ROLE OF MELATONIN

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Q.What about pacemaker mechanisms in vertebrates?

EXPRIMENTAL EVIDANCE

i)Investigations of biological clock mechanisms in rats (*Rattus norvegicus*) led to the finding that a direct neural connection exists between the retina and the hypothalamus, a pathway that terminates in the **suprachiasmatic nuclei** (SCN), a region of the hypothalamus (Hendrickson et al. 1972; Moore and Lenn 1972).

ii)Lesions to cut connections to these nuclei resulted in rats that lost circadian rhythms of drinking behaviour and wheel-running activity (Moore and Eichler 1972; Stephan and Zucker 1972).

iii)Ralph et al. (1990) and Matsumoto et al. (1998) transplanted SCNs into host hamsters where their own SCN had previously been ablated. In about 80 percent of the cases, recipient hamsters exhibited activity patterns of a circadian nature; that is, their rhythmicity was restored. Moreover, the period of the resumed rhythm matched that of the donor hamsters.

iv)Animals receiving a SCN from a normal hamster (Hamsters are rodents belonging to the subfamily **Cricetinae**) exhibited a period of about 24 hours, whereas those given a transplanted SCN from a mutant hamster of the type we mentioned earlier in the chapter, with a period of about 22 hours, resumed their activity with the shortened period, like the mutants (Ralph et al. 1990).

v)In a further study of this phenomenon, Liu et al. (1997) have demonstrated that individual neurons within the cells that comprise the clock have widely varying periods, but the observed rhythm is a mean of these individual rhythms of the neurons that make up the clock within the SCN.

vi)A number of researchers have shown that **SCNs are essential for circadian rhythms** in mammals and that pacemakers located in these neural nuclei drive a variety of rhythms, including sleep-wake cycles, rhythms of various hormones, and feeding behaviour (Rusak and Zucker 1979; Rosenwasser and Adler 1986; Meijer and Rietveld 1989).

vii)There is ample evidence that there must be **other pacemakers** as well. For example*, bilateral SCN lesions in monkeys, resulting in arrhythmicity of the animal's activity-recycle*, do not eliminate the circadian rhythm for body temperature (Fuller et al. 1981). Thus, there must be at least one aiitior.al pacemaker somewhere else in the body. Entraining rats to a particular feeding time followed by lesioning of the SC does not alter the anticipation of feeding time in these animals (Stephan et al. 1979b; Clarke and Coleman 1986).

viii)Evidences suggests the existence of another clock outside of the SC There is some evidence that one location for such a **secondar clock**: could be the **ventromedial hypothalamus** (VME).

ix)Investigations of rhythms in birds and mammals have implicated the **pineal gland as a probable receptor of light stimuli** that entrain and affect circadian patterns (Gaston 1971; Menaker and Zimmerman l1976).

x)Existing evidence supports the hypothesis that both neural processes (Block and Page 1978) and hormone-neuroendocrine products (Zucker et al. 1976; Starkey et al. 1995) are involved in the mechanisms underlying biological rhythms in vertebrates.

xi)**The pineal gland in mammals** lies within the brain. Near the midline; but in some earlier terrestrial vertebrates. This structure was positioned on the top surface of the brain and served as a third or median eye.

xii)In today's reptiles, birds, and amphibians, the pineal gland is located just under the skull indeed, it is still sensitive to light in many of these organisms. We should not find it surprising that the pineal gland plays a key role in regulating certain rhythms based on photoperiod. The role o the SCN as a location for the primary circadian oscillator has been confirmed for reptiles through tests on the ruins Ezard (Podarcis sicula); when the SCN was iesioneć in these lizards they became arrhythmic (Minituni et al. 1995).

Melatonin

i)Melatonin, an **indolamine** (protein) is produced by the pineal gland (Reiter 1980).

ii)Daily subcutaneous injections of melatonin given to pinealectomized male hamsters induce regression of the gonads, mimicking the effect of shortened photoperiods in these animals (Reiter 1974a; Tamaikin et al. 1975).

iii)A series of investigations using hamsters. rats, mice, and other mammals have repeatedly demonstrated the **antgonadotrophic effects of melatonin**.

iv)In these mammals. The pineal normally receives photoperiod information via neural circuitry from the eyes. Reiter (1974b) proposed of **one key function for the pineal may be** the **partial control of annual rhythm of reproduction.**

v)Seasonal changes in photoperiod are translated into physiological effects by the pineal and its endocrine products.

vi)Using **radioactively labeled melanonin** and **autoradiography**, Reppert et al. (198:8) determined that for humans, specific sites in the hypothalamus bind melatonin. In particular, the site where the most binding of the labeled melatonin occurs is the suprachiasmatic nucleus.

Further evidence for the role of melatonin and also its interrelationship with the SCN comes from work on Djungarian hamsters (*Phodopus sungorus*). When a strain of these animals that is not responsive to photoperiod was ivem caily injections of melatonin, it soon exhibited activity patermss and neuronal firing patterns that resembled the>se of mal photosensitive hamsters (Margraf and Lynch 1993).

vii)As an example of the molecular approach of **biological clock mechanisms**, consider again the sea hare (*Aplysia* sp) **Serotonin**, a neurotransmitter, appears to be involved in the pacemaker located in the eve. Studies on sea hares involve the use of light to shift the phases of activity.

viii)**Immunocytochemical studies** confirm the role of serotonin-mediated pathways involving the eye and the capacity of the eye to synthesize serotonin (Corrent and Eskin 1s42). Serotonin, whose production would be increased by appropriate external stimulation, could thus be a prudential messenger from the main oscillator to other.

ix)In addition, **cyclic-AMP (CAMP)** acts as a second messenger within cells, receiving messages from the eye cells, and triggered by the serotonin (Eskin et al. 1982), results in potential alteration of gene expression within the target cells.

x)Further, the use of **pharmacological agents** (e.g., **forskolin or phosphodiesterase**) results in elevation of the cAMPlevels, **mimicking the presence of serotonin**. Thus, we are moving ever closer to having an understanding of the molecular mechanisms by which at least some biological clocks operate.

xii)Several recent studies have extended our knowledge of the genetics and biochemistry of the vertebrate clock mechanism. Several genes, including **CLOCK** and **PER 1**. that are involved in the biological clock mechanism have been found in mice.

xiii)The **Perl gene** exhibits a circadian periodicity of expression in terms of RNA and protein production in the SCN (Xiaowei et al. 1999). Takumi et al. (1998) have isolated another mouse gene, Per2, which exhibits a strong circadian period of expression in the mouse SCN.

xiv)Interestingly. The amino acid sequence for the protein produced by Per2 is similar to the sequence of Per from Drosophila mentioned earlier.

xv)Additional information regarding control mechanisms of circannual rhythms, primarily in vertebrates, has also accumulated. The data collected so far largely concern correlated responses that are probably several steps removed from the actual clock mechanism. In thirteen-lined ground squirrels (*Spermophilus iridecemlineatus*), selected mixtures of dialysates (materials that pass through the membrane in dialysis) and their residues obtained from the blood of other ground squirrels or from woodchucks (*Marmot monar*) accelerate or impede the induction of hibernation (Dawe and Spurrier 1972). The brown fat found in some animals, which was thought for many years to contain chemicals responsible for inducing hibernation (Johansson 1959), has been shown instead to contain a substance that produces arousal (Smith and Hock 1963). When turtles (*Testudo hermanni*) are housed outdoors, the

levels of two compounds from their pineal gland serotonin and melatonin exhibit both circannual and circadían rhythms (Vivien-Roels et al. 1979).

xvi)The turtles synthesize serotonin during the day and melatonin at night; this pattern of synthesis disappears entirely

during hibernation. During the breeding season, concentrations of both chemicals and the amplitude of circadian fluctuations increase. Additional investigations are needed to determine the relationship between the concentrations of these chemicals and the observed circannual and circadian rhythms.

THEORIES ABOUT BIOLOGICAL CLOCK MECHANISM

Two main theories about biological clock mechanism have existed (Smith, 1973).

(1)**Pendulum theory**:

i)An organism is an independent oscillator, with its own intrinsic timing equalling one day.

ii)An ordinary mechanical clock can be an example of pendulum theory.

iii)Certain timing has been built into it and that is the speed with which it will tick.

(2)**Relaxation oscillation theory:**

i)The organism possesses no such timing but acquires a rhythmic timing from rhythmic and cyclic geophysical events going on all the time. The human heart is a near example. Its speed can be adjusted by its environment, quickened by some hormones, slowed down by others, accelerated by activity of body.

ii)Temperature greatly affects the rates of chemical reaction, 10°C increase can double the rate of many biochemical reactions.

Will it also double up the speed of an internal clock?

iii)No, it does not happen, even the cold blooded animals whose body temperature fluctuates can run their biological clocks accurately.

iv)An animal can have many internal clocks, which are perhaps controlled by a master clock may function independently or in synchronization. *Clunio* (mosquito) is found near sea and its habitat is almost always flooded with water except for twice a month i.e., soon after full moon and also when it is new moon at the time of spring low tide. Only during these two dry times the female lays.

v)The various internal clocks eggs in the ground. For adult female, the life is very short after it hatches from pupa, soon she must find a male to mate and lay eggs in the ground. The time of hatching, mating and egg laying has to be matched perfectly with the rhythm of the tide. The males, (have wings) emerge a little earlier than the females (wingless) which hatch earlier than the arrival of spring low-tide, lay eggs when the tide reaches its lowest level they die. All this happens within a few hours and only once hi every fifteen days. In this case two internal clocks: one clock to determine the right time of hatching and another clock to determine the right time of low tide are functioning in synchronization.

vi)In higher animals like rats by destroying certain part of the Nucleus suprachiasmaticus in diencephalon, the circadian eliminated. In most higher vertebrates it is **the pineal body** which controls the circadian rhythm.

It is possible that the substance responsible for rhythmicity may be a **proteinaceous neurohormone** released through axons (Arechiga, 1977).

Melatonin also known chemically known as the "hormone of darkness" is a naturally occurring compound found in animals, plants, and microbes.

In animals, circulating levels of the hormone melatonin vary in a daily cycle, thereby allowing the entrainment of the circadian rhythms of several biological functions.

Melatonin is secreted into the blood by the pineal gland in the brain.

The main pacemaker for endogenous (internal) rhythms is the suprachiasmatic nucleus (SCN). It lies just above the optic chiasm, therefore it can receive information directly from the eye and the rhythm can be rest by the amount of light entering the eye. It is responsible for controlling circadian rhythms. The neuronal and hormonal activities it generates regulate many different body functions in a 24-hours cycle using around 20,000 neurons.

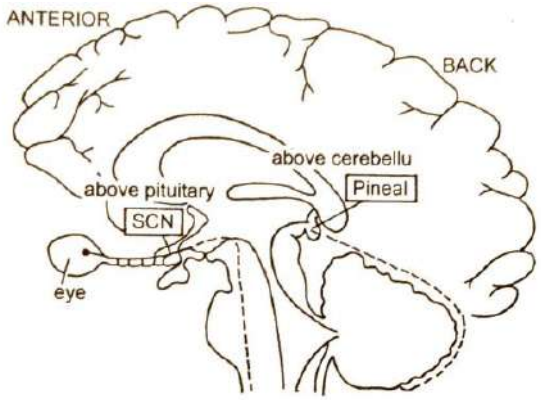

Figure: Human brain showing location of SCN