

## COMMENTARY

## Evolution of Melatonin as a Night Signal: Contribution from a Primitive Photosynthetic Organism

DAVID C. KLEIN,\* PATRICK H. ROSEBOOM,\* SUSAN J. DONOHUE,\* AND BARRY L. MARRS†

\*Section on Neuroendocrinology, Laboratory of Developmental Neurobiology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892; and †E. I. du Pont de Nemours & Company, Central Research and Development Department, Experimental Station, Wilmington, Delaware 19880-0173

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## INTRODUCTION

Circulating melatonin (Fig. 1) levels are elevated at night in essentially all vertebrates as a result of increased synthesis and release from the pineal gland (1). This increase serves as the hormonal signal of night and is used to coordinate daily and seasonal rhythms with the day/night cycle (2). As such, the melatonin signal is essential for survival in many seasonally breeding animals (3).

How did the association of melatonin with night evolve?

## HOMOLOGOUS STRUCTURE AND FUNCTION

The answer may come in part from recent molecular evidence that links a pineal melatonin-synthesizing enzyme with one involved in carotenoid synthesis in *Rhodobacter capsulatus*, a photosynthetic bacterium (4-6). The pineal enzyme is hydroxyindole-*O*-methyltransferase (HIOMT), the last in melatonin synthesis (7) (Fig. 1). The *R. capsulatus* enzyme is hydroxyneurosporene *O*-methyltransferase; HNOMT), which *O*-methylates carotenoids (8) (Fig. 1). Like HIOMT, HNOMT is associated with photic aspects of the environment. Carotenoid substrates of this enzyme function in *R. capsulatus* to absorb light and transfer energy to the photosynthetic apparatus; they also protect against photooxidative damage (9).

The amino acid sequences of bovine HIOMT (revised) and HNOMT are homologous (4) (GenBank/EMBL Data Libraries Accession Numbers M81862 and S04408; Fig. 2). Within a 180-amino-acid-long region of HIOMT, 55 (31%) of the residues are identical and an additional 78 (43%) represent conservative substitutions. The same type of similarity has been noted to exist between chicken HIOMT and *R. capsulatus* HNOMT (6). In contrast to the HIOMT/HNOMT similarity, HIOMT exhibits remarkably little homology with any other vertebrate pro-

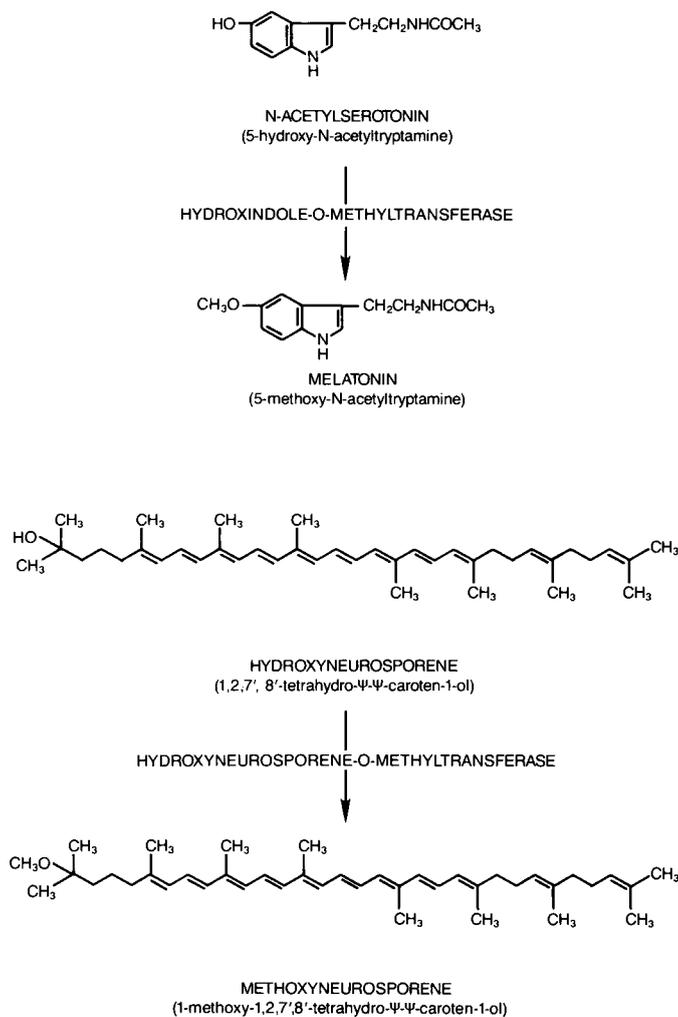


FIG. 1. Hydroxyindole-*O*-methyltransferase (HIOMT) and hydroxyneurosporene-*O*-methyltransferase (HNOMT). In both cases the methyl donor is *S*-adenosylmethionine (7, 8).

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HIOMT 155 QFMQGLQDVWRLEGATVLAADFSLSPFPLICDLGGGSGALAKACVSLYPGCRAIVFDIPGV 214
      : : | : : | : : : : | : : : : | : : : : | : : : : | : : : : | : : : : |
HNOMT 204 RYSQLMADSQRVVADDTLRLVDLRAKRVMDVGGGTGAFRLRVVAKLYPELPLTLFDLPHV 263

HIOMT 215 VQIAKRHFSASEDERISFHEGDFFKDALPE-ADLYILARVLHDWTDKCSHLLQRVYRAC 273
      : : : : | : : : : | : : : : | : : : : | : : : : | : : : : | : : : : |
HNOMT 264 LSVADR-FSP----KLDFAFGSFRDDPIQGADVITLVRVLYDHPDSVVEPLLAKVHAAL 318

HIOMT 274 RTGGGILVIESLLDTRGRPLTLLYSLNMLVQTEGRERTPAEYRALLGPAGFRDVRRCRT 334
      : : | : : | : : : : | : : : : | : : : : | : : : : | : : : : | : : : : |
HNOMT 319 PPGRLTISEAMAGGAKPDRACDVYFAFYTMAMSSGRTRSPEETKQMLEKAGFTKVKPRT 379

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**FIG. 2.** Sequence homology between bovine HIOMT (revised) and *R. capsulatus* HNOMT (4, 5). Identical amino acids are identified by vertical lines, similar or equivalent amino acids are identified by colons, and inserted gaps are indicated by dashes. Analysis was performed using the FASTA program from the Genetics Computer Group software package (10).

tein whose sequence is available, including several methyltransferases (10 and unpublished results). The similarity of the primary structures of HIOMT and HNOMT indicates that both enzymes evolved from a common ancestral protein.

*R. capsulatus* is thought to be closely related to a primitive endosymbiont, existing two to three billion years ago, which evolved within the primitive eukaryotic cell to become the mitochondrion (11, 12). Accordingly, it would appear that the HNOMT-like DNA that evolved to encode HIOMT was introduced to the ancestral eukaryotic cell by this *R. capsulatus*-like endosymbiont. DNA introduced in this manner may subsequently be incorporated into the cell nucleus; this appears to have happened in the case of HIOMT because the human HIOMT gene has a nuclear, not mitochondrial, location (S. J. Donohue, P. H. Roseboom, J. L. Weller, O. W. McBride, H. Illnerova, and D. C. Klein, unpublished findings). Accordingly, it would appear that the HIOMT gene originated in the endosymbiont ancestor of the mitochondrion.

## HOMOLOGOUS REGULATION

Another interesting aspect of the relationship between HIOMT and HNOMT extends their association with light discussed above. The activity of each enzyme decreases as light intensity increases from low to high levels and visa versa. In the case of *R. capsulatus* the entire photosynthetic apparatus, including HNOMT, increases in dim light (13, 14). This is an adaptive survival strategy that increases the efficiency of light energy capture; such an adaptation is an obvious advantage to a photosynthetic organism, especially several billion years ago when light was the primary source of energy and the atmosphere was devoid of oxygen. In the case of the pineal gland, many proteins in addition to HIOMT increase in darkness or very dim light and decrease following long periods of constant bright light (1).

Based on these observations, it seems reasonable to propose that HIOMT and HNOMT represent a family of enzymes characterized by similar structure, function, and regulation. It would appear that photic regulation of

O-methylation originated as part of a general adaptive strategy to increase photosynthetic efficiency and was recruited to support melatonin production.

It is truly remarkable that the association of increased O-methylation and darkness seems to have been preserved during billions of years of evolution. This link is a compelling example of how the relationship between information (light) and a biochemical process (O-methylation) can evolve. It is not clear yet whether *R. capsulatus* can synthesize melatonin or whether melatonin synthesis increases in darkness in this organism. Certainly this would be exciting. However, even if this were not the case, it is fascinating none-the-less to discover how elements of the complex photoneural system that regulates melatonin production evolved and to find that an association of darkness and O-methylation can be traced to a very early point in the evolution of life.

## REFERENCES

1. Klein, D. C. (1985). Photoneural regulation of the mammalian pineal gland. In *Photoperiodism, Melatonin and the Pineal* (D. Evered and C. Clark, Eds.), Ciba Foundation Symposium 117, pp. 38–56. Pittman, London.
2. Evered, D., and C. Clark (Eds.) (1985). *Photoperiodism, Melatonin and the Pineal*, Ciba Foundation Symposium 117. Pittman, London.
3. Karsch, F. J., C. J. I. Woodfill, B. Malpaus, J. E. Robinson, and N. L. Wayne (1991). Melatonin and mammalian photoperiodism: Synchronization of annual reproductive cycles. In *Suprachiasmatic Nucleus: The Mind's Clock* (D. C. Klein, R. Y. Moore, and S. Reppert, Eds.), pp. 217–232. Oxford Press, New York.
4. Donohue, S. J., P. H. Roseboom, and D. C. Klein (1992). Bovine hydroxyindole-O-methyltransferase: Significant sequence revision. *J. Biol. Chem.* **267**, 5184–5185.
5. Armstrong, G. A., M. Alberti, F. Leach, and J. E. Hearst (1989). Nucleotide-sequence, organization, and nature of the protein products of the carotenoid biosynthesis gene-cluster of *Rhodobacter capsulatus*. *Mol. Gen. Genet.* **216**: 254–268.
6. Voisin, P., J. Guerlotté, M. Bernard, J.-P. Collin, and M. Gagné (1992). Molecular cloning and nucleotide sequence of a cDNA encoding hydroxyindole-O-methyltransferase from chick pineal. *Biochem. J.* **282**: 571–576.
7. Sugden, D., V. Ceña, and D. C. Klein (1986). Hydroxyindole-O-methyltransferase. In *Methods in Enzymology* (S. Kaufman, Ed.), Vol. 142, pp. 590–596. Academic Press, San Diego.

8. Scolnik, P. A., M. A. Walker, and B. L. Marrs (1980). Biosynthesis of carotenoids derived from neurosporene in *Rhodopseudomonas capsulata*. *J. Biol. Chem.* **255**: 2427-2432.
9. Krinsky, N. I. (1971) Function. In *Carotenoids* (O. Isler, H. Gutman, and U. Solms, Eds.), pp. 577-636. Birkhauser, Basel.
10. Devereux, J., P. Haerberli, and O. Smithies (1984). A comprehensive set of sequence-analysis programs for the VAX. *Nucleic Acids Res.* **12**: 387-395.
11. Yang, D., Y. Oyaizu, H. Oyaizu, G. J. Olsen, and C. R. Woese (1985). Mitochondrial origins. *Proc. Natl. Acad. Sci. USA* **82**: 4443-4447.
12. Woese, C. R. (1980). The use of ribosomal RNA in reconstructing evolutionary relationships among bacteria. In *Evolution at the Molecular Level* (R. K. Selander, A. G. Clark, and T. S. Whittam, Eds.), pp. 1-24. Sinauer Assocs., Sunderland, MA.
13. Drews, G. (1986). Adaptation of the bacterial photosynthetic apparatus to different light intensities. *Trends Biochem. Sci.* **11**: 255-257.
14. Manwaring, J., C. A. Pullin, E. H. Evans, and G. Britton (1978). Alternation in concentration of carotenoids in *Rhodopseudomonas capsulata* transferred from dark to light growth. *Biochem. Soc. Trans.* **6**: 1041-1043.