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Endothelin Receptors, Mitochondria and Neurogenesis in Cerebral Ischemia

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Abstract: *Background*: Neurogenesis is most active during pre-natal development, however, it persists throughout the human lifespan. The putative role of mitochondria in neurogenesis and angiogenesis is gaining importance. Since, ET_B receptor mediated neurogenesis and angiogenesis has been identified, the role of these receptors with relevance to mitochondrial functions is of interest.

Methods: In addition to work from our laboratory, we undertook an extensive search of bibliographic databases for peer-reviewed research literature. Specific technical terms such as endothelin, mitochondria and neurogenesis were used to seek out and critically evaluate literature that was relevant.

Results: The ET family consists of three isopeptides (ET-1, ET-2 and ET-3) that produce biological actions by acting on two types of receptors (ET_A and ET_B). In the central nervous system (CNS) ET_A receptors are potent constrictors of the cerebral vasculature and appear to contribute in the causation of cerebral ischemia. ET_A receptor antagonists have been found to be effective in animal model of cerebral ischemia; however, clinical studies have shown no efficacy. Mitochondrial functions are critically important for several neural development processes such as neurogenesis, axonal and dendritic growth, and synaptic formation. ET appears to impair mitochondrial functions through activation of ET_A receptors. On the other hand, blocking ET_B receptors has been shown to trigger apoptotic processes by activating intrinsic mitochondrial pathway. Mitochondria are important for their role in molecular regulation of neurogenesis and angiogenesis. Stimulation of ET_B receptors in the adult ischemic brain has been found to promote angiogenesis and neurogenesis mediated through vascular endothelial growth factor and nerve growth factor. It will be interesting to investigate the effect of ET_B receptor stimulation on mitochondrial functions in the CNS following cerebral ischemia.

Conclusion: The findings of this review implicate brain ET_B receptors in angiogenesis and neurogenesis following cerebral ischemia, it is possible that the positive effect of stimulating ET_B receptors in cerebral ischemia may be mediated through mitochondrial functions.

Keywords: Cerebral ischemia, endothelin, ET_B receptor, mitochondria, neurogenesis, nerve growth factor, vascular endothelial growth factor.

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1. INTRODUCTION

1.1. Endothelin

Endothelin (ET) was first isolated from porcine aortic endothelial cells and characterized as the most potent vasoconstrictor substance in 1988 [1]. It consists of 21 amino acid residues with two disulfide intramolecular bonds [1]. It was also found that there are 3 isopeptides of ET in the mammalian tissues: ET-1, ET-2 and ET-3 [1, 2]. All three endogenous isopeptides have since been implicated in a number of physiological and pathological roles including regulation of blood flow and pressure, apoptosis and immune modulation.

The biological responses of ET-1 are mediated through activation of two distinct G-protein-coupled receptors (GPCRs): ET_A and ET_B (Fig. **1**). These receptors consist of seven hydrophobic transmembrane domains, with an intracytoplasmic C terminus and an extracellular N terminus [3]. Variations in the C terminus account for differences in the binding affinities of the three isopeptides to each receptor. While all three ETs have equal affinity for the ET_B receptor, ET-3 has a lower affinity for the ET_A receptor compared to either ET-1 or ET-2 [4].

In the cardiovascular system, vascular smooth muscle cells have ET_A receptors which produce vasoconstriction *via* a biphasic increase in intracellular [Ca2+] [5]. ET_B receptors, on the other hand, are primarily located on vascular endothelial cells, where they are coupled to the activation of nitric oxide synthase (NOS) *via* calcium-calmodulin and protein tyrosine kinase-dependent mechanisms. This coupling causes a release of nitric oxide (NO) which in turn leads to vasodilatation [6]. Thus, ET_A and ET_B receptors have opposing roles in the vascular system (Fig. **1**). In a rat, vascular smooth muscle cells also have ET_B receptors, where along with ET_A receptors, they mediate vasoconstriction [7]. ET_B receptors are also located in the kidney, lung and the brain [8].

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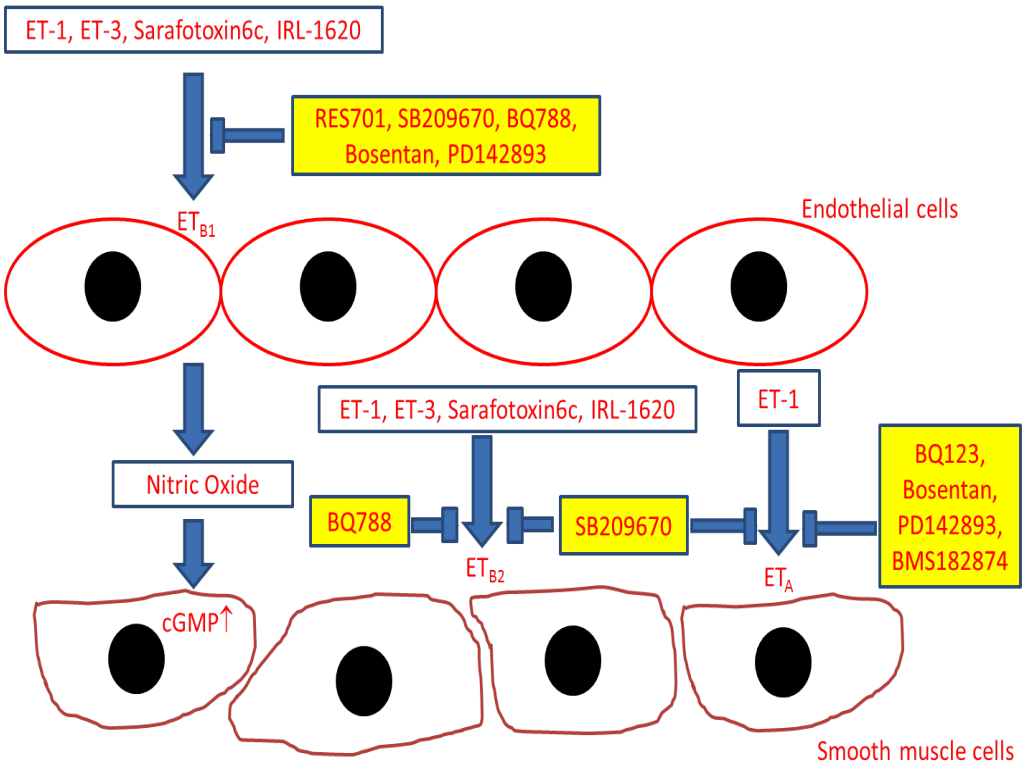

Fig. (1). There are two types of ET receptors: ET_A and ET_B. ET_A receptors are found on the vascular smooth muscle and are vasoconstrictor. ET_B receptors are identified as ET_{B1} and ET_{B2} based upon pharmacological response to RES701. RES701 was found to block ET_{B1} (located on vascular endothelial cells and function as dilator) but not ET_{B2} (located on vascular smooth muscle cells and function as constrictor).

Remarkably, ET-1 is produced in significant amounts by the prostate and metastatic cancers. It is also made in high concentrations by the central nervous system (CNS). Neurons, astrocytes and glial cells of the CNS produce significant amount of ET-1 [8]. The wide spread distribution of ET-1 and its receptors in the brain suggests that, besides having vascular functions, ET-1 may also be involved in the regulation of CNS [9].

1.2. Involvement of Endothelin in the CNS

Studies have shown that ET is involved in the regulation of the sympathetic nervous system [10, 11]. Sympathetic nervous system mediated responses of clonidine have been demonstrated to be blocked by ET antagonists [10] and those of ET-1 by propranolol [11, 12]. Under normal physiological conditions, these centrally located receptors are important regulators of cerebral blood flow as well as developmental neuronal migration, proliferation and apoptosis [13, 14].

It is well established that ET_B receptors are a necessary component of the developing nervous system. ET_B receptors act as regulators in differentiation, proliferation and migration of neural cells during pre- and post-natal development, assisting the formation of melanocytes, neurons and glia of the enteric nervous system as well as the CNS [15, 16]. The presence of ET_B receptors in the subependymal zone, an adult neurogenic niche, of adult rats has introduced the possibility that these receptors may not only regulate the developing CNS, but may play a role in remodeling the adult brain as well [17]. Intracerebroventricular administration of an ET_B receptor agonist was found to increase brain-derived and glial-derived neurotrophic factors, and neurotrophin-3 in the brains of normal adult rats [18, 19].

1.3. Endothelin and Mitochondrial Functions

ET has been shown to produce some of its actions by modulating mitochondrial functions. ET-1 induced positive inotropic effect has been found to be associated with a surge in reactive oxygen species production, and ET-1 induced increases in superoxide anion was inhibited by NADPH oxidase blocker apocynin and by mitochondrial ATP-sensitive K+ channel blocker, glibenclamide [20]. An inhibitor of mitochondrial respiratory chain complex I, rotenone, significantly increased the expression of prepro ET-1 gene in the cardiomyocytes [21] indicating that ET-1 may produce impairment of mitochondrial functions leading to myocardial dysfunction in the failing heart. It has been demonstrated that the beneficial effect of ET_A receptor antagonist, LU135252 in congestive heart failure is mediated through improvement in mitochondrial functions [22]. Acrolein induced mitochondrial generation of reactive oxygen species in the pulmonary artery endothelial cells along with an increase in ET-1 which were both blocked by rotenone indicating involvement of ET in mitochondrial functions [23]. Both ET_A and ET_B receptors are expressed in the glioblastoma cell lines and it has been found that ET_B receptors mediate proliferation of different types of cancer cells [24, 25]. Furthermore, ET_B receptor antagonists, BQ788 and A192621, attenuated the viability and proliferation of glioma cell lines as determined by incorporation of BrdU

and cell cycle analysis. BQ788 and A192621 were found to trigger apoptotic processes by activating the intrinsic mitochondrial pathway [25] indicating involvement of ET_B receptors in mitochondrial functions of glioma cell lines.

1.4. Neurogenesis

The process of neurogenesis is most active during pre-natal development. However, it persists throughout the human lifespan. Neurogenesis occurs predominantly in the subventricular zone (SVZ), lining the wall of the lateral ventricles, subgranular zone (SGZ) of the hippocampal dentate gyrus [26] and spinal cord [27] of the adult CNS. Many pharmacological agents such as insulin-like growth factor [28], vascular endothelial growth factor (VEGF) [29] and antidepressants [30], have been identified to modulate neurogenesis and can provide new therapeutic strategies for several CNS disorders such as stroke, traumatic brain injury, depression, Alzheimer's disease and others. The present review will mainly focus on the neurogenesis in the adult brain and its implications in cerebral ischemia.

There are approximately 100 billion neurons in a mature human brain [31]. Each neuron can make connections with more than 1000 other neurons, and an adult brain can have approximately 60 trillion neuronal connections. Cells of other organs such as the skin and the immune system continuously divide and self-renew; however, a neuron in the adult brain, once formed from the parent stem cell, is not likely to undergo division [32]. It has long been the belief that plasticity of the nervous system involves modulating the connections between existing neurons. However, evidence shows that new neurons are being formed in the adult brain also [33, 34].

Neuronal production in human starts in the embryonic period around day 42 and occurs until mid-gestation. At first neural progenitor cells, which are mitotic, are formed in a symmetrical fashion till 42 embryonic days. After that, the mode of cell division shifts from symmetrical to asymmetrical. During asymmetrical division, one neuron and one neural progenitor are produced [35]. The newly formed progenitor neurons remain in the proliferative zone while the neurons migrate to the neocortex. The cortical neurogenesis is completed in about 108 embryonic days [36]. A naturally occurring process that is essential in the establishment of complex networks of the developing brain involves a loss of about 50% of the neurons. This non-pathological process of neuronal cell death occurs prenatally. Similarly, elimination of about 50% of exuberant connections between neurons occurs postnatally [31, 36]. Neurogenesis mostly occurs in the ventricular zone and newly formed neurons migrate radially out to the developing neocortex. It has been demonstrated that ET_B receptors in the brain are over expressed at the time of birth and their expression decreases with age and maturity of the brain [37]. It appears that ET_B receptors are important in the development of the brain and once the brain is developed, the need for ET_B receptors decreases and therefore the expression of these receptors decreases. ET_B receptors have been shown to increase the expression of various growth factors, such as VEGF and nerve growth factor (NGF), and have been implicated in playing an important role in the development of vascular and neuronal components of the CNS [38-40].

1.5. Mitochondria and Neurogenesis

The neuronal cells are highly dependent upon mitochondria for energy production. Mitophagy is the process by which undesired or damaged mitochondria are removed by autophagy and in this manner healthy functioning mitochondria are maintained. Mitochondria have a short life-span of 10 to 25 days compared to the life of neurons, mitophagy induced turnaround of mitochondria is the key to survival of neurons [41]. Impairment of mitophagy has been implicated in diseases such as Alzheimer's disease [42-44], Parkinson's disease [45] and in ischemic insults of the brain [46]. Mitophagy can be dependent or independent of parkin and prevents mitochondria from fusing with healthy ones and releasing pro-apoptotic proteins [42].

Physiological functioning of mitochondria is important for adult neurogenesis, a critical feature required to repair damaged neuronal tissue by cerebral ischemia. Neurogenesis requires adequate amount of ATP supply to facilitate cytoskeletal rearrangement, neuronal sprouting and organelle transport. Being a primary source of cellular ATP, healthy mitochondrial function is an important prerequisite to carryout neurogenesis effectively [47]. An enhanced mitochondrial mass appears to be the hallmark of adult neuronal differentiation, which indicates the importance of mitochondria in adult neurogenesis [48]. Increased ATP production is likely to be utilized for cytoskeletal rearrangement, mitochondrial dynamics and membrane turnover involved in neurite outgrowth. Some of the key mitochondrial proteins and transcription factors have been found to be elevated to high levels during neuronal differentiation. Increased expression of uncoupling protein (UCP4) and NeuroD6 mediated kinensin protein expression were observed at various stages of neurite outgrowth [49]. Mitochondria have been identified to be important for axonal growth cone formation, neural polarization and dendrite plasticization aspects of neurite outgrowth [50].

In addition to adult neurogenesis, mitochondria are also important for their role in molecular regulation of angiogenesis and vasculogenesis as evident from the experimental findings in cardiac tissue and cultured endothelial cells. Mitochondria have been found to directly influence hypoxia inducible factor (HIF-1α) signaling by release of reactive oxygen species and α-ketoglutarate, a cofactor for prolyl hydroxylation and destruction of HIF components [51]. Mitochondria thus link the metabolic derangements to the process of vascularization in both physiology and pathology. Mitofusins, functional proteins responsible for fusion of mitochondria have also been found to modulate the VEGF mediated Akt-eNOS signaling in endothelial cells [52].

The putative role of mitochondria in the neurogenesis and vasculogenesis emphasizes the importance of maintaining a healthy mitochondrial network in the context of cerebral ischemia. Various lines of evidence clearly indicate mitochondrial functional impairment in the ischemic nervous tissue and hence therapeutic alleviation of mitochondrial function can be an important target to treat cerebral ischemia

[53]. The relation between ET receptor activation and mitochondrial function has been understudied in the case of nervous tissue. Although several reports of ET induced impairment of mitochondrial function in the cardiomyocytes exist, most of the effects mediated through ET_A receptor activation. The role of ET_B receptors should be studied in a neuronal ischemia model with relevance to mitochondrial function. Since, ET_B mediated neurogenesis and vasculogenesis has been identified to play significant role in cerebral ischemia, a molecular assessment of downstream consequences of ET_B activation on mitochondrial function could lead to better understanding of pathophysiology of stroke and help us to devise better therapeutic strategies.

1.6. Type of ET Receptors Involved in Neurogenesis

The release of neurotrophic and angiogenic factors, such as VEGF increases significantly *via* stimulation of ET_B receptors on the astrocytes [54]. Both ET_A and ET_B receptors exist in the brain and play an important role. ET_A receptor selective antagonists, BQ123 and BMS182874, were found to prevent amyloid beta (Aβ)-induced cognitive deficits. However, a nonspecific ET_A and ET_B receptor antagonist, TAK044, did not produce any improvement in memory deficit. This lack of improvement with the non-specific ET_A and ET_B antagonist indicated specific involvement of ET_B receptors in memory functions [55]. These findings indicate that ET_B receptors play an important role in CNS disorders. ET_B receptor deficiency at birth results in a decrease in neuronal progenitor cells and an increase in apoptosis in the postnatal cerebellum and dentate gyrus of rats [13, 14]. ET_B receptor expression is enhanced in astrocytes following brain injury, while ET production is increased in the injured neurons [56, 57]. The stimulation of the glial ET_B receptors by ET-1 results in the release of angiogenic and neurotrophic factors [54, 57].

1.7. Potential Clinical Implications of using ETB Receptor Agonist in Cerebral Ischemia

Several decades ago, it was recognized that ET and its receptors could be potential therapeutic targets to treat and/or prevent ischemic stroke. ET levels in the blood were elevated following ischemic stroke and subarachnoid hemorrhage, furthermore, ET immunoreactivity was increased in the ipsilateral compared with the contralateral hemisphere (119% after 24 h; 184% after 48 h and 459% after 72 h) in rats with cerebral ischemia [58]. ET has been reported to have pathophysiological role in neuronal injury due to ischemia [59]. ET-1 has a strong contractile effect on the cerebral arterial blood vessels [58, 60], producing major reduction in cerebral blood flow leading to infarction and neurological deficits [61]. An increase in ET-1 levels coincided with a decrease in regional cerebral blood flow in the ischemic areas following experimental stroke, these findings prompted investigation of ET receptor antagonists in the treatment of focal ischemic stroke [62]. Selectively blocking ET_A receptors in closed head injury and ischemic stroke was found to significantly improve neurological outcome [63, 64]. The volume of infarction following focal cerebral ischemia in rat was reduced by non-selective ET_A and ET_B receptor antagonist TAK-044 and selective ET_A antagonist, BQ123 [65, 66]. ET_A specific and non-specific ET_A and ET_B receptor antagonists showed promising results in experimental stroke models [63, 65, 67] but were not successful in clinical trials [68, 69]. A majority of research has focused on selectively antagonizing the ET_A receptors to prevent vasoconstriction following stroke.

We have demonstrated that ET_B receptors in the brain are over expressed at the time of birth and their expression decreases with maturity of the brain [37, 40]. It has been shown that damaged brain exhibits a re-emergence of childhood organizational patterns, reminiscent of an ontogenetic state [70] and is primed for recovery. However, endogenous remodeling of the CNS is not sufficient to restore neurological function. Evidence that a deficiency in ET_B receptors leads to a poorer outcome following cerebral ischemia [71] and deficiency or blockade of ET_B receptors leads to exacerbation of damage to the CNS following ischemia [72] suggesting that a role of ET_B receptors in pathophysiological process of ischemic stroke should be investigated (Fig. **2**).

We have shown that selectively activating ET_B receptors, with IRL-1620, in a focal stroke model has been shown to be effective in reducing the infarct volume to 24.47±4.37 mm^3 versus 153.23±32.18mm^3 in vehicle-treated rats 24 hours after infarction. In another study, rats received three injections of either vehicle or IRL-1620 (each dose of 5 μg/kg) intravenously at 2, 4, and 6 hours after permanent occlusion, rats were observed for 7 days and it was found that treatment with IRL-1620 significantly reduced infarct volume (54.06 ± 14.12 mm^3 vs. 177.06 ± 13.21 mm^3) and improved all the parameters depicting neurological and motor functions when compared to the vehicle-treated group [73-75]. An increase in plasma ET-1 levels and tissue ET immunoreactivity, combined with evidence that a deficiency in ET_B receptors leads to a poorer outcome following cerebral ischemia [58, 71] indicates that there is involvement of ET_B receptors in brain ischemia. Deficiency or blockade of ET_B receptors exacerbates ischemic brain damage, possibly due to a shift in ET vasomotor balance [71, 72]. It was found that protection and recovery from cerebral ischemia was at least partially due to an increase in angiogenesis and neurogenesis within 7 days following treatment with IRL-1620. The count of VEGF-positive vessels/30 μm brain slice in the IRL-1620 group were significantly higher (11.33±2.13) versus vehicle group (4.19±0.79) [75]. An increase in the vascular and nerve growth factors in the ischemic brain hemisphere of IRL-1620-treated animals coincided with an increase in the expression of ET_B receptors. Moreover, functional ET_B receptors have been shown to protect against apoptosis and enhance the proliferation of neuronal progenitors in the dentate gyrus, olfactory epithelium and cortical neurons [72, 76-78].

ET_B receptor stimulation, *via* IRL-1620, significantly reduced neurological deficit, improved motor functions and oxidative stress markers and decreased infarct volume following ischemia in rats [73, 74]. Additionally, IRL-1620 provided marked neuroprotection at both 24 hours [73] and 7 days [74] following occlusion of the middle cerebral artery

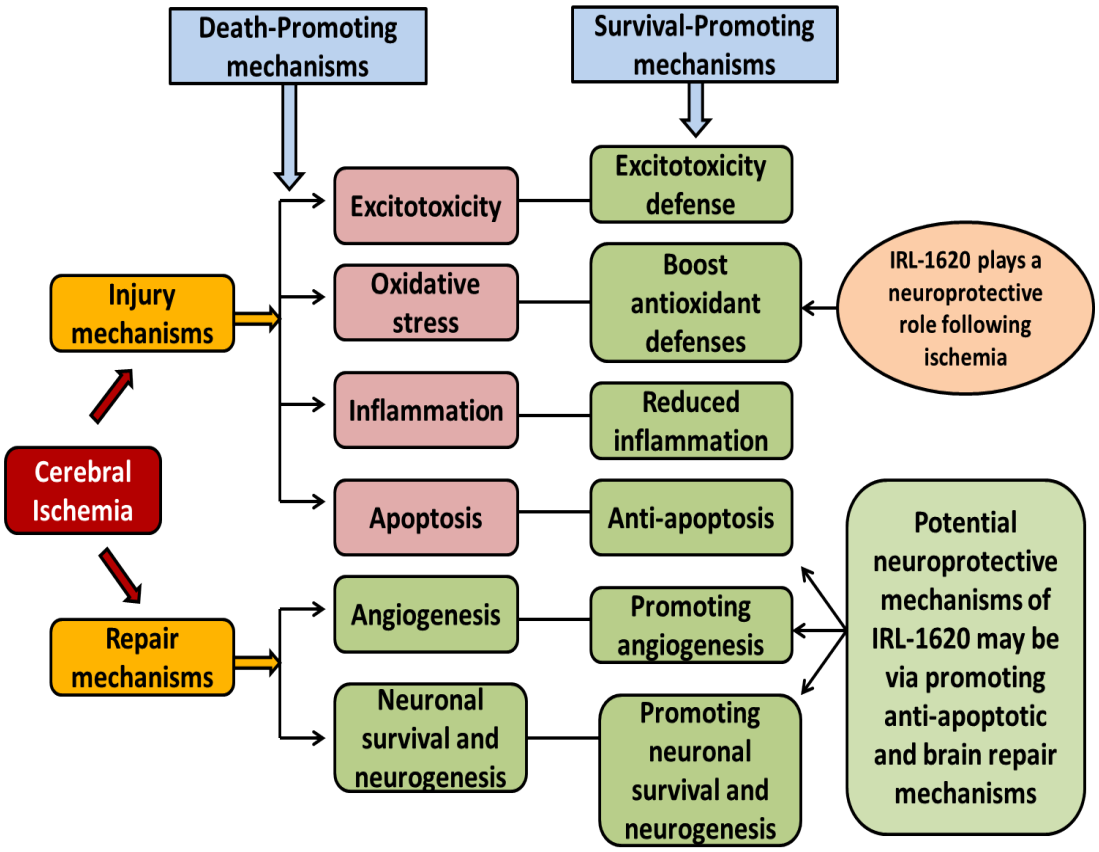

Fig. (2). Cerebral ischemia produces a wide variety of changes in the CNS. They can broadly be classified as injury and repair mechanisms. It is our hypothesis that ET_B receptor agonist, IRL-1620, may be acting a neuroprotective and may also participate in the repair mechanism following cerebral ischemia. It has been demonstrated that IRL-1620 is both neuroprotective and participates in the repair mechanism in animal model of cerebral ischemia.

and reduced infarct volume by 83.66% in the acute study and 69.49% in the chronic study. IRL-1620 treatment preserved neuronal numbers in the cerebral cortex, striatum and SVZ and also increased ET_B receptor expression in the ischemic hemisphere of the rat brain. IRL-1620 treatment also enhanced the number of blood vessels that labeled positive with VEGF when compared to the vehicle treatment [75]. Thus, IRL-1620, when administered intravenously, was found to be highly effective in preventing damage following stroke and helped in the neurovascular remodeling of the ischemic brain by angiogenesis and neurogenesis [75].

2. CONCLUSION

About 795,000 people experience a new or recurrent stroke each year and 610,000 of these are first attacks, and balance 185,000 are recurrent attacks. Eighty seven percent of all strokes are ischemic and balance thirteen percent are hemorrhagic [79]. The two major approaches that can be used for the treatment of cerebral ischemia are neuroprotection, which requires an acute intervention, and neurorestoration, which can be instituted during the stroke recovery phase [80-82] (Fig. **2**). Several trials have been conducted or are in progress using pharmacological agents such as amphetamine, methylphenidate, levodopa, sildenafil, serotonin uptake inhibitors, erythropoietin, statins, and granulocyte colony stimulating factor but none involves stimulation of ET_B receptors. It will be of great interest to determine whether stimulation of ET_B receptors produces neuroprotection or neurorestoration (reparative and regenerative) or both through the involvement of mitochondria. It is also worthwhile exploring the neuroprotective and neurorestorative role of ET_B receptors in the brain and may form the basis for the design of novel and effective strategies for the treatment of ischemia-induced brain damage.

CONFLICT OF INTEREST

Pending patent application related to neurogenesis.

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REFERENCES

[1] Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature,* **1988**, *332*(6163), 411-415. [http://dx.doi.org/10.1038/332411a0] [PMID: 2451132]

[2] Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Masaki, T. The human endothelin family: three

structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc. Natl. Acad. Sci. USA,* **1989**, *86*(8), 2863-2867. [http://dx.doi.org/10.1073/pnas.86.8.2863] [PMID: 2649896]

[3] Arai, H.; Hori, S.; Aramori, I.; Ohkubo, H.; Nakanishi, S. Cloning and expression of a cDNA encoding an endothelin receptor. *Nature,* **1990**, *348*(6303), 730-732. [http://dx.doi.org/10.1038/348730a0] [PMID: 2175396]

[4] Sakurai, T.; Yanagisawa, M.; Masaki, T. Molecular characterization of endothelin receptors. *Trends Pharmacol. Sci.,* **1992**, *13*(3), 103-108. [PMID: 1315462]

[5] Goto, K.; Kasuya, Y.; Matsuki, N.; Takuwa, Y.; Kurihara, H.; Ishikawa, T.; Kimura, S.; Yanagisawa, M.; Masaki, T. Endothelin activates the dihydropyridine-sensitive, voltage-dependent Ca2+ channel in vascular smooth muscle. *Proc. Natl. Acad. Sci. USA,* **1989**, *86*(10), 3915-3918. [http://dx.doi.org/10.1073/pnas.86.10.3915] [PMID: 2542956]

[6] Tsukahara, H.; Ende, H.; Magazine, H.I.; Bahou, W.F.; Goligorsky, M.S. Molecular and functional characterization of the non-isopeptide-selective ETB receptor in endothelial cells. Receptor coupling to nitric oxide synthase. *J. Biol. Chem.,* **1994**, *269*(34), 21778-21785. [PMID: 7520443]

[7] Warner, T.D.; Allcock, G.H.; Corder, R.; Vane, J.R. Use of the endothelin antagonists BQ-123 and PD 142893 to reveal three endothelin receptors mediating smooth muscle contraction and the release of EDRF. *Br. J. Pharmacol.,* **1993**, *110*(2), 777-782. [http://dx.doi.org/10.1111/j.1476-5381.1993.tb13879.x] [PMID: 8242251]

[8] MacCumber, M.W.; Ross, C.A.; Snyder, S.H. Endothelin in brain: receptors, mitogenesis, and biosynthesis in glial cells. *Proc. Natl. Acad. Sci. USA,* **1990**, *87*(6), 2359-2363. [http://dx.doi.org/10.1073/pnas.87.6.2359] [PMID: 2156267]

[9] Gulati, A.; Srimal, R.C. Endothelin mechanisms in the central nervous system - A target for drug development. *Drug Dev. Res.,* **1992**, *26*(4), 361-387. [http://dx.doi.org/10.1002/ddr.430260402]

[10] Gulati, A.; Srimal, R.C. Endothelin antagonizes the hypotension and potentiates the hypertension induced by clonidine. *Eur. J. Pharmacol.,* **1993**, *230*(3), 293-300. [http://dx.doi.org/10.1016/0014-2999(93)90564-X] [PMID: 8440307]

[11] Kumar, A.; Gulati, A.; Shahani, B.T. Central cardiovascular effects of endothelin-1 (ET-1) could be attenuated by propranalol in rats. *Circulation,* **1995**, *92*(8), 1054-1054.

[12] Kumar, A.; Shahani, B.T.; Gulati, A. Modification of systemic and regional circulatory effects of intracerebroventricular administration of endothelin-1 by propranolol in anesthetized rats. *Gen. Pharmacol.,* **1996**, *27*(6), 1025-1033. [http://dx.doi.org/10.1016/0306-3623(95)02134-5] [PMID: 8909986]

[13] Ehrenreich, H.; Nau, T.R.; Dembowski, C.; Hasselblatt, M.; Barth, M.; Hahn, A.; Schilling, L.; Sirén A-L, ; Brück, W. Endothelin b receptor deficiency is associated with an increased rate of neuronal apoptosis in the dentate gyrus. *Neuroscience,* **2000**, *95*(4), 993-1001. [http://dx.doi.org/10.1016/S0306-4522(99)00507-2] [PMID: 10682706]

[14] Vidovic, M.; Chen, M.M.; Lu, Q.Y.; Kalloniatis, K.F.; Martin, B.M.; Tan, A.H.; Lynch, C.; Croaker, G.D.; Cass, D.T.; Song, Z.M. Deficiency in endothelin receptor B reduces proliferation of neuronal progenitors and increases apoptosis in postnatal rat cerebellum. *Cell. Mol. Neurobiol.,* **2008**, *28*(8), 1129-1138. [http://dx.doi.org/10.1007/s10571-008-9292-z] [PMID: 18683040]

[15] Druckenbrod, N.R.; Powers, P.A.; Bartley, C.R.; Walker, J.W.; Epstein, M.L. Targeting of endothelin receptor-B to the neural crest. *Genesis,* **2008**, *46*(8), 396-400. [http://dx.doi.org/10.1002/dvg.20415] [PMID: 18693272]

[16] Riechers, C.C.; Knabe, W.; Sirén, A.L.; Gariepy, C.E.; Yanagisawa, M.; Ehrenreich, H. Endothelin B receptor deficient transgenic rescue rats: a rescue phenomenon in the brain. *Neuroscience,* **2004**, *124*(4), 719-723. [http://dx.doi.org/10.1016/j.neuroscience.2003.10.023] [PMID: 15026112]

[17] Castañeda, M.M.; Cubilla, M.A.; López-Vicchi, M.M.; Suburo, A.M. Endothelinergic cells in the subependymal region of mice. *Brain Res.,* **2010**, *1321*, 20-30. [http://dx.doi.org/10.1016/j.brainres.2010.01.056] [PMID: 20116370]

[18] Koyama, Y.; Baba, A.; Matsuda, T. Endothelins stimulate the expression of neurotrophin-3 in rat brain and rat cultured astrocytes. *Neuroscience,* **2005**, *136*(2), 425-433. [http://dx.doi.org/10.1016/j.neuroscience.2005.08.004] [PMID: 16181740]

[19] Koyama, Y.; Tsujikawa, K.; Matsuda, T.; Baba, A. Intracerebroventricular administration of an endothelin ETB receptor agonist increases expressions of GDNF and BDNF in rat brain. *Eur. J. Neurosci.,* **2003**, *18*(4), 887-894. [http://dx.doi.org/10.1046/j.1460-9568.2003.02797.x] [PMID: 12925014]

[20] De Giusti, V.C.; Correa, M.V.; Villa-Abrille, M.C.; Beltrano, C.; Yeves, A.M.; de Cingolani, G.E.; Cingolani, H.E.; Aiello, E.A. The positive inotropic effect of endothelin-1 is mediated by mitochondrial reactive oxygen species. *Life Sci.,* **2008**, *83*(7-8), 264-271. [http://dx.doi.org/10.1016/j.lfs.2008.06.008] [PMID: 18625248]

[21] Yuki, K.; Miyauchi, T.; Kakinuma, Y.; Murakoshi, N.; Suzuki, T.; Hayashi, J.; Goto, K.; Yamaguchi, I. Mitochondrial dysfunction increases expression of endothelin-1 and induces apoptosis through caspase-3 activation in rat cardiomyocytes *in vitro*. *J. Cardiovasc. Pharmacol.,* **2000**, *36*(5)(Suppl. 1), S205-S208. [http://dx.doi.org/10.1097/00005344-200036051-00062] [PMID: 11078378]

[22] Marín-García, J.; Goldenthal, M.J.; Moe, G.W. Selective endothelin receptor blockade reverses mitochondrial dysfunction in canine heart failure. *J. Card. Fail.,* **2002**, *8*(5), 326-332. [http://dx.doi.org/10.1054/jcaf.2002.127770] [PMID: 12411984]

[23] Ouyang, J.S.; Li, Y.P.; Li, C.Y.; Cai, C.; Chen, C.S.; Chen, S.X.; Chen, Y.F.; Yang, L.; Xie, Y.P. Mitochondrial ROS-K+ channel signaling pathway regulated secretion of human pulmonary artery endothelial cells. *Free Radic. Res.,* **2012**, *46*(12), 1437-1445. [http://dx.doi.org/10.3109/10715762.2012.724532] [PMID: 22928487]

[24] Bagnato, A.; Natali, P.G. Endothelin receptors as novel targets in tumor therapy. *J. Transl. Med.,* **2004**, *2*(1), 16. [http://dx.doi.org/10.1186/1479-5876-2-16] [PMID: 15165288]

[25] Paolillo, M.; Russo, M.A.; Curti, D.; Lanni, C.; Schinelli, S. Endothelin B receptor antagonists block proliferation and induce apoptosis in glioma cells. *Pharmacol. Res.,* **2010**, *61*(4), 306-315. [http://dx.doi.org/10.1016/j.phrs.2009.11.003] [PMID: 19931393]

[26] Alvarez-Buylla, A.; Lim, D.A. For the long run: maintaining germinal niches in the adult brain. *Neuron,* **2004**, *41*(5), 683-686. [http://dx.doi.org/10.1016/S0896-6273(04)00111-4] [PMID: 15003168]

[27] Barnabé-Heider, F.; Göritz, C.; Sabelström, H.; Takebayashi, H.; Pfrieger, F.W.; Meletis, K.; Frisén, J. Origin of new glial cells in intact and injured adult spinal cord. *Cell Stem Cell,* **2010**, *7*(4), 470-482. [http://dx.doi.org/10.1016/j.stem.2010.07.014] [PMID: 20887953]

[28] Anderson, M.F.; Aberg, M.A.; Nilsson, M.; Eriksson, P.S. Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. *Brain Res. Dev. Brain Res.,* **2002**, *134*(1-2), 115-122. [http://dx.doi.org/10.1016/S0165-3806(02)00277-8] [PMID: 11947942]

[29] Thau-Zuchman, O.; Shohami, E.; Alexandrovich, A.G.; Leker, R.R. Vascular endothelial growth factor increases neurogenesis after traumatic brain injury. *J. Cereb. Blood Flow Metab.,* **2010**, *30*(5), 1008-1016. [http://dx.doi.org/10.1038/jcbfm.2009.271] [PMID: 20068579]

[30] Malberg, J.E.; Eisch, A.J.; Nestler, E.J.; Duman, R.S. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.,* **2000**, *20*(24), 9104-9110. [PMID: 11124987]

[31] Pakkenberg, B.; Gundersen, H.J. Neocortical neuron number in humans: effect of sex and age. *J. Comp. Neurol.,* **1997**, *384*(2), 312-320. [http://dx.doi.org/10.1002/(SICI)1096-9861(19970728)384:2<312::AID-CNE10>3.0.CO;2-K] [PMID: 9215725]

[32] Kriegstein, A.; Alvarez-Buylla, A. The glial nature of embryonic and adult neural stem cells. *Annu. Rev. Neurosci.,* **2009**, *32*, 149-184. [http://dx.doi.org/10.1146/annurev.neuro.051508.135600] [PMID: 19555289]

[33] Eriksson, P.S.; Perfilieva, E.; Björk-Eriksson, T.; Alborn, A.M.; Nordborg, C.; Peterson, D.A.; Gage, F.H. Neurogenesis in the adult human hippocampus. *Nat. Med.,* **1998**, *4*(11), 1313-1317. [http://dx.doi.org/10.1038/3305] [PMID: 9809557]

[34] Kempermann, G.; Kuhn, H.G.; Gage, F.H. More hippocampal neurons in adult mice living in an enriched environment. *Nature,* **1997**, *386*(6624), 493-495. [http://dx.doi.org/10.1038/386493a0] [PMID: 9087407]

[35] Wodarz, A.; Huttner, W.B. Asymmetric cell division during neurogenesis in Drosophila and vertebrates. *Mech. Dev.,* **2003**,

120(11), 1297-1309. [http://dx.doi.org/10.1016/j.mod.2003.06.003] [PMID: 14623439]

[36] Clancy, B.; Darlington, R.B.; Finlay, B.L. Translating developmental time across mammalian species. *Neuroscience,* **2001**, *105*(1), 7-17. [http://dx.doi.org/10.1016/S0306-4522(01)00171-3] [PMID: 11483296]

[37] Briyal, S.; Lavhale, M.S.; Gulati, A. Repeated administration of centhaquin to pregnant rats did not affect postnatal development and expression of endothelin receptors in the brain, heart or kidney of pups. *Arzneimittelforschung,* **2012**, *62*(12), 670-676. [http://dx.doi.org/10.1055/s-0032-1329985] [PMID: 23154885]

[38] Briyal, S.; Shepard, C.; Gulati, A. Endothelin receptor type B agonist, IRL-1620, prevents beta amyloid (Aβ) induced oxidative stress and cognitive impairment in normal and diabetic rats. *Pharmacol. Biochem. Behav.,* **2014**, *120*, 65-72. [http://dx.doi.org/10.1016/j.pbb.2014.02.008] [PMID: 24561065]

[39] Leonard, M.G.; Prazad, P.; Puppala, B.; Gulati, A. Selective Endothelin-B receptor stimulation increases vascular endothelial growth factor in the rat brain during postnatal development. *Drug Res (Stuttg),* **2015**. [http://dx.doi.org/10.1055/s-0034-1398688]

[40] Puppala, B.; Awan, I.; Briyal, S.; Mbachu, O.; Leonard, M.; Gulati, A. Ontogeny of endothelin receptors in the brain, heart, and kidneys of neonatal rats. *Brain Dev.,* **2015**, *37*(2), 206-215. [http://dx.doi.org/10.1016/j.braindev.2014.04.008] [PMID: 24815227]

[41] Yuan, Y.; Zhang, X.; Zheng, Y.; Chen, Z. Regulation of mitophagy in ischemic brain injury. *Neurosci. Bull.,* **2015**, *31*(4), 395-406. [http://dx.doi.org/10.1007/s12264-015-1544-6] [PMID: 26219224]

[42] Banerjee, K.; Munshi, S.; Frank, D.E.; Gibson, G.E. Abnormal Glucose Metabolism in Alzheimer's Disease: Relation to Autophagy/Mitophagy and Therapeutic Approaches. *Neurochem. Res.,* **2015**, *40*(12), 2557-2569. [http://dx.doi.org/10.1007/s11064-015-1631-0] [PMID: 26077923]

[43] Meijer, A.J.; Codogno, P. Autophagy: regulation and role in disease. *Crit. Rev. Clin. Lab. Sci.,* **2009**, *46*(4), 210-240. [http://dx.doi.org/10.1080/10408360903044068] [PMID: 19552522]

[44] Santos, R.X.; Correia, S.C.; Wang, X.; Perry, G.; Smith, M.A.; Moreira, P.I.; Zhu, X. A synergistic dysfunction of mitochondrial fission/fusion dynamics and mitophagy in Alzheimer's disease. *J. Alzheimers Dis.,* **2010**, *20*(Suppl. 2), S401-S412. [PMID: 20463393]

[45] Vives-Bauza, C.; Przedborski, S. Mitophagy: the latest problem for Parkinson's disease. *Trends Mol. Med.,* **2011**, *17*(3), 158-165. [http://dx.doi.org/10.1016/j.molmed.2010.11.002] [PMID: 21146459]

[46] Zhang, X.; Yan, H.; Yuan, Y.; Gao, J.; Shen, Z.; Cheng, Y.; Shen, Y.; Wang, R.R.; Wang, X.; Hu, W.W.; Wang, G.; Chen, Z. Cerebral ischemia-reperfusion-induced autophagy protects against neuronal injury by mitochondrial clearance. *Autophagy,* **2013**, *9*(9), 1321-1333. [http://dx.doi.org/10.4161/auto.25132] [PMID: 23800795]

[47] Xavier, J.M.; Rodrigues, C.M.; Solá, S. Mitochondria: Major Regulators of Neural Development. *Neuroscientist,* **2015**, 1073858415585472. [PMID: 25948649]

[48] Cheng, A.; Hou, Y.; Mattson, M.P. Mitochondria and neuroplasticity. *ASN Neuro,* **2010**, *2*(5), e00045. [http://dx.doi.org/10.1042/AN20100019] [PMID: 20957078]

[49] Mattson, M.P.; Liu, D. Mitochondrial potassium channels and uncoupling proteins in synaptic plasticity and neuronal cell death. *Biochem. Biophys. Res. Commun.,* **2003**, *304*(3), 539-549. [http://dx.doi.org/10.1016/S0006-291X(03)00627-2] [PMID: 12729589]

[50] Kann, O.; Kovács, R. Mitochondria and neuronal activity. *Am. J. Physiol. Cell Physiol.,* **2007**, *292*(2), C641-C657. [http://dx.doi.org/10.1152/ajpcell.00222.2006] [PMID: 17092996]

[51] Acker, T.; Acker, H. Cellular oxygen sensing need in CNS function: physiological and pathological implications. *J. Exp. Biol.,* **2004**, *207*(Pt 18), 3171-3188. [http://dx.doi.org/10.1242/jeb.01075] [PMID: 15299039]

[52] Schänzer, A.; Wachs, F.P.; Wilhelm, D.; Acker, T.; Cooper-Kuhn, C.; Beck, H.; Winkler, J.; Aigner, L.; Plate, K.H.; Kuhn, H.G. Direct stimulation of adult neural stem cells *in vitro* and neurogenesis *in vivo* by vascular endothelial growth factor. *Brain Pathol.,* **2004**, *14*(3), 237-248. [http://dx.doi.org/10.1111/j.1750-3639.2004.tb00060.x] [PMID: 15446578]

[53] Sisalli, M.J.; Annunziato, L.; Scorziello, A. Novel Cellular Mechanisms for Neuroprotection in Ischemic Preconditioning: A View from Inside Organelles. *Front. Neurol.,* **2015**, *6*, 115. [http://dx.doi.org/10.3389/fneur.2015.00115] [PMID: 26074868]

[54] Koyama, Y.; Michinaga, S. Regulations of astrocytic functions by endothelins: roles in the pathophysiological responses of damaged brains. *J. Pharmacol. Sci.,* **2012**, *118*(4), 401-407. [http://dx.doi.org/10.1254/jphs.11R13CP] [PMID: 22447302]

[55] Briyal, S.; Philip, T.; Gulati, A. Endothelin-A receptor antagonists prevent amyloid-β-induced increase in ETA receptor expression, oxidative stress, and cognitive impairment. *J. Alzheimers Dis.,* **2011**, *23*(3), 491-503. [PMID: 21116051]

[56] Nakagomi, S.; Kiryu-Seo, S.; Kiyama, H. Endothelin-converting enzymes and endothelin receptor B messenger RNAs are expressed in different neural cell species and these messenger RNAs are coordinately induced in neurons and astrocytes respectively following nerve injury. *Neuroscience,* **2000**, *101*(2), 441-449. [http://dx.doi.org/10.1016/S0306-4522(00)00345-6] [PMID: 11074166]

[57] Rogers, S.D.; Demaster, E.; Catton, M.; Ghilardi, J.R.; Levin, L.A.; Maggio, J.E.; Mantyh, P.W. Expression of endothelin-B receptors by glia *in vivo* is increased after CNS injury in rats, rabbits, and humans. *Exp. Neurol.,* **1997**, *145*(1), 180-195. [http://dx.doi.org/10.1006/exnr.1997.6468] [PMID: 9184120]

[58] Viossat, I.; Duverger, D.; Chapelat, M.; Pirotzky, E.; Chabrier, P.E.; Braquet, P. Elevated tissue endothelin content during focal cerebral ischemia in the rat. *J. Cardiovasc. Pharmacol.,* **1993**, *22*(Suppl. 8), S306-S309. [http://dx.doi.org/10.1097/00005344-199322008-00080] [PMID: 7509972]

[59] Willette, R.N.; Ohlstein, E.H.; Pullen, M.; Sauermelch, C.F.; Cohen, A.; Nambi, P. Transient forebrain ischemia alters acutely endothelin receptor density and immunoreactivity in gerbil brain. *Life Sci.,* **1993**, *52*(1), 35-40. [http://dx.doi.org/10.1016/0024-3205(93)90286-C] [PMID: 8417278]

[60] Lee, M.E.; de la Monte, S.M.; Ng, S.C.; Bloch, K.D.; Quertermous, T. Expression of the potent vasoconstrictor endothelin in the human central nervous system. *J. Clin. Invest.,* **1990**, *86*(1), 141-147. [http://dx.doi.org/10.1172/JCI114677] [PMID: 2195059]

[61] Robinson, M.J.; Macrae, I.M.; Todd, M.; Reid, J.L.; McCulloch, J. Reduction of local cerebral blood flow to pathological levels by endothelin-1 applied to the middle cerebral artery in the rat. *Neurosci. Lett.,* **1990**, *118*(2), 269-272. [http://dx.doi.org/10.1016/0304-3940(90)90644-O] [PMID: 2274283]

[62] Patel, T.R.; Galbraith, S.L.; McAuley, M.A.; Doherty, A.M.; Graham, D.I.; McCulloch, J. Therapeutic potential of endothelin receptor antagonists in experimental stroke. *J. Cardiovasc. Pharmacol.,* **1995**, *26*(Suppl. 3), S412-S415. [http://dx.doi.org/10.1097/00005344-199506263-00121] [PMID: 8587430]

[63] Barone, F.C.; Ohlstein, E.H.; Hunter, A.J.; Campbell, C.A.; Hadingham, S.H.; Parsons, A.A.; Yang, Y.; Shohami, E. Selective antagonism of endothelin-A-receptors improves outcome in both head trauma and focal stroke in rat. *J. Cardiovasc. Pharmacol.,* **2000**, *36*(5)(Suppl. 1), S357-S361. [http://dx.doi.org/10.1097/00005344-200036051-00104] [PMID: 11078420]

[64] Legos, J.J.; Lenhard, S.C.; Haimbach, R.E.; Schaeffer, T.R.; Bentley, R.G.; McVey, M.J.; Chandra, S.; Irving, E.A.; Andrew A Parsons, ; Barone, F.C. SB 234551 selective ET(A) receptor antagonism: perfusion/diffusion MRI used to define treatable stroke model, time to treatment and mechanism of protection. *Exp. Neurol.,* **2008**, *212*(1), 53-62. [http://dx.doi.org/10.1016/j.expneurol.2008.03.011] [PMID: 18462720]

[65] Briyal, S.; Gulati, A. Endothelin-A receptor antagonist BQ123 potentiates acetaminophen induced hypothermia and reduces infarction following focal cerebral ischemia in rats. *Eur. J. Pharmacol.,* **2010**, *644*(1-3), 73-79. [http://dx.doi.org/10.1016/j.ejphar.2010.06.071] [PMID: 20638381]

[66] Briyal, S.; Gulati, A.; Gupta, Y.K. Effect of combination of endothelin receptor antagonist (TAK-044) and aspirin in middle cerebral artery occlusion model of acute ischemic stroke in rats. *Methods Find. Exp. Clin. Pharmacol.,* **2007**, *29*(4), 257-263. [http://dx.doi.org/10.1358/mf.2007.29.4.1106409] [PMID: 17609737]

[67] Gupta, Y.K.; Briyal, S.; Sharma, U.; Jagannathan, N.R.; Gulati, A. Effect of endothelin antagonist (TAK-044) on cerebral ischemic volume, oxidative stress markers and neurobehavioral parameters in the middle cerebral artery occlusion model of stroke in rats. *Life Sci.,* **2005**, *77*(1), 15-27. [http://dx.doi.org/10.1016/j.lfs.2004.11.025] [PMID: 15848215]

[68] Kohan, D.E.; Cleland, J.G.; Rubin, L.J.; Theodorescu, D.; Barton, M. Clinical trials with endothelin receptor antagonists: what went

wrong and where can we improve? *Life Sci.,* **2012**, *91*(13-14), 528-539. [http://dx.doi.org/10.1016/j.lfs.2012.07.034] [PMID: 22967485]

[69] Shah, R. Endothelins in health and disease. *Eur. J. Intern. Med.,* **2007**, *18*(4), 272-282. [http://dx.doi.org/10.1016/j.ejim.2007.04.002] [PMID: 17574100]

[70] Cramer, S.C.; Chopp, M. Recovery recapitulates ontogeny. *Trends Neurosci.,* **2000**, *23*(6), 265-271. [http://dx.doi.org/10.1016/S0166-2236(00)01562-9] [PMID: 10838596]

[71] Chuquet, J.; Benchenane, K.; Toutain, J.; MacKenzie, E.T.; Roussel, S.; Touzani, O. Selective blockade of endothelin-B receptors exacerbates ischemic brain damage in the rat. *Stroke,* **2002**, *33*(12), 3019-3025. [http://dx.doi.org/10.1161/01.STR.0000039401.48915.9F] [PMID: 12468806]

[72] Ehrenreich, H.; Oldenburg, J.; Hasselblatt, M.; Herms, J.; Dembowski, C.; Löffler, B.M.; Brück, W.; Kamrowski-Kruck, H.; Gall, S.; Sirén, A.L.; Schilling, L. Endothelin B receptor-deficient rats as a subtraction model to study the cerebral endothelin system. *Neuroscience,* **1999**, *91*(3), 1067-1075. [http://dx.doi.org/10.1016/S0306-4522(98)00663-0] [PMID: 10391484]

[73] Leonard, M.G.; Briyal, S.; Gulati, A. Endothelin B receptor agonist, IRL-1620, reduces neurological damage following permanent middle cerebral artery occlusion in rats. *Brain Res.,* **2011**, *1420*, 48-58. [http://dx.doi.org/10.1016/j.brainres.2011.08.075] [PMID: 21959172]

[74] Leonard, M.G.; Briyal, S.; Gulati, A. Endothelin B receptor agonist, IRL-1620, provides long-term neuroprotection in cerebral ischemia in rats. *Brain Res.,* **2012**, *1464*, 14-23. [http://dx.doi.org/10.1016/j.brainres.2012.05.005] [PMID: 22580085]

[75] Leonard, M.G.; Gulati, A. Endothelin B receptor agonist, IRL-1620, enhances angiogenesis and neurogenesis following cerebral ischemia in rats. *Brain Res.,* **2013**, *1528*, 28-41. [http://dx.doi.org/10.1016/j.brainres.2013.07.002] [PMID: 23850649]

[76] Laziz, I.; Larbi, A.; Grebert, D.; Sautel, M.; Congar, P.; Lacroix, M.C.; Salesse, R.; Meunier, N. Endothelin as a neuroprotective factor in the olfactory epithelium. *Neuroscience,* **2011**, *172*, 20-29. [http://dx.doi.org/10.1016/j.neuroscience.2010.10.063] [PMID: 21035524]

[77] Lee, H.O.; Levorse, J.M.; Shin, M.K. The endothelin receptor-B is required for the migration of neural crest-derived melanocyte and enteric neuron precursors. *Dev. Biol.,* **2003**, *259*(1), 162-175. [http://dx.doi.org/10.1016/S0012-1606(03)00160-X] [PMID: 12812796]

[78] Yagami, T.; Ueda, K.; Sakaeda, T.; Okamura, N.; Nakazato, H.; Kuroda, T.; Hata, S.; Sakaguchi, G.; Itoh, N.; Hashimoto, Y.; Fujimoto, M. Effects of an endothelin B receptor agonist on secretory phospholipase A2-IIA-induced apoptosis in cortical neurons. *Neuropharmacology,* **2005**, *48*(2), 291-300. [http://dx.doi.org/10.1016/j.neuropharm.2004.09.011] [PMID: 15695168]

[79] Go, A.S.; Mozaffarian, D.; Roger, V.L.; Benjamin, E.J.; Berry, J.D.; Borden, W.B.; Bravata, D.M.; Dai, S.; Ford, E.S.; Fox, C.S.; Franco, S.; Fullerton, H.J.; Gillespie, C.; Hailpern, S.M.; Heit, J.A.; Howard, V.J.; Huffman, M.D.; Kissela, B.M.; Kittner, S.J.; Lackland, D.T.; Lichtman, J.H.; Lisabeth, L.D.; Magid, D.; Marcus, G.M.; Marelli, A.; Matchar, D.B.; McGuire, D.K.; Mohler, E.R.; Moy, C.S.; Mussolino, M.E.; Nichol, G.; Paynter, N.P.; Schreiner, P.J.; Sorlie, P.D.; Stein, J.; Turan, T.N.; Virani, S.S.; Wong, N.D.; Woo, D.; Turner, M.B. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation,* **2013**, *127*(1), 143-152. [http://dx.doi.org/10.1161/CIR.0b013e318282ab8f] [PMID: 23283859]

[80] Andres, R.H.; Horie, N.; Slikker, W.; Keren-Gill, H.; Zhan, K.; Sun, G.; Manley, N.C.; Pereira, M.P.; Sheikh, L.A.; McMillan, E.L.; Schaar, B.T.; Svendsen, C.N.; Bliss, T.M.; Steinberg, G.K. Human neural stem cells enhance structural plasticity and axonal transport in the ischaemic brain. *Brain,* **2011**, *134*(Pt 6), 1777-1789. [http://dx.doi.org/10.1093/brain/awr094] [PMID: 21616972]

[81] Bacigaluppi, M.; Pluchino, S.; Peruzzotti-Jametti, L.; Kilic, E.; Kilic, U.; Salani, G.; Brambilla, E.; West, M.J.; Comi, G.; Martino, G.; Hermann, D.M. Delayed post-ischaemic neuroprotection following systemic neural stem cell transplantation involves multiple mechanisms. *Brain,* **2009**, *132*(Pt 8), 2239-2251. [http://dx.doi.org/10.1093/brain/awp174] [PMID: 19617198]

[82] Liu, Z.; Li, Y.; Zhang, X.; Savant-Bhonsale, S.; Chopp, M. Contralesional axonal remodeling of the corticospinal system in adult rats after stroke and bone marrow stromal cell treatment. *Stroke,* **2008**, *39*(9), 2571-2577. [http://dx.doi.org/10.1161/STROKEAHA.107.511659] [PMID: 18617661]