ERRATUM

Physiol. Res. 40: 11–23, 1991

Mechanism of Melatonin Action

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p. 11 (Summary)

Melatonin transduces the effect of photoperiod on the neuroendocrine system. Synthesis of melatonin in the pineal gland is well described, but the location of its target(s) and the mechanism of its action are little known. In attempt to localize melatonin target(s), the presence of high affinity binding sites in rat brain was determined. Such sites were detected in discrete brain areas, including the hypothalamus and anterior pituitary. Subcellular analysis indicated these binding sites were on plasma membranes, which suggests that melatonin modulates cell functions through intracellular second messengers. The effects of melatonin on second messengers were studied using the neonatal anterior pituitary, in which melatonin is known to inhibit the LHRH-induced release of LH. Studies on the effects of melatonin on second messenger indicated that melatonin inhibits accumulation of cAMP and cGMP as well as synthesis of diacylglycerol and release of arachidonic acid. Time-course analysis indicates that inhibition by melatonin of the LHRH-induced release of LH increases following long preincubation. Since the effect of melatonin on LHRH-induced release of LH is prevented by dibutyryl cAMP, we conclude that melatonin might act by inhibiting production of cAMP.

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Most temperate zone animals undergo seasonal rhythms in reproduction, thermoregulation, weight gain, hibernation, etc. (Glass 1984, Reiter 1980, Ortavant *et al.* 1964). These rhythms are important elements in survival, ensuring that physiological changes are coordinated with seasonal changes in ambient conditions and that births occur during spring time. This allows the most favorable circumstances for young to grow and develop. Seasonal rhythms are driven by changes of photoperiod, the most reliable indicator of the season: decreasing photoperiod lengths indicates that winter is approaching and allows species to prepare in advance. In hamsters, for example, short photoperiods induce gonadal involution, decrease of gonadal and gonadotropic hormones and inhibition of reproduction (Reiter 1967, 1980). These changes ensure that hamsters breed in the spring and that young hamsters are born in the spring and summer after a short gestation period. In contrast, sheep, which have a longer gestation period, breed during the autumn as a result of shortening days but still bear young during the spring (Ortavant *et al.* 1964).

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Melatonin affects also other potential second messengers: it decreases cGMP and diacylglycerol accumulation in immature rat AP and inhibits arachidonic acid release from the gland (Fig. 7, Vaněček and Vollrath 1989, 1990a,b). Since all these messengers were shown to affect cell functions, it remains to be determined which messenger transduces which effect of melatonin. To inhibit metabolism of intracellular messengers, melatonin may act through pertussis toxin-sensitive G-protein. This was indicated by the finding that preincubation with the toxin abolished the melatonin effect on cAMP accumulation as well as its effect on diacylglycerol accumulation (Carlson *et al.* 1989, Vaněček and Vollrath 1989b).

p. 19 (Legend to Fig.9)

Effect of melatonin on LHRH-induced release of LH from neonatal rat hemipituitaries and on cAMP accumulation in the gland in the absence (left) or in presence (right) of dibutyryl cAMP (1 mM). * Significantly different from LHRH alone ($p<0.05$)

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The potentiation by prolonged co-incubation suggests that melatonin may primarily inhibit synthesis of LH rather than its release: cAMP, after a lag phase, stimulates LH synthesis (Tang *et al.* 1984, Starzec *et al.* 1988) and melatonin decreases cAMP levels in AP. The diminished LH release may be then secondary to the decreased intracellular levels of LH. Potentiation of the inhibitory effect of melatonin by long pretreatment with the hormone may explain the mechanism of its action as an endocrine calendar. Short melatonin pulses which are a result of long photoperiods in summer, do not decrease LH release, but the long pulses during autumn and winter inhibit LH release, what may result in gonadal involution and in reproductive collapse. Although this is not necessarily the main mechanism of melatonin action on reproduction, it is the only hypothesis supported by experimental data from investigations of the effects of melatonin on cell physiology.