Advances in Bioresearch
Adv. Biores., Vol 10 (2) March 2019: 01-04

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.10.2.14

Advances in Bioresearch

REVIEW ARTICLE

Role of Endothelin-1 in Memory Loss

Ahsas Goyal*[1], Jeetendra Kumar Gupta[1],Debapriya Garabadu[1], Nitin Wahi[2],Anshima Sharma[1], Megha[1] Varshney
*Division of Pharmacology, Institute of Pharmaceutical Research, GLA University, Mathura-281406, Uttar Pradesh, India.
*Department of Biotechnology, Institute of Applied Sciences and Humanities, GLA University, Mathura-281406, Uttar Pradesh, India.
Corresponding Author's Email: ahsasgoyal1990@gmail.com

ABSTRACT
Endothelin (ET-1) is a 21 amino acid peptide produced by vascular endothelium from 39 amino acid precursor, big ET-1, through the actions of endothelin converting enzyme(ECE) present on the endothelial cell membrane.It is known that cerebral blood flow (CBF) as well as vascular functions are reduced in patients with Alzheimer's disease (AD) and this reduction occurs prior to the onset of dementia. The brain damage and memory disruptions that occur in AD are considered as a result of accumulation of a substance known as amyloid beta (Aβ) in the brain. Aβ increases the production of endothelin-1 (ET-1), by acting on endothelin converting enzyme-2 (ECE-2), which cleaves big endothelin resulting in the formation of ET-1 and Aβ-40. The triggered production of ET-1 in the lining of blood vessels of the brain causes them to constrict, narrowing their lumen,which reduces blood flow through the brain in patients with AD, and thereby deteriorate the oxygen and nutrients supply to nerve cells and slowdown the pace of removal of waste products, resulting to cause adverse effects on nerve cell function. The reduction in blood supply may increase the production of Aβ and thereby accelerate the progression of the AD. ET-1reduction in blood flow is achieved by targeting on specific endothelin receptors (ET_A) in the vessel walls. The down regulation of ET_A receptor could be a possibility in maintaining CBF in AD and also emphasizing use of endothelin converting enzyme (ECE) as a novel Aβ degrading enzyme can reduce memory loss to an extent.
Keywords: *Endothelin-1; ET_A receptors; Memory loss; Alzheimer's disease; Cerebralblood flow*

Received 01.01.2019 Revised 09.02.2019 Accepted 26.02.2019

How to cite this article:
A Goyal, J K Gupta, D Garabadu, N Wahi, A Sharma, M Varshney. Role of Endothelin-1 in Memory Loss . Adv. Biores., Vol 10 [2] March 2019.01-04.

INTRODUCTION

Endothelin-1 (ET-1) is a potent vasoconstrictor with proliferative, profibrotic and proinflammatory properties that may contribute to cognitive dysfunction. ET-1 exhibits its effect through two apparent G-protein coupled receptor subtypes i.e., ET_A and ET_B. ET_A is the dominant endothelin receptor subtype expressed in vascular smooth muscle cells (VSMC)which mediates strong vasoconstriction, whereas, ET_B receptors subtype promotes vasodilation via release of nitric oxide (NO) and prostacyclin under normal condition. However, several studies revelET_Bmediated constriction of isolated blood vessels [1, 2]. Elevated circulating ET-1 levels are outcome of endothelial dysfunction [3] and neurodegeneration [4]. ET-1 overexpression and ET_A receptor activation acts as risk factors for increased oxidative stress, water accumulation and blood brain barrier breakdown leading to an increase in severity of neurological deficit, vasoconstriction and reduction in cerebral blood flow [5]. A component of Renin-Angiotensin system (RAS) i.e. angiotensin II, increases ET-1 production, which activates $ET_A$and mediates change in vascular structure of cerebral circulation [6]. Both the ECE-1expressed in endothelial cells and ECE-2 expressed in neurons, are known tosplit 'big endothelin' in order to produce the vasoconstrictor ET-1 and degrade Aβ [7, 8]. ECE-2 is increased in the CNS as a resultant of hiked levels of NO to cause AD [9]. ET-1 immunoreactivity was observed in various parts of the brain which includes neurons of the cerebral cortex, striatum, amygdala, hippocampus, paraventricular and supraoptic nuclei of the hypothalamus, subfornical organ, median eminence, raphe nuclei, and pituitary gland. On this histological proof, a

verification that ET-1 is synthesized in neurons was made, with a possibility that ET-1 may act as a neuromodulator in CNS. This study also shows the predominant nature of ET-1 to be present in the human temporal cortex and sometimes within the walls of some blood vessels [10].

METHODS

Relevant studies were identified through electronic searches of Pubmed, Medline, Scopus, Google scholar. The search used the terms "endothelin,"or "endothelin receptor (ET_A)," paired with "memory loss," "cerebral blood flow". In addition, we searched the bibliographies of relevant studies, reviews and editorial letters for articles in English.

Authors	Model	Mechanism of Action	References
Jennifer *et al.,* 2012	SH-SY5Y human neuroblastoma cells	ECE-2 levels were increased at both mRNA and protein level in post mortem brain tissue as a secondary response towards accumulated Aβ. The increased ECE-2 levels releases ET-1 which reduces cerebral blood flow and leads to memory loss.	[8]
Calhan*et al.,* 2017	Mutant mouse model of inactive cathepsin A	In absence of Cathepsin-A (catalytically enzyme) activity an increase in endothelin-1 level in hippocampus is observed which leads to reduction in cognitive functions and hence memory loss.	[11]
Karhunen *et al.,* 2017	Male Sprague-Dawley rats (Infusion of ET-1 in middle cerebral artery)	Impairment in caudate nucleus due to low supply of blood which will lead to decrease in feedback processing. Sprouting of granule cell axons in supra- granular regions and inner molecular layer of dentate gyrus cause reduction in CBF and hence memory loss.	[12]
Mateffyova *et al.,* 2006	Intrahippocampal injection of endothelin-1 cognitive impairment in rats	Increased level of ET-1 in immature brains leads to loss in spatial memory and slow learning abilities. Also, after 3 months, cognitive impairment is observedwhich finally lead to memory loss.	[13]
Palmer*et al.,* 2011	Tg2576 mice model of AD	Increased level of ET-1 causes neuronal dysfunction and vasoconstriction which leads to diminished metabolic activity resulting in reduction of CBF associated to AD patients. It was found that for any measured level of cerebral glucose level, there was 30% reduction in CBF in case of Tg 2576 mouse strain	[14]
Daulatzai *et al.,* 2016	Male AβPPswe /PS1dE9 mice	Increased level of ET-1 leads to reduced blood flow which causes detrimental effect on neuroaxonal function as well as on clearance of Abeta from brain and also upregulation of A beta PP-enzyme, ultimately increasing Abeta production. The damage brought to the cerebral capillaries lead to memory loss.	[15]
Cameron*et al.,* 1994 Stevens *et al.,* 1995	Neurovascular abnormalities in streptozotocin-diabetic rats	When applied locally ET-1reduces axonal conduction by affecting the epineural microvessels which may act as a risk factor for diabetic neuropathy by impairing nerve perfusion.	[16, 17]
Blasi *et al.,* 2014	Endothelin-1 induced focal ischemic lesion in WT and NOTCH3 knockout mice	Increased level of ET-1 causes CBF deficit, BBB opening and lesion in white matter. It causes neurodegeneration and microglial infiltration leading to sustained recognition memory deficit.	[18]

Amtul *et al.,* 2019	Endothelin-1 induced ischemia (ET1) in the striatum	In thalamus, elevated astroglial expression, vascular deterioration, BBB disturbances and manifestation of pyknotic neurons causes an interferencein thalamus-hippocampal associationleading to working memory and short-term memory impairment. In hippocampus, CA1 region gets damaged due to origination of afferent projections from medial septum and basal forebrain to CA1 and fornix. This leads to cellular and vascular degeneration.	[19]
Hung *et al.,* 2015	Transient middle cerebral artery occlusion mediated neurologic and cognitive deficit in GET-1 mice	An in-vitro study showed that overexpression of ET-1 by astrocytic cells leads to amyloid secretion after ischemic condition and stimulates both endothelin A as well as endothelin B receptors in P13K/AKT-dependent manner. This shows a possibility of astrocytic ET-1 in dementia to have an association with stroke by astrocyte-derived amyloid production.	[20]
Barker *et al.,* 2014	Age-matched post-mortem cohorts of Alzheimer's disease and vascular dementia	Among three cohort studies the white matter perfusion was associated with ET-1 concentration. The concentration of ET-1 were found reduced in AD but the case was not the same with vascular dementia.	[21]
Palmer *et al.,* 2013	Primary cultures of human brain endothelial cells	The outcome of the study both Aβ40 and Aβ42 are responsible for causing a noticeable increment in ET-1 release especially Aβ40. The cerebral vasoconstriction caused by Aβ accumulation concludes to an elevation in both ECE-1 activity and ET-1 production via free radical pathways.	[22]
Freeman *et al.*, 2016	Long-Term Cognitive Impairment in a Model of Experimental Cerebral Malaria	This study has displayed that an ETA receptor antagonist was found to inhibit experimental cerebral malaria-induced neurocognitive impairments also with an improved survival. ETA antagonist not only blocked blood-brain barrier disruption but also ceased cerebral vasoconstriction during experimental cerebral malaria. It also reduced brain endothelial activation, by diminishing brain microvascular congestion. An exogenous administration of endothelin-1to P. berghei NK65-infected mice, displayed experimental cerebral malaria-like memory deficits. This data leads to a conclusion that ET-1 has a crucial role in evolution of cerebrovascular and cognitive impairments with experimental cerebral malaria.	[23]

CONCLUSION

Endothelin-1, a potent vasoconstrictor is solemnly responsible for memory loss. The current data presented in this review shows that how ET-1 is responsible for cognitive dysfunction through various mechanisms. The involvement of ET-1 in the pathogenesis of endothelial dysfunction associated with elevated Aβindicates the potential for endothelin receptor antagonists in the treatment of AD.

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