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Pathophysiological roles of the prostaglandin D2 system in the central and peripheral nervous system

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Prostaglandin (PG) D_2 is a major prostanoid produced in the CNS of various mammals including humans and acts as an endogeneous sleep-promoting substance and an inflammatory lipid mediator. PGD_2 is produced by two distinct synthases, i.e., lipocalin-type PGD synthase (L-PGDS) and hematopoietic PGD synthase (H-PGDS), and stimulates two distinct G-protein-coupled receptors, Gs-coupled DP1 receptor and Gi-coupled DP2 (CRTH-2/GPR-44) receptor. (1) In the CNS, L-PGDS is dominantly expressed in the leptomeninges, choroid plexus and oligodendrocytes, and secreted into the cerebrospinal fluid (CSF) as beta-trace protein, a major human CSF protein, whereas H-PGDS is localized in microglia and mast cells. DP1 receptor is localized in subpopulation of cells within the leptoneninges and glial limitance and upregulated in hypertrophied astrocytes in various neuro-inflammatory circumstances. DP2 receptor is expressed in various inflammatory cells including activated microglia and invaded macrophages after brain damages. By using gene-knockout mice and pharmacological blockades with enzyme inhibitors or receptor antagonists, we revealed that the L-PGDS/DP1 receptor system is involved in the regulation of sleep; [(2)] the L-PGDS/DP2 system, in myelination of Schwann cells; [(3)] the H-PGDS/DP1 system, in the suppression of epilepsy; [(4)] and the H-PGDS/DP2 system, in the chemotaxis of inflammatory cells during neuroinflammation. We reported that L-PGDS/beta-trace protein secreted into the human CSF is upregulated after subarachnoid hemorrhage and acts as a scavenger for biliverdin, a harmful heme-degrading product.[(5)] We recently found that L-PGDS/beta-trace protein binds PGD_2 at a high affinity with Kd value in a submicromoler range and also covalently binds PGJ_2 derivatives, nonenzymic dehydration products of PGD_2. These results are useful to develop new drugs targeting the PGD_2 system and diagnostic kits for various neuroinflammatory and neuroimmunological diseases.

Biography

Yoshihiro Urade has completed his PhD at the age of 29 years from Kyoto University in 1983 and postdoctoral studies from ERATO project of Japan Science and Technology Agency. He was the visiting professor of Roche Institute of Molecular Biology in 1988, the senior scientist of International Laboratories of CIBA-GEIGY Japan in 1990, and the vise-head of Department of Molecular Behavioral Biology of Osaka Bioscience Institute in 1993, and the head of this department in 1998 to 2014. In 2014, he became a principal investigator of a newly established institute in Tsukuba University. He has published more than 300 papers in reputed journals and has been serving as an editorial board member of Prostaglandins, Leukotriens and Essential Fatty Acids and as the secretary general of Asian Society of Sleep Medicine (ASSM).

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