ISSN: 2687-8100
DOI: 10.33552/ABEB.2019.03.000559
Archives in Biomedical Engineering & Biotechnology
Iris Publishers

Mini Review

ET-traps-a Novel Therapeutic for Treatment of Neurological Disorders

Arjun Jain[1,2]*

[1]Department of Physiology, Development and Neuroscience, United Kingdom

[2]Accelerate Cambridge, Judge Business School, United Kingdom

***Corresponding author:** Arjun Jain, Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, United Kingdom. Email: arjun.jain@cantab.net

Received Date: October 24, 2019

Published Date: November 06, 2019

Abstract

Different neurodegenerative disorders affect millions of people around the world and currently there is no cure for them. Certain neurodegenerative conditions are associated with pathologically elevated Endothelin (ET)-1 levels. There are currently various drugs in use to block the ET system, but these are associated with various side effects. In this paper, the potential use of ET-traps is discussed, which provide a potent way of lowering the pathologically elevated ET-1 levels found in these different neurodegenerative disorders and are non-toxic for use.

Keywords: Endothelin-1; ET-traps; Neurodegenerative disorders; Multiple sclerosis; Alzheimer's disease; Parkinson's disease; Amyotrophic lateral sclerosis

Abbreviations: Aβ: Amyloid Beta; AD: Alzheimer's Disease; ALS: Amyotrophic Lateral Sclerosis; ET-1: Endothelin-1; BBB: Blood Brain Barrier; CBF: Cerebral blood flow; MS: Multiple Sclerosis; PD: Parkinson's Disease

Introduction

The ET-traps are molecular constructs that have previously been shown to potently and significantly sequester endothelin (ET)-1 [1]. Further work then showed that the ET-traps effectively returned different markers of diabetes disease pathology back to control, non-disease levels [2,3].

Discussion

Increased ET-1 in neurodegenerative disorders

There are elevated levels of ET-1 in neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple Sclerosis (MS) [4]. It has previously been shown that increased levels of ET-1 in MS resulted in reduced cerebral blood flow (CBF) [5]; given that ET-1 is a potent vasoconstrictor [6], it is unsurprising that it can compromise CBF. Use of an ET-antagonist, such as Bosentan reversed certain markers of disease pathology in MS. CBF was significantly lower in patients with MS than in control subjects and increased to control values after administering bosentan. Therefore, the reduced CBF in MS appears to be mediated by ET-1, and ET-traps, which potently and significantly bind and reduce the levels of circulating ET-1, could become a potential therapy for MS.

In addition to the reduction in CBF caused by circulating ET-1, the increase in ET-1 levels in the brain itself is caused by the release of ET-1 from astrocytes in brain lesions. It remains to be tested whether ET-traps can cross the blood–brain barrier (BBB). Previous work showed that not only the size but also the level of how hydrophobic a molecule is both determine whether a molecule would be able to cross the BBB [7]. Given that the ET-traps are both small in size (37.1 kDa) and are hydrophobic in nature (37.1%), it is likely that they would be able to cross the BBB. Furthermore, as has been previously reported [3], the ET-traps potently and significantly sequester increased ET-1 levels in the blood. This in turn would reduce the levels of the increased reactive white blood cells that freely cross the cerebral spinal fluid and BBB. The white blood cell count is increased by inflammation [8] and ET-1 is a potent inducer of inflammation [9]. This increase in inflammation is characterized by increases in the levels of reactive white blood cells [9] and systemic inflammation, which affects different organs in the body

[10]. The various neurodegenerative disorders mentioned earlier are all associated with systemic inflammation. Thus, a tool such as ET-traps could have an efficacious effect by reducing pathologically elevated ET-1 levels.

In addition to MS, there are various studies showing an important role for systemic inflammation in the pathogenesis of AD. AD is a common cause of dementia, accounting for ~60–90% of all cases [11]. Different disease-modifying therapies for AD, such as immunotherapy against amyloid beta (Aβ), are now under investigation and have been tested in clinical trials, although with little success so far. Therefore, there is an urgent need to identify new therapeutics. Previous AD research using disease models and clinical studies has demonstrated a significant contribution of inflammation in general to pathological features and symptoms of AD.

Systemic inflammation is also an important pathological factor in PD [12,13]. Ferrari and Tarelli reported that systemic inflammation triggers exacerbation of damage in the brain in several neurodegenerative diseases, including PD [13]. Chiang et al. revealed that damage to the white matter of patients with PD is associated with systemic inflammation [12].

Another neurodegenerative disease associated with pathologically elevated ET-1 levels [14] is amyotrophic lateral sclerosis (ALS) which is a fast progressive and disabling neurodegenerative disease that is characterized by upper and lower motor neuron loss, leading to respiratory insufficiency and death after a few years [15]. There is currently no cure for this disease. Current treatments merely delay a patient's disease progression. Given that ET-1 level is significantly elevated in ALS, perhaps the ET-traps that have been shown to significantly sequester the increased levels of ET-1, may be a cure for this debilitating and devastating disease. Previous in vivo work has also shown that the ET-traps have a positive effect on cardiovascular markers of ventricular function [3] and given that ALS leads to respiratory insufficiency, ET-traps may well help with this condition.

Conclusion

Given the increased levels of ET-1 in different neurodegenerative disorders and that this increased ET-1 is a cause of pathology in these diseases, ET-traps, which potently and significantly reduce the circulating levels of ET-1, would have a therapeutic effect in ameliorating disease pathology.

Acknowledgement

AJ would like to thank Vidhi Mehrotra for her help and support.

Conflict of Interest

AJ is a member of Accelerate Cambridge.

References

1. Jain A (2017) Creating a Soluble Binder to Endothelin-1 based on the natural ligand binding domains of the endothelin-1 (Gprotein-coupled) receptor. International Journal of Peptide Research and Therapeutics 107-114.
2. Arjun J, Chen S, Yong H, Chakrabarti S (2018) Endothelin-1 traps potently reduce pathologic markers back to basal levels in an in vitro model of diabetes. Journal of Diabetes & Metabolic Disorders 17(2): 189-195.
3. Jain A, Mehrotra V, Jha I, Jain A (2019) *In vivo* studies demonstrate that endothelin-1 traps are a potential therapy for type I diabetes. Journal of Diabetes and Metabolic Disorders. 133-143.
4. Jain A (2013) Endothelin-1-induced endoplasmic reticulum stress in disease. J Pharmacol Exp Ther 346(2): 163-172.
5. Dhaeseleer M (2013) Cerebral hypoperfusion in multiple sclerosis is reversible and mediated by endothelin-1. Proc Natl Acad Sci USA 110(14): 5654-5658.
6. Lin YJ, Kwok CF, Juan CC, Hsu YP, Shih KC, et al. (2014) Angiotensin II enhances endothelin-1-induced vasoconstriction through upregulating endothelin type A receptor. Biochem Biophys Res Commun, 451(2): 263-269.
7. Banks WA (2009) Characteristics of compounds that cross the blood-brain barrier. BMC Neurol 9 (Suppl 1): S3.
8. Farhangi MA, Keshavarz SA, Eshraghian M, Ostadrahimi A, Saboor-Yaraghi AA. (2013) White blood cell count in women: relation to inflammatory biomarkers, haematological profiles, visceral adiposity, and other cardiovascular risk factors. J Health Popul Nutr 31(1): 58-64.
9. Molero L, Farre J, Garcia-Mendez A, Jimenez Mateos-Caceres P, Carrasco Martin C, Milláas I, Navarro F, et al. (2003) Endothelin-1 induced proinflammatory markers in the myocardium and leukocytes of guinea-pigs: role of glycoprotein IIB/IIIA receptors. Cardiovasc Res 57(1): 109-118.
10. Hasturk H, Kantarci A, Van Dyke TE (2012) Oral inflammatory diseases and systemic inflammation: role of the macrophage. Front Immunol 3: 118.
11. (2013) Alzheimer's disease facts and figures. Alzheimers Dement 9(2): 208-245.
12. Chiang PL, Chen HL, Lu CH, Chen PC, Chen MH, et al. (2017) White matter damage and systemic inflammation in Parkinson's disease. BMC Neurosci 18(1): 48.
13. Ferrari CC, Tarelli R (2011) Parkinson's disease and systemic inflammation. Parkinsons Dis 2011: 436813.
14. Ranno E, D Antoni S, Spatuzza M, Berretta A, Laureanti F, et al. (2014) Endothelin-1 is over-expressed in amyotrophic lateral sclerosis and induces motor neuron cell death. Neurobiol Dis 65: 160-171.