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Review Article

ROLE OF ENDOTHELIN SYSTEM IN ISCHEMIC STROKE

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ABSTRACT

Stroke is the devastating neurological disease with limited functional recovery and is the third leading cause of death in the western world. Cerebral ischemia causes disturbances in a variety of cellular and molecular mechanisms, including oxidative phosphorylation, membrane function, neurotransmitter release, and free radical generation. During the ischemia, multiple biochemical changes take place like excessive of ca^{2+} entry and resulting cytosolic Ca^{2+} overload is essential for ischemic brain injury. Several cell signaling pathways are associated with the protective mechanisms of postconditioning, including the Akt, MAPK, PKC pathways and K_{ATP} channels. Several studies have shown the involvement of endothelin system in ischemic stroke. The present review aims to examine the neuroprotective effect of endothelin antagonists on ischemic cerebral injury. The results observed from the study provide the perspectives on the pathophysiology of stroke and may give beneficial effects of treatment by use of endothelin antagonists.

Keywords: Stroke, Cerebral ischemia, Cell signaling pathways, Endothelins

INTRODUCTION:

A stroke is caused by rapid loss of brain functions due to disturbance in blood supply to the brain. This can be caused by ischaemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism) or a hemorrhage [1]. Stroke is the leading cause of disability worldwide, the second most common cause of dementia and the third leading cause of death [2]. Understanding the cellular and molecular mechanisms underlying ischemic brain injury is essential for establishing effective therapeutic interventions. Although multiple biochemical changes take place during brain ischemia, it is generally believed that excessive Ca^{2+} entry and resultant cytosolic Ca^{2+} overload is essential for ischemic brain injury [3]. Stroke symptoms typically start suddenly, over seconds to minutes, and in most cases do not progress further. 95% of strokes occur in people age 45 and older, and two-thirds of strokes occur in those over the age of 65 [4]. Due to increase in life expectancy in many countries, the number of individuals at risk from stroke is anticipated to rise, making the burden of stroke disability an even more serious public health care concern that needs to be urgently addressed.

Mechanism of ischemic brain damage

Ischemic brain injury occurs when oxygen and glucose supply decreases to the brain, due to which production of ATP decreases in the tissue. Pathophysiological changes that occur as response to stroke are excitotoxicity, disruption of sodium and calcium influx,

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free radical production, inflammatory process stimulation, enzymatic changes, release of endothelins, platelets and leucocytes activation, dysfunction of endothelial and delayed coagulation. All these pathophysiological changes may contribute to brain injury following the onset of stroke (Figure: 1) [5].

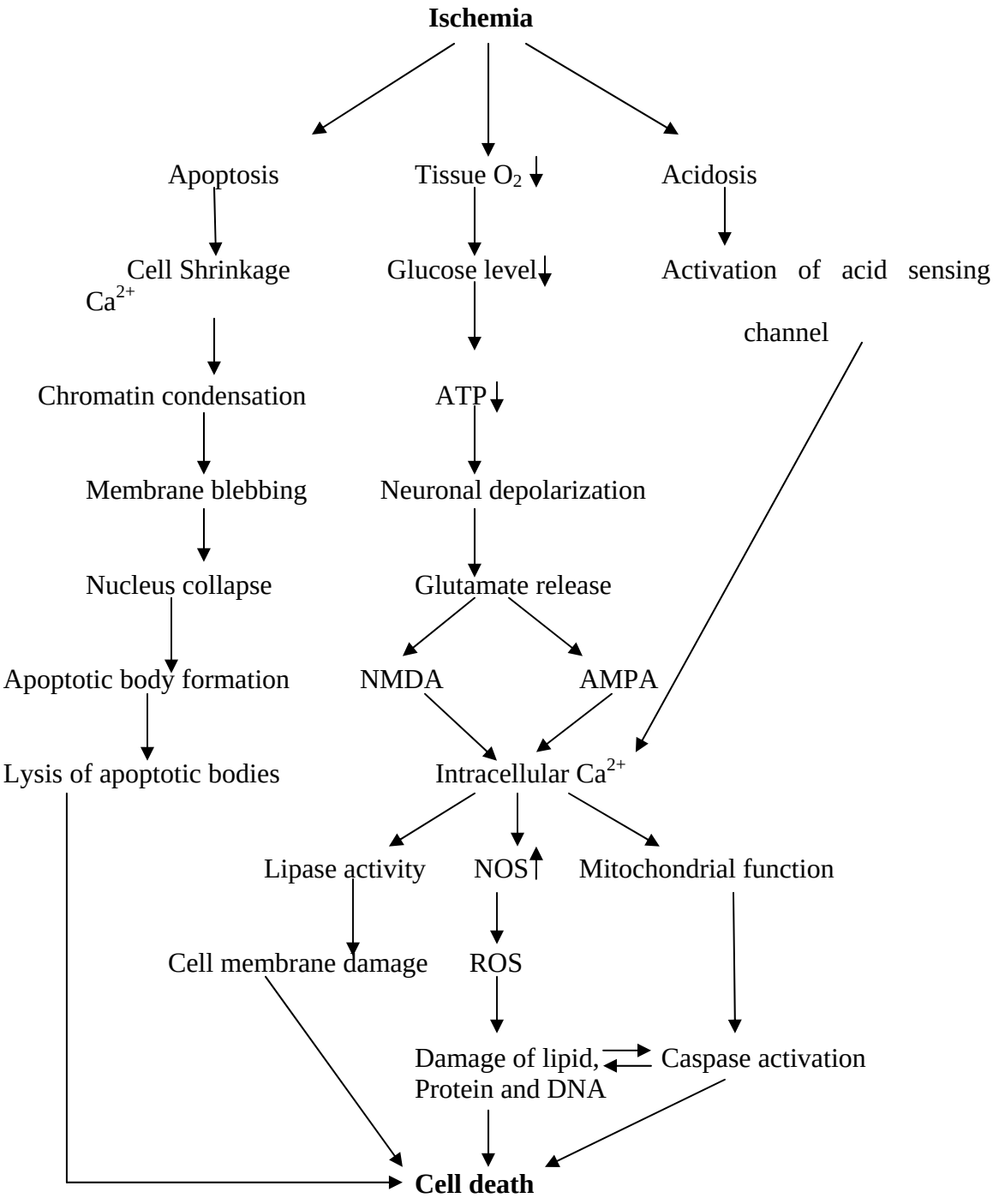

Figure: 1.Mechanism of Ischemic Brain Injury

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COMMON DRUG TREATMENT FOR STROKE

Thrombolytic agents: Evidence from various experimental stroke models that thrombolytics agents could reduce the ischemic effect provided the impetus for the evaluation of thrombolytic therapy in acute ischemic stroke [6]. Various thrombolytic agents like urokinase, streptokinase and recombinant tissue plasminogen activator (rt-PA) have been tried in experimental studies. Despite the risk of potential side effects associated with rt-PA (0.9 mg/kg, i.v), it is the only drug approved by FDA so far for emergency treatment within three hours of onset of ischemic stroke. This emphasizes the limited resources available for improving ischemic stroke mortality and morbidity [7].

Neuroprotection: Several mechanisms of neuronal injury have been proposed including increased excitotoxicity, calcium overload, radicals formation and inhibition of protein synthesis [8]. These factors may not be sequential but certainly are interlinked. The neuroprotective drugs inhibit the ongoing ischemic cascade by acting at various sites that ultimately lead to neuronal death.

Combination therapy: The objective for combination therapy is based on the increasing knowledge of the pathophysiological mechanisms of ischemic brain damage. A number of independent lethal mechanisms (excitotoxicity, radical damage, proteolytic activation, induction of apoptosis) are involved in the ischemic processes that ultimately lead to cell death. Each agent affects only one of the several mechanisms in the ischemic cascade whereas combination therapy has the potential to affect various points in the cascade [9, 10]. Combining neuroprotection with thrombolytics may decrease or eliminate the untoward effects of thrombolysis i.e. hemorrhagic conversion, frank parenchymal hemorrhage, and reperfusion injury, which may partially or totally eliminate the benefits of reperfusion itself. Neuroprotective agents if administered early may prolong the time interval that the brain can tolerate ischemia before reperfusion.

Thrombolytic agents and neuroprotective agents may act synergistically and may result in more complete attenuation of ischemic damage and better functional outcome than either of the two treatments [11]. There is substantial evidence in experimental studies that a combination of neuroprotective and thrombolytic agents or two or more neuroprotective agents with a different mechanism of action is more effective than the any single agent [12]. In humans, use of pre hospital antiexcitotoxic and calcium antagonist therapies, early thrombolysis on arrival followed by free radical scavenger and anti-inflammatory therapies, and finally antiapoptotic and growth factor therapies can be a beneficial approach [13].

Endothelin

After an ischaemic stroke the levels of ET-1 is increased in plasma, cerebrospinal fluid and cerebral tissue. Endothelins are regulatory peptides, distributed in many organ systems and produces various physiological effects like hypertension, pulmonary

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hypertension, preeclampsia, ischemic heart diseases, renal failure, subarachnoidal hemorrhage, and cerebral ischemia [14]. 21 amino acid peptides isolated from porcine endothelial cells [15], synthesize to maintain potency of blood vessels and fluidity of blood [16]. Endothelins are widely distributed in the body, cells of brain choroid pluxes and peripheral nerves. Isoforms of endothelins: ET-1 (Endothelin-1); ET-2 (Endothelin-2); ET-3 (Endothelin-3). Physiological effects of these four ET subtypes are mediated via two receptor subtypes, endothelin type A (ET_A) and endothelin type B (ET_B) [17].

Endothelin-A receptor are found in smooth muscle tissues of blood vessels and binding of endothelin to ET_A increases vasoconstriction and retention of sodium leading to increased blood pressure. Endothelin-B receptor located on endothelial cells that line the interior of blood vessels. When endothelial bind to ET_B-receptor, this lead to release of nitric oxide, natriuresis, diuresis and the mechanisms that lower the blood pressure [18].

Both ET-l and ET-3 are present in the brain and specific binding sites have been identified ET in the central nervous system is localized in neurons and micro vessel endothelial cells [18]. The pharmacological activities of ET-l are expected to contribute to neuronal injury associated with ischemic and hemorrhagic stroke. ET can cause subarachnoid hemorrhage in the anesthetized rabbit, it is increased in both the plasma; and the cerebrospinal fluid after subarachnoid hemorrhage related to vasospasm, and the experimental application of ET - 1 into the brain produces focal infarctions. Since ET can produce prolonged vasospasm, hypoperfusion, and neuronal damage, it might exacerbate tissue damage in hemorrhagic and ischemic stroke.

Endothelin receptors

ET act through a number of particular G-protein linked receptors of which several have been cloned so far [19]. Three subtypes of mammalian ET-receptors have been identified: ET_A (50-70 kDa), ET_{B1} and ET_{B2} (30-40 kDa). The amino acid structure of both subtypes is in 50% identical, and each subtype can be frequently found across mammalian species (85-90%) [20]. ET-1 induced constriction occurs via ET_A in the smaller resistance vessels [20]. All the same, ET_B can work either as vasoconstrictor or as vasodilator depending on the species or the specific type and location of the vasculature [21]. ET_A and ET_B are up-regulated in ischemic stroke [22].

ET_A is found chiefly in cerebrovascular smooth-muscle cells, arbitrates a potent and long-lasting vasoconstriction or cell proliferation and preferentially binds ET-1 [23]. To stimulate PLC, ET_A-induced vasoconstriction is related to the receptor's ability, that leads to the formation of inositol 1, 4, 5-tripshosphate and diacylglycerol [19]. The former increases $[Ca^{2+}]_i$, which in turn causes increased myosin light chain phosphorylation and vascular smooth muscle cells contraction [24]. This vasoconstriction occurs after ET-1 is removed from the receptor [25], probably because the $[Ca^{2+}]$i remains elevated. NO shortens the duration of vasoconstriction by accelerated return of $[Ca^{2+}]$i to its basal concentration [26]. Diacylglycerol and calcium stimulates proteinkinase C (PKC), which mediates

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the mitogenic action of ET-1 [27]. ET_B is distributed generally on vascular endothelial cells and follows the endothelium-dependent vasodilatation via NO and prostacyclin-synthesis [28]. This effect is equal for ET-1 and ET-3. Vascular constriction in peripheral vessels are caused by activation of the ET_{B2} on vascular smooth muscle cells [28], but so far, this has not been proved for cerebral circulation. Recent data, however, suggest an ET_B-dependent delayed vasoconstriction in subarachnoid hemorrhage (SAH) [29]. The (intra)cellular effect of ETB activation is similar to that of activation of ET_A in stimulating PLC activation, the generation of inositol 1,4,5-triphosphate or diacylglycerol, and the different Ca^{2+}-mobilization mechanisms, including Ca^{2+} release from intracellular Ca^{2+} stores or activation of L-type and nonselective Ca^{2+} channels[19]. However, ETB is linked to inhibitory G proteins, which in some cells leads to inhibition of cAMP generation and activation of Na^{+}-H^{+} antiporter [30]. Transient vasodilatation is caused by binding of ET-3 to ET_B and is probably caused by increased NO and prostacyclin production [31].

Role of endothelin in stroke

Mechanisms contributing to evolution of ischemic brain injury are complex and multifunctional [32]. To constrict a number of cerebral vessels in vivo and to reduce CBF below the ischemic threshold to induce infarction, ET-1 has been demonstrated to override cerebral autoregulatory mechanisms [33].

Neuronal injury causes by endothelin in stroke

Endothelins proliferate or differentiate the astrocytes and microglia may also be stimulated by ETs, since alveolar macrophages are activated by ET-1to produce superoxide anions. Astrocyte and microglia both aggregated in the neuronal lesion can express the both ET and NOS [20]. In the endothelium, stimulation of ET_B increases NO production [31] or ET and NO reciprocally modulate the production and action [34]. ET-1 inhibits cytokine-stimulated transcription of iNOS, and in CHO cells expressing ETA, NO terminates the ET-1 response in the mesengial cell [26]. Thus, it may be suggested that in the rat's brain, glial ET system and NOS may participate in neuronal damage, possibly through mutual regulation in astrocytes and microglia.

Clinical aspects of endothelin in stroke

ET-1 levels are significantly higher in CSF of patients with large cortical than with smaller subcortical infarctions [35]. Higher plasma ET-1 levels in patients with cardioembolic stroke may be explained by warfarin use [36].

Different risk factors for stroke are associated with increased ET levels. One study demonstrates a correlation between plasma ET activity and age [37], whereas several others do not show any difference [38, 39]. A significant positive correlation is reported between cholesterol and ET-1 levels [39]. The elevation of plasma ET-1 activity observed in hypercholesterolemic patients even without atherosclerotic lesions may reflect endothelial dysfunction [40]. Arterial hypertension correlates with ET-1 levels [41], although perfectly normal ET-1 levels were also observed [39]. These data may contribute to enhancement of severity and size of infracted tissue by the amount of increased ET-1 levels in stroke patients.

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Neuroprotection by endothelin receptor antagonists in stroke

After focal cerebral ischemia, ET receptor antagonists have been shown to decrease brain damage [42, 44]. The deprecative evaluation of data is difficult because there is difference in experimental design, species and receptor antagonist used. Most of the studies have been intervened with ET receptors antagonists after focal ischemia have concentrated on the role of ET_A as mediator of brain injury. The role of ET_B in ischemic disease is still to be clarified.

Selective ET_A or mixed ET_A/ET_B antagonists have been shown in some, but not all, studies to increase CBF or improve neurological outcome and to reduce infarction volume in different models of global and focal cerebral ischemia [45]. One of the key issues is whether selective ET_A or mixed ET_A/ET_B antagonists are likely to be effective in treating ischemic stroke [46]. Recently, it was reported that selective ET_A antagonism provides protection after focal ischemia, whereas the role of mixed ET_A/ET_B antagonists is not yet clarified [47]. In addition, it has been suggested that ET_B may be a clearance receptor in ischemic stroke. The direct adventitial application of an ET_B agonist onto dilated arterioles after focal ischemia showed that ET_B receptor-induced dilation in normal pial arterioles is lost in postischemic vessels suggesting that ET_B receptor-induced vascular effects may vary in pathologic situations such as acute stroke. More importantly, ET_{B1}/ET_{B2} antagonist in dilated arterioles, compared to vehicle treated control group, suggest that ET_B participate significantly in restricting postischemic dilatation of cortical arterioles in the ischemic penumbra [44]. Nonetheless, this contribution of ET_B in limiting vasodilatation is less pronounced compared with that of ET_A [48]. ET_A blockage completely prevented the development of brain edema by decreased blood pressure, which may well contribute to this protection [49]. Polymorphonuclear leukocytes play an important role in the development of ischemic damage by reducing microvascular blood flow, initiating thrombosis, and releasing free-oxygen radicals [48]. But anti-leukocyte interventions cannot attenuate ischemic brain damage [48]. ETs enhance the expression of intracellular adhesion molecule-1 and IL-8 on brain capillary endothelial cells via ET_A [50] suggesting the possibility of polymorphonuclear leukocytes being implicated in ET-induced brain tissue damage. Inactivation of vascular ET_B accelerates pathological vascular remodeling in which gene expression of ET-1 mRNA is comparably increased, whereas tissue basal NO level is significantly decreased [51]. Gene expression of ET-1 and endothelial NO synthase is reciprocally regulated by flow or shear stress in cultured endothelial cells [52]. Therefore, it may be suggested that decreased CBF initially induces an increased ET-1 expression and a decreased NO production, resulting in an imbalance between ET-1 and NO levels in ischemic lesions [51]. Furthermore, failure of ET_B-mediated NO release cause a significant decrease in tissue NOx (Nitrogen oxidase) level and consequently leads to pathological aggravation of ischemia [52]. In addition, ET_B blockade following ischemia modulates glial scar formation and may provide a more permissive substrate for neuronal survival and regeneration [53]. One important

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question remains whether ET receptors also directly or indirectly drive astrocyte changes following neuronal damage. In addition, ET acting at astrocyte ET_B can have a significant worsening impact on the glial environment after brain damage favoring the use of a mixed ET_A- and ET_B-antagonist. Furthermore, ET_B expressed by astrocytes is accessible to pharmacological manipulation, as either stimulation or antagonism of this receptor subtype significantly alters the damage-induced hypertrophy and number of astrocytes expressing this receptor.

ET_A receptor antagonists also appear to offer an essential advantage of multiple neuroprotective mechanisms, including prevention of blood-brain barrier disruption and leukocyte infiltration [54].

CONCLUSION

Stroke is most common cause of mortality and morbidity and is very common problem in young patients mostly in developing countries. Despite the multifactorial manifestations of stroke, there are fortified reasons to believe that oxidative stress is the common factor that plays an important middle role in pathogenesis of thsssese diseases. Formation of reactive oxygen species has been found as common factor for etiology of stroke. Treatment of stroke is still not satisfactory so lot of research is undergoing to find the newer drugs and newer avenues for the treatment of stroke that can treat the stroke satisfactorily and show the fewer side effects. One such approach is endothelin receptor antagonists, can be used for the treatment of stroke. It can prevent the brain edema by reducing the blood pressure.

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