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Prostaglandin D synthase (β-trace protein): a molecular clock to trace the origin of REM sleep?

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Abstract — In 1965, Zuckerkandl and Pauling proposed a novel concept that some important molecules termed semantides, which carry the information of the genes or a transcript thereof, can be used as molecular clocks to trace evolutionary history. According to this concept, enzymes are designated as tertiary semantides, following genes (primary semantides) and the mRNA (secondary semantides). Based on this idea, I propose that prostaglandin D synthase (which has been demonstrated recently as identical to the β-trace protein present in the cerebrospinal fluid of mammals) may serve as a molecular clock to trace the origin and evolution of rapid eye movement sleep in the vertebrates.

Introduction

In 1953, Aserinsky and Kleitman (1) provided the first experimental evidence for the occurrence of dream sleep (also called rapid eye movement sleep or REMS), which is characterized by the movement of eyelids. REMS is believed to be present only in birds and mammals. However, no consensus exists among the researchers regarding the physiological significance of REMS. For example, Crick and Mitchison (2,3) proposed that dreams 'result in reverse learning', akin to the forgetting function of the brain. Thus this provides an important mechanism in preventing brain from being 'overloaded'. However, Winson (4) had postulated in the opposite direction, stating that crucial evidence acquired during the waking state may be reprocessed during the dream state and thus dreams reflect an individual's strategy for survival.

More than three decades ago, Zuckerkandl and Pauling (5) proposed a novel concept that some important molecules which carry the information of the genes or a transcript thereof can be used as molecular clocks to trace evolutionary history. They classified molecules occurring in life forms into three categories as follows:

1. Semantophoretic molecules or *semantides*, which carry the information of the genes or a transcript thereof. These were further subdivided into
   (a) genes – *primary semantides*
   (b) mRNA – *secondary semantides*
   (c) most of the polypeptides such as enzymes (*tertiary semantides);*
2. Episemantic molecules, which are synthesized under the control of tertiary semantides;
3. Asemantic molecules, that are not produced by the organism.

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According to Zuckerkandl and Pauling (5), 'the relevance of molecules to evolutionary history decreases as one passes from semantides to asemantic molecules'. Based on the concept of molecular clocks, Doolittle et al (6) reported recently the divergence times of major kingdoms of living organisms determined from the amino acid sequence data of 57 different enzymes.

In this communication, I propose the idea that prostaglandin (PG) D synthase (a 27 kDa monomeric protein with 190 amino acid residues, first isolated in the rat brain) can serve as a molecular clock to trace the evolution of REMS in the vertebrates.

Prostaglandin D synthase as a molecular clock

Among the more than thirty endogenous sleep substances elucidated so far (7), the significance of PGD_2 has been studied in detail in the laboratory of Hayaishi (reviewed in references 8–10). PGD synthase, the enzyme primarily responsible for the production of PGD_2 in the brain, was also biochemically characterized by Hayaishi's group (11–13). They have also demonstrated that the PGD synthase exists mainly in the choroid plexus, leptomeninges and oligodendrocytes of the mammalian central nervous system (14). Concurrently, β-trace protein, a major polypeptide which was isolated from the cerebrospinal fluid of humans for the first time in 1961 and which remained a puzzling substance without any known function for three decades, has been shown to be identical to PGD synthase (15,16).

In terms of the classification provided by Zuckerdandl and Pauling (5), PGD synthase is a tertiary semantide and PGD_2 is an episemantic molecule. PGD synthase is the only member with an enzyme function, among the lipocalin superfamily of lipophilic ligand-carrier proteins, widely distributed among the invertebrates and five vertebrate classes (17–19). Preliminary data from studies conducted in Australia (20) and Switzerland (21) show that brain prostaglandin D synthase does possess some activity in the nervous systems of cane toad and chick, respectively. If this is so, one could present a case that PGD synthase, being a tertiary semantide, may serve as an appropriate molecular clock to trace the origin of complex sleep behavior (consisting of REMS) on the evolutionary time scale.

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References

1. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena during sleep. Science 1953; 118: 273–274.
2. Crick F H C, Mitchison G. The function of dream sleep. Nature 1983; 304: 111–114.
3. Crick F H C. Neural networks and REM sleep. Bio Sci Rep 1988; 8: 531–535.
4. Winson J. The meaning of dreams. Sci Am 1990; 263(5): 86–96.
5. Zuckerkandl E, Pauling L. Molecules as documents of evolutionary history. J Theoret Biol 1965; 8: 357–366.
6. Doolittle R F, Feng D F, Tsang S, Cho G, Little E. Determining divergence times of the major kingdoms of living organisms with a protein clock. Science 1996; 272: 470–477.
7. Borbely A A, Tobler I. Endogenous sleep-promoting substances and sleep regulation. Physiol Rev 1989; 69: 605–670.
8. Hayaishi O. Molecular mechanisms of sleep–wake regulation roles of prostaglandins D_2 and E_2. FASEB J 1991; 5: 2575–2581.
9. Hayaishi O. Tryptophan, oxygen and sleep. Annu Rev Biochem 1994; 63: 1–24.
10. Hayaishi O, Sri Kantha S. Sleep substance: fact and not fancy. World Fed Sleep Res Soc Newsletter 1994; 3(2): 7–8.
11. Urade Y, Fujimoto N, Hayaishi O. Purification and characterization of rat brain prostaglandin D synthase. J Biol Chem 1985; 260: 12410–12415.
12. Urade Y, Nagata A, Suzuki Y, Fujii Y, Hayaishi O. Primary structure of rat brain prostaglandin D synthetase deduced from cDNA sequence. J Biol Chem 1989; 264: 1041–1045.
13. Hayaishi O, Matsumura H, Urade Y. Prostaglandin D synthase is the key enzyme in the promotion of physiological sleep. J Lipid Mediat 1993; 6: 429–431.
14. Urade Y, Kitahama K, Ohishi H, Kaneko T, Mizuno N, Hayaishi O. Dominant expression of mRNA for prostaglandin D synthase in leptomeninges, choroid plexus and oligodendrocytes of the adult brain. Proc Natl Acad Sci (USA) 1993; 90: 9070–9074.
15. Hoffman A, Conradt H S, Gross G, Nimtz M, Lottspeich F, Wurster U. Purification and chemical characterization of β-trace protein from human cerebrospinal fluid; its identification as prostaglandin D synthase. J Neurochem 1993; 61: 451–456.
16. Watanabe K, Urade Y, Mader M, Murphy C, Hayaishi O. Identification of β-trace as prostaglandin D synthase. Biochem Biophys Res Commun 1994; 203: 1110–1116.
17. Nagata A, Suzuki Y, Igarashi M et al. Human brain prostaglandin D synthase has been evolutionarily differentiated from lipophilic-ligand carrier proteins. Proc Natl Acad Sci (USA) 1991; 88: 4020–4024.
18. Igarashi M, Nagata A, Toh H, Urade Y, Hayaishi O. Structural organization of the gene for prostaglandin D synthase in the rat brain. Proc Natl Acad Sci (USA) 1992; 89: 5376–5380.
19. Toh H, Urade Y, Tanabe T. Molecular evolution of enzymes involved in the arachidonic acid cascade. Mediat Inflamm 1992; 1: 223–233.
20. Achen M G, Harms P J, Thomas T, Richardson S J, Wettenhall R E H, Schreiber G. Protein synthesis at the blood–brain barrier: the major protein secreted by amphibian choroid plexus is a lipocalin. J Biol Chem 1992; 267: 23170–23174.
21. Vesin M F, Urade Y, Hayaishi O, Droz B. Neuronal and glial prostaglandin D synthase isozymes in chick dorsal root ganglia: a light and electron microscopic immunocytochemical study. J Neurosci 1995; 15: 470–476.