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Review article

The pathophysiological role of astrocytic endothelin-1

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ABSTRACT

In the normal central nervous system, endothelin-1 (ET-1) is found in some types of neurons, epithelial cells of the choroid plexus, and endothelial cells of microvessels, but it is usually not detectable in glial cells. However, in different pathological conditions, astrocytes adapting a reactive phenotype express high levels of ET-1 and its receptors, mainly the ET_B receptor. ET-1 released by reactive astrocytes appears mainly to have neurodeleterious effects by mechanisms that include constriction of cerebral arterioles leading to impairment of the cerebral microcirculation, increase of blood brain barrier permeability, inflammation, excitotoxicity, impairment of fast axonal transport, and astrogliosis. A few studies in rodents found that ET-1 increased the astrocytic expression of brain-derived neurotrophic factor, glial cell-line derived neurotrophic factor and neurotropin-3, and the production of endocannabinoids. However, whether this occurs in physiological or pathological conditions is unclear. This review summarizes current knowledge about the role of the astrocytic ET-1 system in acute and chronic neurological conditions, including multiple sclerosis, ischemic stroke and hypoxic/ischemic brain injury, traumatic brain injury, subarachnoid hemorrhage, Alzheimer's disease, Binswanger's disease and post-stroke dementia, amyotrophic lateral sclerosis, and CNS infections. Counteracting the harmful effects of astrocytic ET-1 may represent a promising therapeutic target for mitigating secondary brain damage in a variety of neurological diseases. We also briefly address the role of astrocytic ET-1 in astrocytic tumors and pain.

Contents

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; Akt, protein kinase B; ALS, amyotrophic lateral sclerosis; AP-1, activator protein-1; BBB, blood brain barrier; BDNF, brain-derived neurotropic factor; CB, cannabinoid; CBF, cerebral blood flow; CSF, cerebrospinal fluid; ECE, endothelin-converting enzyme; ET, endothelin; EAE, experimental autoimmune encephalomyelitis; ERK, extracellular signal-regulated kinase; GDNF, glial cell line-derived neurotropic factor; HIV, human immunodeficiency virus; HIF-1, hypoxia inducible factor-1; IL, interleukin;; IP3, inositol triphosphate; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MMP, matrix metalloproteinase; MS, multiple sclerosis; OPCs, oligodendrocyte progenitor cells; PI 3-kinase, phosphoinositide 3-kinase; RCT, randomized controlled trial; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TNFα, tumor necrosis factor alfa; VEGF, vascular endothelial growth factor.

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1. Introduction

1.1. Synthesis of endothelins

The endothelin (ET) family comprises three isoforms of 21-amino acid cyclic peptides that are the products of different genes. They all contain an N-terminal which determines the affinity for their receptor and a C-terminal which mediates the receptor binding itself (Khimji and Rockey, 2010). The first ET, now denoted as ET-1, was initially identified in conditioned media from primary cultures of porcine aortic endothelial cells, as a very potent endogenous vasoconstrictor (Yanagisawa et al., 1988). Shortly afterwards, ET-2 and ET-3 differing from ET-1 in two and six amino acid residues were identified (Ehrenreich et al., 1991; Kedzierski and Yanagisawa, 2001).

The biosynthetic pathway of ETs proceeds via a range of molecular processes. Through transcription and translation, the large precursor proteins of about 200 amino acid residues in size, known as pre-pro-ETs, are synthesized from the pre-pro-ET gene. These precursor proteins are cleaved by a neutral endopeptidase to form an inactive precursor of about 37-41 amino acids, called big ET. The rate-limiting step is the conversion of big ET to the mature peptides, through a family of ET-converting enzymes (ECEs). Three isoforms of ECE have been reported, namely ECE-1, ECE-2 and ECE-3, who differ from each other in cellular distribution, localization and substrate specificity. ECE-1 and ECE-2 are the most prominent isoforms, both showing preference for big-ET1. ECE-1 is mainly expressed in endothelial cells and smooth muscle cells, but has also a weak neuronal and astrocytic expression. ECE-2 has mainly been found in neurons (Kedzierski and Yanagisawa, 2001; Khimji and Rockey, 2010).

1.2. Endothelin receptors

ETs exert their actions through two subtypes of seven-transmembrane G-protein coupled receptor subtypes, known as ET_A and ET_B receptors. The deduced amino acid sequences for the two human receptors, which have been cloned and isolated, display 59% similarity. When studying agonists and antagonists, it should be taken into consideration that the amino acid sequences of both ET receptors differ between humans and other species; for example by 9% between human and rat ET_A receptors and by 12% for the ET_B receptors (Davenport, 2002). The ET_A receptor binds ET-1 and ET-2 with a higher affinity than ET-3. The ET_B receptor has equal affinities for the three ET isoforms (Khimji and Rockey, 2010).

Signaling mechanisms of ET_A receptors are complex and may vary from tissue to tissue (Khimji and Rockey, 2010). The classical signaling pathway of ET_A receptors consists of activation of phospholipase C, leading to the formation of inositol triphosphate (IP3) and diacylglycerol from phosphatidylinositol 4,5 bisphosphate. However, in some tissues, for example ventricular myocytes and renal medullary interstitial cells (Clerk and Sugden, 1997; Friedlaender et al., 1993), stimulation of ET_A receptors activates phosphatidyl choline-specific phospholipase yielding phosphatidic acid, which is dephosphorylated by phosphatidic phosphorylase to diacylglycerol. Activation of ET_A receptors in neoplastic cells has been shown to stimulate tyrosine kinases resulting in the induction of the mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) pathway (Nelson et al., 2003). Stimulation of the ET_B receptor activates the phosphatidylinositol-3-kinase (PI3-K)/Akt pathway (Khimji and Rockey, 2010).

Both ET receptor subtypes are rapidly desensitized by phosphorylation through the G protein–coupled receptor kinase type 2. Desensitization occurs within 4 min with either the human ET_A receptor or ET_B receptor, corresponding temporally with agonist-induced phosphorylation of each receptor (Freedman et al., 1997). Both ET_A and ET_B receptors are internalized via clathrin-dependent pathways, and subsequently ET_A receptors are recycled back to the surface, whereas ET_B receptors are sorted to the lysosome and degraded (Bremnes et al., 2000; Gregan et al., 2004). A third type of receptor, namely ET_C, has been cloned from Xenopus laevis oocytes and has an affinity higher for ET-3 than ET-1 (Karne et al., 1993). However, no homologue has been identified in mammalian tissues.

1.3. ET-1: a key regulator of vascular function

ET-1 is the only isoform that is released by endothelial cells lining the blood vessels. In the vasculature, ET_A receptors reside on vascular smooth muscle cells and their activation mediates vasoconstriction. This is mediated through activation of phospholipase C, leading to the formation of inositol triphosphate (IP3), which induces the release of Ca^{2+} from the endoplasmatic reticulum stores. The increase in cytosolic Ca^{2+} causes contraction of the vascular smooth muscle cells (Khimji and Rockey, 2010). Ca^{2+} −independent pathways leading to cellular contraction,