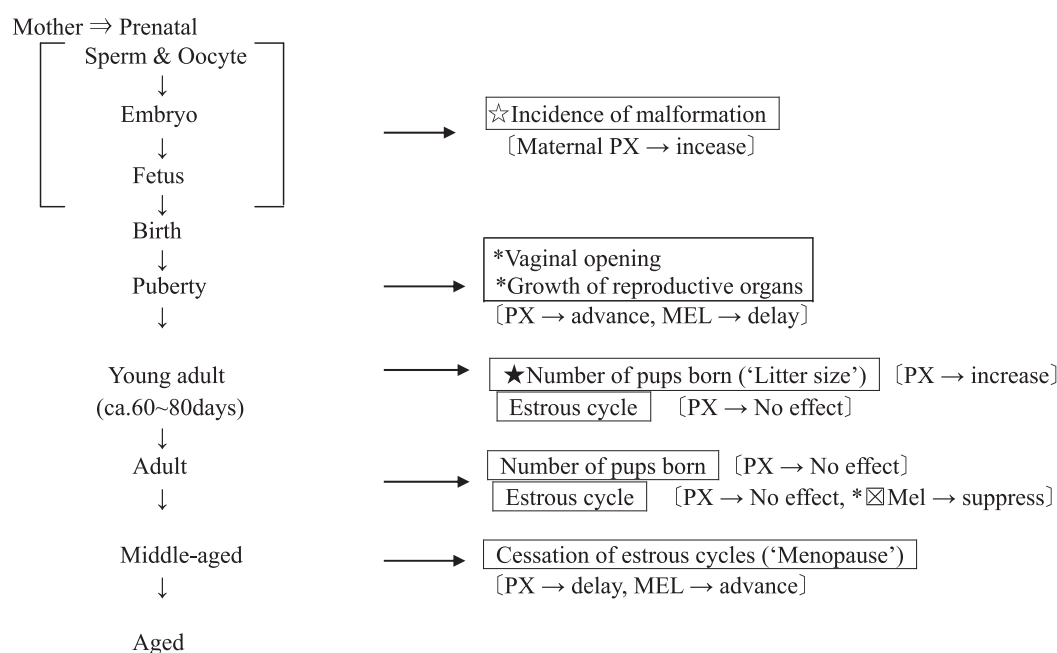
an interesting problem<sup>150)</sup>. Recently, melatonin has been reported to induce the expression of many immune-related genes<sup>151-153)</sup>.

### Age-related physiological roles of pineal hormone in regulatory mechanisms of female reproductive activities

It has long been known that the pineal hormone causes the retardation of puberty onset and growth of reproductive organs<sup>154-156)</sup>. In relation to the mechanism, recently attention has been paid to kisspeptin<sup>157)</sup>. But during other stages of life, pineal functions still remain to be clarified.

From the pioneering work on the melatonin synthesis and other chemical activities in human pineals, Wurtman et al. (1964)<sup>158)</sup> suggested that the pineal gland may be active throughout the entire life span. From an experiment on phase shifting of the rat's activity rhythm after reversing the light-dark cycle, Quay (1972)<sup>159)</sup> found that PX animals phase-shifted more quickly than controls during an early stage of life, and more slowly during a late stage. He hypothesized that mammalian pineal organ is part of a mechanism bringing about stabilization of circadian phase-shift rate. Around the same time, we first showed that the 24 h rhythm of pinealocyte chemical activity (glycogen level) and its light responsiveness persist till old, 1.5 ~2 years of age, with peak levels at about 3 months of age in mice<sup>39,40)</sup> (Table 1). Melatonin synthesis/secretion and its circadian change have been observed to persist till old age by many investigations in humans and rodents, although the level, amplitude and/or pattern of day-night difference are various among reports and may change relating to age<sup>79,85,160-170)</sup>. In addition, individual differences and disease effects have been reported to exist<sup>79,160,163,167,169)</sup>.

From the results showing a marked age-related decline in melatonin secretion<sup>164-166)</sup>, the theory of anti-aging effect of melatonin appeared



**Figure 1** Pineal effects on female reproductive activities: summary of previous and our studies.

☆: Results of previous studies. ☆: Mother's ages were various. ★: Pups were delivered from mothers at 3 months of age. ☒: Since melatonin increases the diestrous phase in murine<sup>177)</sup>, the pineal hormone may play a role in the stress-induced anovulation in wild life<sup>18)</sup>.

and supplements of melatonin have widely been used for delaying aging and aging-related diseases<sup>171-173)</sup>. Such possible anti-aging effect of melatonin has been attributed to its anti-oxidating and free radical-scavenging activities, at least partly. However, more experimental data would be needed before final conclusion about the 'general' anti-aging activity of the pineal hormone, melatonin.

Recently we systematically investigated the effects of pineal hormone on female reproductive activities throughout life in Wistar rats, non-seasonal breeder, kept under a 24 h (12L: 12D) cycle and constant temperature. Main results are as follows: 1) more pups with congenital malformation were born from PX mother rats irrespective of mother's age; 2) more pups were born from PX female rats when mothers were at about 3 months of age, but not at later ages; 3) the cessation of estrous cycle at the middle age was delayed in PX rats and advanced by melatonin administration, but PX was ineffective

on the estrous cycle in younger adults<sup>174-177)</sup> (Figure 1).

Thus, physiological functions of pineal hormone in adult female reproductive activities of laboratory rats under constant conditions were clearly shown for the first time, even in the middle age, namely ca. 1.5 years of age. The mechanisms of these phenomena are unknown. But several points are noted. 1) Concerning the pineal's antimetamorphic effect<sup>175,176)</sup>, an immunological mechanism<sup>178-180)</sup> may additionally be included. 2) Concerning the pineal effect manifested restrictedly in early adulthood, structures of the reticular zone of adrenal cortex in mice<sup>181)</sup>, serum DHEAS levels in human<sup>182)</sup> and PGE<sub>2</sub>-related activities in the hypothalamus of rats<sup>183)</sup> have been reported to show related changes. Melatonin has also been reported to synergistically increase the production/secretion of DHEA<sup>184)</sup>. 3) Present results did not support the anti-aging hypothesis of Trentini's group (1992)<sup>185)</sup> that melatonin retards the cessation



of estrous cycle in middle-aged rats, but demonstrated that melatonin exerts proaging effects on female reproductive activities at least in the middle age. Several papers relating to our results have appeared<sup>186,187)</sup>.

### Pathology

We found enlarged pineals in several disease cases<sup>48)</sup> (Table 1). Experimental studies on the relation between the pineal hormone and diseases, e.g. tumor<sup>188-191)</sup>, neurodegenerative diseases<sup>192-196)</sup> and diabetes mellitus<sup>137,148,197,198)</sup>, are in progress.

### Conclusions

The synthesis/secretion of pineal hormone is usually cyclical, but changeable under various circumstances. Even if the melatonin secretion level remains within normal range, pineal effects are markedly changeable due to the sensitivity/state of target mechanisms. The pineal hormone participates in the body's regulatory system mostly by cooperative and modulatory mechanisms, particularly in relation to the changes of environment including stress/invasion, timing of physiological processes including reproduction-related ones, and also possibly exogenous and endogenous pathological changes. Pineal actions are mainly inhibitory but can be stimulatory also.

It has generally been considered that the process of evolution from submammals to mammals brought about many complex mechanisms including the characteristic development of brain, autonomic nervous system and emotion as well as pregnancy, suckling and nursing<sup>199-201)</sup>. From these it is hypothesized that in mammals the pineal hormone was involved in the drastic reorganization of regulatory system occurred in such evolutionary processes and became participated in the system which regulates the complex body mechanisms<sup>176)</sup>.

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