J Pharmacol Sci **118**, 401 – 407 (2012)

Journal of Pharmacological Sciences

Current Perspective

Regulations of Astrocytic Functions by Endothelins: Roles in the Pathophysiological Responses of Damaged Brains

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Received December 5, 2011; Accepted January 12, 2012

Abstract. The receptors for endothelins (ETs) are classified into the ET_A and ET_B types. ET_B receptors are highly expressed in astrocytes, but pharmacological usages of this receptor are not clarified. In this article, recent studies on the pathophysiological roles of astrocytic ET_B receptors in the brain are reviewed. The administration of ET_B agonists and antagonists in nerve injury models showed that several astrocytic functions are regulated by ET_B receptors. The activation of ET_B receptors causes morphological alterations and proliferation of cultured astrocytes. Astrocytes produce various bio-active substances that can affect damage to nerve tissues. ETs stimulate the production of neurotrophic factors by astrocytes. This action improves impaired brain functions. On the other hand, the production of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF), which induce brain edema, also are stimulated by ETs. These findings indicate that astrocytic functions are effectively regulated by modulations of ET_B receptors. In brain insults and neurodegenerative diseases, these functions of astrocytes affect the protection and repair of damaged nerve tissues. Thus, astrocytic ET_B receptors could be a target for novel types of neuroprotective drugs.

Keywords: ET_B receptor, astrocyte, neuroprotection, brain edema, endothelin

1. Introduction

Endothelins (ETs) belong to a vasoconstrictor family originally found as vascular endothelial cell–derived peptides. Many studies have shown that ETs are produced by various types of cells and affect cellular functions in many tissues besides vascular tissues. The increases in ETs have been observed in several pathological conditions and the involvement of ETs in the pathogenesis of vasospasm, cardiac hypertrophy, vascular re-modeling, tumors, and renal failure have been reported (1). The receptors for ETs are classified into ET_A and ET_B types. Several agonists and antagonists for the ET receptors have been made; some of them are now in clinical use (Table 1) (1). Because of the potent vasoconstricting actions, much attention has been focused on the possible roles of ET_A receptors. ET_A receptors are the target for drugs that improve vasospasms and reduce blood flow in the lungs, kidneys, and brain. On the other hand, ET_B receptors are highly expressed in the brain, especially in astrocytes (2, 3). However, the roles of ET_B receptors in brain functions are less clarified.

Astrocytes, a type of glial cell in the brain, play pivotal roles to support functions of neuronal cells, such as viability, maturation, excitation, and re-generation. These astrocytic functions are altered in several brain pathologies, which can be both detrimental and beneficial to damaged nerve tissues (4). Studies using nerve injury models provided several experimental evidences that control of the astrocytic functions improves brain pathologies, suggesting management of astrocytes as a therapeutic strategy for neurological disorders (5). Administrations of ET agonists or antagonists into animal brains showed that activation of brain ET_B receptors promotes functional alterations of astrocytes (6 – 9). Based on these findings, ET_B receptors may be an effective target to control astrocytic functions in the damaged brain. In this article, recent investigations of the

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Published online in J-STAGE on March 14, 2012 (in advance)
doi: 10.1254/jphs.11R13CP

Invited article

Table 1. Agonists and antagonists for ET receptors

	Agonists	Antagonists
ET non-selective	ET-1	SB209670, bosentan, TAK-044, tezosentan
ET_A-selective	sarafotoxin 6b	ambrisentan, sitaxsentan, clazosentan, darusentan
ET_B-selective	sarafotoxin 6c, IRL-1620, BQ3020, $Ala^{1,3,11,15}$-ET-1	BQ788, IRL-2500, A-192621, RES-701-1

pathophysiological roles of brain ET_B receptors are reviewed and their significance as a target molecule of "neuroprotective drugs" is discussed.

2. ET ligands and receptors in brain

The ET peptide family consists of three isopeptides, ET-1, ET-2, and ET-3. In the adult brain, ET-1 and ET-3 are both expressed, with ET-1 being predominantly expressed. Similar to peripheral tissues, levels of brain ET-1 increase in pathological states such as Alzheimer's disease, Parkinson's disease, subarachnoid hemorrhage (SAH), brain stroke, and head trauma (2, 3). Immunohistochemical observations of damaged nerve tissues showed that "reactive" astrocytes produced ET-1, while resting astrocytes rarely produced ET-1 (3). Thus, reactive astrocytes serve as a major source of ET-1 in brain pathologies.

The cellular distributions of the ET_A and ET_B receptors are different in the brain. ET_A receptors are predominantly expressed in brain vessels. The activation of brain ET_A receptors constricts brain vessels, which appears as a vasospasm of brain arteries after stroke, SAH, and head trauma. ET_A antagonists prevent this vasospasm in animal models of brain injuries and the possible beneficial effects of some ET_A antagonists on brain dysfunctions by stroke and SAH have been examined in clinical trials (1). ET_B receptors are the prominent ET receptor subtype in the brain with high expression levels in astrocytes (2). Many astrocytic responses are modulated by activated ET_B receptors, indicating the important roles of ET_B receptors in regulating astrocytic functions. The expression levels of astrocytic ET_B receptors are increased after brain injuries (10). The up-regulation of astrocytic ET_B receptors shows the significant roles that this receptor plays in brain pathologies. The production of astrocytic ET-1 is stimulated by signal molecules released at injured sites. Ehrenreich et al. (11) showed that ETs also stimulated ET-1 production in astrocytes, suggesting that ETs regulate astrocytic functions as autocrine factors.

3. Stimulation of ET_B receptors promotes the conversion to reactive astrocytes

Astrocytes often change their phenotype to become "reactive astrocytes" in brain pathological states (4). The conversions to reactive astrocytes accompanied by their morphological alterations are characterized by the hypertrophy of cell bodies and glial processes. Besides the morphological properties, a notable function of reactive astrocytes is to produce a variety of signal molecules, including neurotrophic factors, growth factors, cytokines, chemokines, and proteases (Table 2). Because these signal molecules affect neuronal viability, the re-modeling of brain vascular tissue and the activation of inflammatory cells, conversion to reactive astrocytes can determine the prognoses for damaged brains (4, 5). Several reports indicate that ETs promote the conversion to reactive astrocytes through ET_B receptors. The injection of $Ala^{1,3,11,15}$-ET-1, a selective ET_B receptor agonist, into the rat striatum increased the number of reactive astrocytes (6). Despite this activation of astrocytes, $Ala^{1,3,11,15}$-ET-1 did not induce neuronal degradation or activate microglia, which indicates that the ET_B agonist–induced astrocytic activation is not a consequence of neuronal damage. In stab wound and demyelination brain injuries, BQ788, a selective ET_B antagonist, prevented the generation of reactive astrocytes (7, 12). Bosentan and SB209670, non-selective ET antagonists, also reduced lesion-induced increases of reactive astrocytes (12, 13). Many signal molecules may induce reactive astrocytes (4, 5). Among these factors, ETs have the characteristic of being produced by reactive astrocytes. This autocrine property may suggest a possible role of ETs in astrocytic activation to prolong the activation states, even after the effects of other activating factors are largely reduced.

4. Astrocytic functions are regulated by ET_B receptors

Accompanied by the conversion to the reactive phenotype, astrocytic functions are altered. These astrocytic functions include proliferation, cytoskeletal re-organization, and the production of extracellular signal molecules. Recent reports showed that alterations of these astrocytic

Table 2. ETs regulate the production of various signal molecules in cultured astrocytes and the brain

		Cultured astrocytes	Brain	References
Neurotrophic factors	NGF	↑	↑	(17), (20)
	NT-3	↑	↑	(18)
	bFGF	↑	—	(17), a)
	BDNF	↑	↑	(17), b)
	GDNF	↑	↑	(17), (19)
Cytokines, chemokines	IL-1β	↑		c)
	IL-6, TNFα	↑		d)
	CCL2 (MCP-1), CXCL1 (CINC-1)		↑	e)
VEGFs	VEGF-A		↑	(23)
	VEGF-B		—	(23)
MMPs	MMP2, MMP9	↑	↑	(22)
	MMP3	↑	—	(22), f)
Aquaporins	AQP4	↓	↓	(27), (28)
	AQP9	↓	—	(27), (28)
Others	TIMP1, TIMP3	↑	↑	g)
	COX2	↑		h)
	iNOS	↑		i)
	↑: increased ↓: decreased —: unchanged			

Effects of exogenously applied ETs in cultured astrocytes and in the brain are summarized. IL: interleukin, TNF: tumor necrosis factor, TIMP: tissue inhibitor of matrixmetalloproteinase, COX2: cyclooxygenase-2, iNOS: inducible NO synthase. [a)]Biesiada et al., *J Biol Chem*. 1996;271:18576–18581. [b)]Koyama et al., *J Neurosci Res*. 2005;80:809–816. [c)]Didier et al., *J Neurochem*. 2003;86:246–254. [d)]Morga et al., *J Neurochem*. 2000;74:603–612. [e)]Koyama et al., *Neuroreport*. 2007;18:1275–1279. [f)]Koyama & Tanaka, *Biochem Biophys Res Commun*. 2008;371:659–663. [g)]Koyama et al., *Neuroscience*. 2007;147:620–630. [h)]Koyama et al., *J Neurochem*. 1999;73:1004–1011. [i)]Wang et al., *J Cell Physiol*. 2011;226:2244–2256.

functions are induced by activating ET_B receptors.

4.1. Cytoskeletal re-organization

Reactive astrocytes are characterized by hypertrophic cell bodies and glial processes. The cellular morphology is altered by the re-organization of cytoskeletal proteins. ETs cause cytoplasmic expansions of stellate astrocytes, which accompany re-organization of cytoskeletal actin filaments (14). After the actin re-organization of cultured astrocytes, ETs stimulate formations of focal adhesions (FAs) (14). FAs are transmembrane protein complexes where actin filaments connect to extracellular matrix (ECM) proteins through integrins. FAs serve as receptors for ECM proteins and trigger adhesion-dependent intracellular signals to regulate cell adhesion, migration, and proliferation. The formation of astrocytic FAs indicates that ETs can affect the cell adhesion–dependent astrocytic functions triggered by interactions with ECM proteins (see below).

4.2. Proliferation

Reactive astrocytes are highly proliferative. Uesugi et al. showed that bromodeoxiuridine incorporation into astrocytes in a rat spinal cord injury model was inhibited by SB209670 (13). This study found that ETs induce the G1/S cell cycle progression of astrocytes in pathological conditions. The potent mitogenic activities of ETs are observed in cultured astrocytes. In the astrocytic proliferation, protein kinase C and extracellular signal-regulated kinase (ERK) mediate the ET_B receptor signals to the progression of the cell cycle. Beside these cell adhesion–independent signal pathways, cell adhesion–dependent signals triggered by FAs also regulate the G1/S phase cell cycle progression. Focal adhesion kinase (FAK), a tyrosine kinase associated with FAs, is a key molecule in cell adhesion–dependent proliferation. ETs activate astrocytic FAK, and the activation is inhibited by a disruption of actin filaments (14, 15). We found that expression of dominant-negative FAK mutants in cultured astrocytes prevented the ET-induced G1/S cell cycle progression (16). These findings indicate that FAK is required for

adhesion-dependent astrocytic proliferation by ETs.

The expressions of cyclin D proteins are increased in the late G1 phase, which triggers the G1/S phase progression. While ETs increase both cyclin D1 and D3 expression levels in cultured astrocytes (15), their signal mechanisms in astrocytic ET_B receptors are different. The ET-induced activation of FAK is required for the expression of astrocytic cyclin D3, but not cyclin D1 (15). On the other hand, the expression of astrocytic cyclin D1 is stimulated by ERK-mediated adhesion-independent mechanisms. Thus, ETs can activate both cell adhesion–dependent and –independent mechanisms in astrocytes. This cooperative action of two distinct signal pathways may underlie the potent mitogenic effects that ETs have on astrocytic proliferation.

4.3. Production of neurotrophic factors

Astrocytes produce various kinds of neurotrophic factors. In nerve tissues injured by neurodegenerative diseases and brain insults, the activities of astrocytes to produce neurotrophic factors are enhanced. Because neurotrophic factors support the viability and re-generation of injured nerve cells, the induction of astrocyte-derived neurotrophic factors are likely an effective therapeutic strategy to improve brain functions impaired by neurodegenerative diseases and brain insults. The intracerebroventricular administration of $Ala^{1,3,11,15}$-ET-1 increased the production of brain-derived neurotrophic factor (BDNF), glial cell line–derived neurotrophic factor (GDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) in rat brain (17, 18). Immunohistological observations of the $Ala^{1,3,11,15}$-ET-1–infused rat brains showed that these neurotrophic factors were produced by reactive astrocytes. In cultured astrocytes, ETs stimulated the production and release of BDNF, GDNF, NGF, and NT-3 through ET_B receptors (17 – 20). These findings indicate that activation of astrocytic ET_B receptors effectively increases production of various kinds of neurotrophic factors in nerve tissues. The application of neurotrophic factors into damaged brains is a promising therapeutic strategy for neurodegenerative diseases and brain insults (21). Thus, the stimulations of neurotrophic factor productions by ETs are expected to have beneficial actions on nerve functions impaired by brain pathologies.

4.4. Production of vascular permeability factors

Surrounding brain vessels by end-feet of glial processes, astrocytes make close contact with brain vascular endothelial cells across basal membranes. This microstructure is responsible for the blood–brain barrier (BBB). While restricted influxes of blood components into brains are built by a low permeability to brain vascular endothelial cell layers, their permeability is not static, but increased by astrocyte-derived permeability factors (4). In the acute phase of brain stroke, SAH and head trauma, brain microvessels show an excessively high permeability and allow plasma proteins to enter brains. The influx of plasma proteins, followed by increases in brain water content, is a pathogenesis of vasogenic brain edema. With this increased permeability of brain microvessels and vasogenic brain edema, various permeability factors including matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), and chemokines are produced by reactive astrocytes (4). In brain stroke and head trauma models, the expression levels of MMPs, an endoprotease family cleaving ECM proteins, are increased in reactive astrocytes. The increases in MMP activities degenerate the basal membranes around brain microvessels and reduce the integrity of vascular endothelial cells. ETs stimulate the production and activities of MMP2 and MMP9 in rat brains and

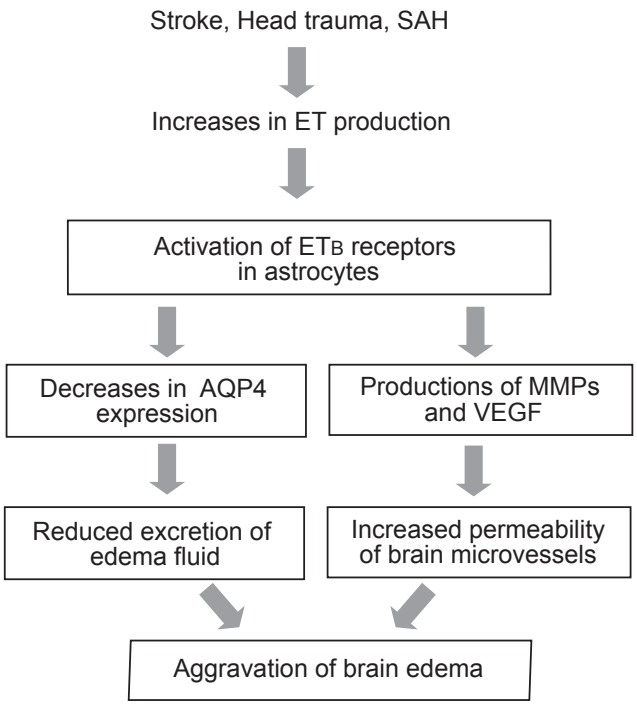

Fig. 1. Possible roles of brain ET_B receptors in brain edema. In the acute phase of stroke, head trauma, and SAH, the production of ET-1 is enhanced in the damaged nerve tissues. The activation of brain ET_B receptors by increased ET-1 levels stimulates the production of MMP2, MMP9, and VEGF-A in reactive astrocytes. These molecules increase the permeability of brain microvessels and allow the influx of plasma proteins into the brain. This causes vasogenic brain edema. Simultaneously, activation of ET_B receptors decreases AQP4 expression in astrocytes, which reduces the efflux of water from the edematous brain. Therefore, activation of brain ET_B receptors aggravates brain edema in stroke, SAH, and head trauma.

in cultured astrocytes (22). Reactive astrocytes also produce VEGFs, potent permeability factors with high proliferative activity on vascular endothelial cells. The administration of an ET_B agonist into the rat brain enhanced the expression of astrocytic VEGF-A and activated VEGF receptors in brain vascular endothelial cells (23). These findings suggest the involvement of astrocytic ET_B receptors in the production of MMPs and VEGF in brain pathologies. Because inhibition of MMPs and VEGF signals prevented the elevated vascular permeability, expressions of these factors are likely pathogenic for vasogenic brain edema (24, 25). The production of brain ETs increases in the acute phases of brain insults (3). The activation of ET_B receptors by the increased ETs can aggravate brain edema by increasing MMP and VEGF production in astrocytes.

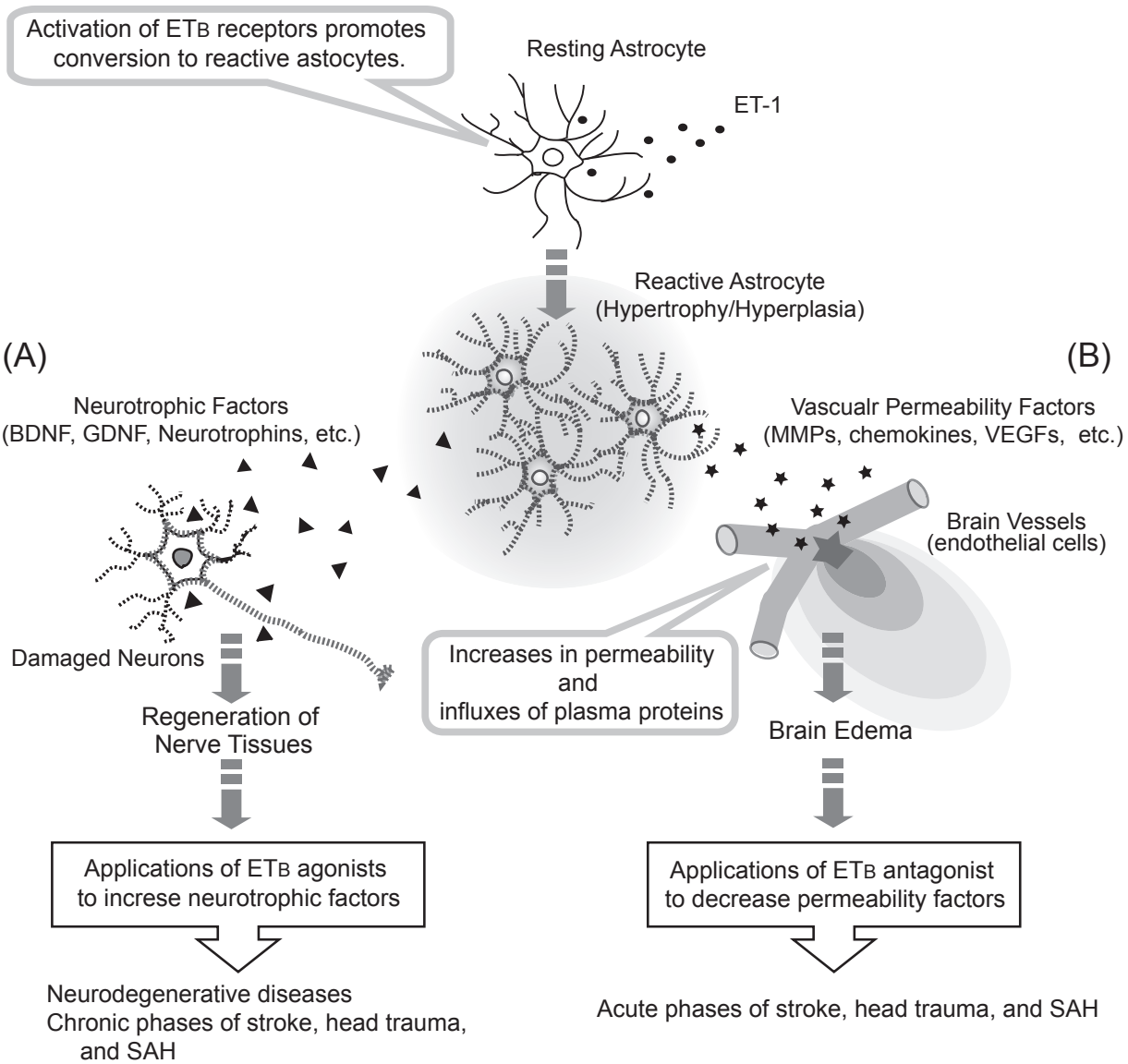

Fig. 2. Two possible clinical applications of ET receptor agonists and antagonists in brain pathologies. In damaged nerve tissues, astrocytic ET_B receptors are activated and a variety of signal molecules is produced by reactive astrocytes. Because the astrocyte-derived signal molecules are involved in the pathophysiological responses of the damaged brain, management of this astrocytic function can be a therapeutic strategy of neuroprotective drugs. Two different applications of ET_B receptor–related drugs are expected to show beneficial actions in brain pathologies. A: Applications of ET_B agonists: Activation of astrocytic ET_B receptors increases the production of neurotrophic factors. Enhancement of this function in brain pathologies promotes the re-generation of damaged neurons. B: Applications of ET_B antagonists: The activation of ET_B receptors increases the levels of vascular permeability factors and reduces AQP4 levels. Because the ET-induced alterations of astrocytes aggravate vasogenic brain edema, application of ET_B antagonists may show preventive effects of brain edema in the acute phase of brain insults.

In addition to the inhibition of vascular permeability factors, modulations of aquaporin-4 (AQP4), a major sub-type of water channel proteins in the brain, is another target to prevent brain edema. AQP4 is expressed in astrocytic end-feet and regulates the water movements between blood and brain fluids. Studies on AQP4-null mice showed that astrocytic AQP4 serves as an efflux pathway for brain fluid from edematous areas (26). In the acute phase of brain insults, astrocytic AQP4 expression is decreased, which aggravates brain edema to reduce the water effluxes from the brain. The activation of astrocytic ET_B receptors decreased the expression of AQP4 in the rat cerebrum and in cultured astrocytes (27, 28). The decreases in astrocytic AQP4 by ETs also support the notion that activation of ET_B receptors in the acute phase of brain insults is harmful by inducing vasogenic brain edema (Fig. 1).

5. ET_B receptors as a target of neuroprotective drugs

The management of brain pathophysiological responses is a basic therapeutic strategy to protect nerve tissues against brain insults and neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. By releasing various extracellular signal molecules, reactive astrocytes modulate many pathophysiological responses of nerve tissues. Some astrocyte-derived factors show detrimental actions in the damaged brain, whereas others show beneficial actions. As described above, the activation of astrocytic ET_B receptors stimulates the production of both detrimental and beneficial factors. As a target of neuroprotective drugs, astrocytic ET_B receptors could have two possible clinical applications in different states of brain pathologies (Fig. 2). One possible application is to block ET receptors in the acute phase of brain stroke, SAH, and head trauma. In this state, alleviations of vasospasm and brain edema are required for protection of nerve tissues. The activation of ET_B receptors stimulates MMP and VEGF production in astrocytes and decreases the expression of AQP4. Because these functional alterations of astrocytes lead to brain edema, a blockage of ET_B receptors would protect against the acute nerve damage. The increased ETs activate ET_A receptors in brain vessels and cause vasospasms. The effectiveness of ET_A receptor antagonists as neuroprotective drugs has been presented (1). As well as ET_A receptors, blockage of ET_B receptors can be a novel strategy to protect nerve tissues against brain insults.

The other possible application of ET_B receptors is to activate these receptors in the chronic phase of brain insults and in neurodegenerative diseases. In these states, promotion of tissue repair processes, that is, axonal elongation, synaptogenesis, and neurogenesis, is therapeutic, to allow recovery of brain functions. BDNF, GDNF, and neurotrophins stimulate the re-generation of neuronal cells in various brain regions. As recent studies have shown (17 – 20), the activation of astrocytic ET_B receptors can effectively increase the production of these neurotrophic factors. In addition to the effects on astrocytes, activating ET_B receptors have anti-apoptotic effects in neuronal cells (29) and proliferative actions in neuronal progenitors (30). These roles of ET_B receptors suggest that applications of ET_B-selective agonists can be a promising therapeutic strategy to recover brain function impaired by brain insults and neurodegenerative diseases.

6. Conclusions

Two decades have passed since the discovery of ETs, and now there are ET receptor antagonists for clinical use. Previous investigations of ETs have focused mainly on the roles of ET_A receptors in the circulatory system, while the roles of ET_B receptors in brain pathologies have been less studied. As described in this article, recent studies indicate the importance of ET_B receptors in the regulation of astrocytic functions. The management of astrocytes in pathological states improves brain damage (5). The modulations of many astrocytic functions by ETs suggest that ET_B receptors can be a novel target of neuroprotective drugs. Thus, the roles of astrocytic ET_B receptors in brain pathologies are pharmacologically interesting. Investigating astrocytic ET_B receptors may lead to the creation of novel neuroprotective drugs in the future.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research (C) from JSPS (21590108).

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