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Mini Review

Role of Plasma and CSF PGDS Levels in Neurological Disease-Update of all Literatures Till Date

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Received: March 09, 2020; **Published:** March 24, 2020

Abstract

Prostaglandin D2 (or PGD2) is a prostaglandin that binds to the receptor PTGDR (DP1), as well as CRTH2 (DP2). It is a major prostaglandin produced by mast cells - recruits Th2 cells, eosinophils and basophils. In mammalian organs, large amounts of PGD2 are found only in the brain and in mast cells. PGDS, mainly L and H are responsible for PGD2 synthesis. PGD2 has many important physiological function in our body and serous fluid levels of PGDS (prostaglandin D synthase) are being linked to renal failure, allergic asthma etc. Plasma and CSF levels of PGDS are being studied in sleep disorders like obstructive sleep apnea and narcolepsy and various neurological diseases like Alzheimer's disease (AD), Parkinson's disease (PD), severe traumatic brain injury, autistic spectrum disorder etc. Here in this review article role of plasma and CSF PGDS levels in neurological disease has been discussed with maximum focus on published literatures till date.

Keywords: *Prostaglandins; PGD2; PGDS; Neurology*

Abbreviations

PTGDR: Prostaglandin D Receptor; CRTH2: Chemoattractant Receptor-Homologous Molecule Expressed on TH2 Cells; RCT: Randomized Controlled Trial

Introduction

Prostaglandin (PG) is responsible for many physiological function in human body. The most abundant prostaglandin in mammalian brain is PGD2 [1], which includes the leptomeninges [4], choroid plexus and oligodendrocytes. PGD2 is synthesized by synthases mainly glutathione-dependent hematopoietic PGD synthase (H-PGDS) [23], present in mast cells and Th lymphocytes and lipocalin-type PGD synthase (L-PGDS), localized in the arachnoid mater [22]. PGD2 activates nonrapid eye movement sleep (NREM) and is considered to be the most potent sleep-promoting substance *in vivo* [2,3]. Administration of PGD2 from outside promotes sleep, whereas L-PGDS inhibitors suppress sleep [5].

Higher levels of L-PGDS is seen in patients with OSAS (Obstructive sleep apnea syndrome) with excessive daytime sleepiness (EDS) [6]. Role of L-PGDS in narcolepsy where one showed low values [7] and another increased values [8] are reported in literature. However, none of the studies talked about involvement of brain damage or deficiency of any neurotransmitter or substances like involvement of orexin or hypocretin [21]. A lot of studies of PGDS is linked to renal failure, diabetes, obstructive azoospermia, coronary or vascular atherosclerosis etc. which are not.

PGDS and its link to central nervous system

Suzuki., *et al*. 2020 in their study reported higher levels of plasma L-PGDS in patients with neurodegenerative diseases such as Parkinson's disease (PD) with EDS and PDWS and Alzheimer's disease (AD) [9]. Mohri., *et al*. 2007 showed increased expression of H-PGDS in the frontal cortex of patients with Alzheimer's disease (AD) [10], supported by other studies [11,12]. In a recent study, CSF samples from 33 children with medulloblastomas were analyzed using two-dimensional electrophoresis and mass spectrometry, which showed six-fold mean reduction in prostaglandin D2 synthase (PGD2S) levels in medulloblastoma patients as compared to age-matched controls [13]. One study reported plasma levels of PGDS were significantly lower in severe traumatic brain injury(sTBI) compared with controls. The authors suggest ratios of NSE and S100B with hK6 and PGDS might be able to determine the presence of sTBI better than single markers alone [14].

Hamed., *et al*. 2019 demonstrated the usefulness of plasma H-PGDS as a diagnostic tool to differentiate between ASD (autism spectrum disorder) and neurotypical control children, but was not significant among subgroups of ASD children having sensory dysfunction of variable severity in middle east population [15]. Plasma PDS-TTR (prostaglandin-D-synthase- transthyretin) complex is comparable to Aβ(1-42) in both MCI and probable AD subjects [16] and can be considered as a biomarker of the disease. L-PGDS and Gpr44 are considered to be components of an axo-glial interaction that controls PNS (peripheral nervous system) myelination and maintenance of myelin [17]. Plasma L-PGDS is known to play an important role in the development of dementia in patients on dialysis and of AD by increasing levels of reactive oxygen species, IL6 and TNFα [18].

Argüelles., *et al*. 2010 showed early increase of plasma and CSF prostaglandin D synthase in response to bilateral intranigral injection of LPS (lipopolysaccharide) in patients with PD [19]. In LPS-induced neuroinflammatory states, L-PGDS are downregulated, making brain more vulnerable to the accumulation of oxidative/nitrosative mediators in the brain like NF-kappaB, NOS-2 and COX-2 [20]. Its role is also studied in major depressive disorder [1].

Discussion

PGD2 is the special prostaglandin which is mostly present in mammalian brain like leptomeninges, choroid plexus and oligodendrocytes etc. PGDS can be divided into H and L type and each has its own significance as discussed earlier. PGDS is also localized in male genital organs, human heart and is secreted into body fluids, as beta-trace. Here in this review article we have discussed its role in inducing sleep and its relation to neuroinflammation and neurodegenerative diseases like AD and PD. It has been studied as a marker in severe TBI and pediatric brain tumors like medulloblastoma. H-PGDS can be used as a diagnostic tool to differentiate ASD phenotype and neurotypical controls. L-PGDS is also responsible for maintaining myelin which can be interesting for future studies in demyelinating disorders like multiple sclerosis (MS), neuromyelitis optica etc. At this moment of time there are only handful of studies which studied the correlation of plasma and CSF levels of PGDS and CNS diseases.

Conclusion

In this review article role of plasma and CSF levels of PGDS, related to neurological conditions especially neurodegenerative diseases has been discussed. However not much studies has been done in this field. Large RCTs are required in future to know more about pathophysiology of neurodegenerative diseases and related conditions.

Acknowledgment

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. Special thanks to my supervisor Professor Dr. Huifang Shang

who gave initial ideas and supported me through this research study. I would also like to thank Dr. Swatilekha Roy Sarkar for her valuable feedback on the manuscript and PubMed literature screening.

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Volume 12 Issue 4 April 2020
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