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ROLE OF SOVATELTIDE IN PROMOTING NEURAL REPAIR FOLLOWING ISCHEMIC STROKE: MECHANISTIC AND THERAPEUTIC PERSPECTIVES

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Abstract : Sovateltide, a selective endothelin-B receptor (ETBR) agonist, is emerging as a promising therapy for acute ischemic stroke. Unlike current treatments such as mechanical thrombectomy and intravenous thrombolysis, which are limited by narrow time windows and bleeding risks, sovateltide offers a novel approach that goes beyond restoring blood flow. It enhances cerebral circulation, reduces oxidative stress, protects against cell death, supports mitochondrial function, promotes the growth of new neurons, and decreases inflammation in the brain. Clinical trials (Phase II and III) show that patients receiving sovateltide alongside standard care experience significant improvements in neurological function and overall disability, as measured by NIHSS and mRS scores. Preclinical studies further indicate a 40–60% reduction in brain tissue damage. Although most data come from Indian populations and certain groups remain underrepresented, sovateltide appears safe and effective, representing a meaningful advance in neuroprotective and regenerative strategies for stroke recovery.

Keywords: Sovateltide, Ischemic Stroke, Endothelin, Blood Brain Barrier, Neuroprotective.

INTRODUCTION:

Stroke is a leading cause of disability and ranks as the second most common cause of death worldwide, after ischemic heart disease. It occurs when the brain's blood supply is interrupted, either by a blockage, known as ischemic stroke, or by a rupture, called hemorrhagic stroke. Prompt diagnosis and timely treatment are crucial to minimize brain damage and improve patient outcomes.[1] Ischemic stroke is one of the most common cerebrovascular disorders, and its incidence is rising worldwide. Factors contributing to this increase include aging, underlying conditions such as diabetes, heart disease, and hypertension, as well as lifestyle choices like smoking and alcohol consumption.[2] In 2021, approximately 7.8 million new cases of ischemic stroke were reported worldwide, corresponding to an age-standardized incidence of about 92 per 100,000 people.[3] Worldwide, ischemic stroke was responsible for approximately 3.6 million deaths and contributed substantially to long-term disability.[4] Although age-standardized rates of ischemic stroke have declined globally, the overall burden continues to rise due to population growth and aging. The impact is particularly pronounced in regions such as East Asia, Sub-Saharan Africa, and Southeast Asia, especially among individuals over 50 years of age.[5] Between 1990 and 2021, global age-standardized rates of ischemic stroke declined, yet the total number of cases and deaths increased due to population growth and aging. Major risk factors include high blood pressure, elevated LDL cholesterol, and air pollution, with the greatest burden observed in low-income regions.[6] The central nervous system has a limited ability to regenerate after injury, underscoring the urgent need for therapies that promote neural repair and functional recovery. Current treatments often fall short of fully restoring lost brain function.[7] Stroke care involves prevention, acute treatment, and post-stroke rehabilitation. Currently, alteplase is the only medication approved by both the FDA and the EU for ischemic stroke. However, its short half-life and the risk of intracerebral hemorrhage limit its widespread use, highlighting the need for more effective and safer therapies.[8] The use of thrombolytic therapy is often limited due to concerns about symptomatic intracerebral hemorrhage and other bleeding complications.[9] Although preclinical studies have shown promise, neuroprotective drugs and cytoprotective strategies have largely failed in clinical trials, leaving a critical gap in therapies that can preserve or repair brain tissue beyond the initial reperfusion phase.[10,11] Mechanical thrombectomy can be effective for up to 24 hours in selected patients, and outcomes improve when it is combined with intravenous thrombolysis. Complications can be minimized with early aspirin administration, short-term dual antiplatelet therapy for mild strokes, and delayed anticoagulation in patients with atrial fibrillation. However, due to time constraints and contraindications, only about 20% of patients are eligible for endovascular therapy, while roughly 10% can benefit from intravenous thrombolysis.[9]

PATHOPHYSIOLOGY OF ISCHEMIC STROKE:

When a blood clot or embolus blocks a cerebral artery, ischemic stroke triggers a cascade of damaging events. Energy depletion, glutamate-driven excitotoxicity, ionic imbalance, oxidative stress, and inflammation collectively disrupt the blood–brain barrier and impair mitochondrial function, ultimately leading to cell death through apoptosis and necrosis.[12] These cellular processes lead to neuronal death, which spreads from the ischemic core to the surrounding salvageable penumbra. Therapeutic strategies that target excitotoxicity, oxidative stress, inflammation, and preserve the blood–brain barrier are critical for limiting tissue damage and improving outcomes.[13]

1. **Excitotoxicity:** Glutamate (Glu)-mediated excitotoxicity occurs when excess glutamate overstimulates N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), and kainate receptors (KARs), leading to neuronal injury.[14] This overactivation results in calcium ions (Ca^{2+}) overload, mitochondrial dysfunction, accumulation of reactive oxygen species (ROS), and ultimately neuronal cell death.[15]

2. **Blood-brain barrier (BBB) disintegration:** Disruption of the blood–brain barrier (BBB), as can occur in stroke, trauma, or dementia, allows blood-derived substances to enter the brain, leading to neuroinflammation, edema, and neuronal damage.[16] During stroke, the blood–brain barrier (BBB) is disrupted within hours. Enzymes degrade the tight junctions between cells, chemical mediators increase transport across the endothelial barrier, and astrocytes (star-shaped glial cells) swell or detach, collectively contributing to barrier breakdown.[17] In ischemic stroke, the blood–brain barrier (BBB) is disrupted when matrix metalloproteinases (MMP-2 and MMP-9) degrade key tight junction and adhesion proteins, including claudin-5, occludin, zona occludens-1 (ZO-1), and vascular endothelial cadherin (VE-cadherin). Inhibitors of MMPs can reduce this damage, while astrocyte aquaporin-4 (AQP4) and agrin help maintain BBB integrity.[18]

3. **Apoptosis:** In ischemic stroke, apoptosis, or programmed cell death, occurs in neurons within the penumbra—the area surrounding the ischemic core, primarily as a result of mitochondrial damage and DNA (deoxyribonucleic acid) injury.[19] Ischemic stroke, neuronal death is triggered by reactive oxygen species (ROS), calcium ions (Ca^{2+}), cytochrome c, and caspase-9/3, as well as the extrinsic tumor necrosis factor-alpha (TNF-α) pathway. These mechanisms act on inhibitors of apoptosis proteins (IAPs) and the B-cell lymphoma-2 (Bcl-2) family, promoting programmed cell death.[20]

4. **Neuroinflammation:** In ischemic stroke, neuroinflammation involves the activation of microglia and the release of cytokines. These processes can both protect and further damage brain tissue, highlighting their dual role in stroke pathology.[21] Brain ischemia activates microglia and astrocytes, leading to the release of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), as well as chemokines that recruit neutrophils and monocytes. This response disrupts the blood–brain barrier (BBB) and contributes to neuronal death, making it central to ischemic stroke pathology. While acute inflammation helps clear cellular debris, prolonged or chronic inflammation can impede recovery and promote neurodegeneration.[22]

5. **Oxidative stress:** During a stroke, the sudden return of blood flow to the brain, known as ischemia-reperfusion, triggers the production of highly reactive molecules called reactive oxygen species (ROS) and reactive nitrogen species (RNS). When these molecules overwhelm the body's natural antioxidant defenses such as superoxide dismutase (SOD), catalase, and glutathione (GSH), an imbalance occurs, leading to oxidative stress. This stress damages vital cellular components, including lipids, proteins, and DNA, ultimately harming brain cells and contributing to the severity of stroke injury.[23] In ischemic stroke, the loss of adenosine triphosphate (ATP) leads to mitochondrial dysfunction and an overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These harmful molecules attack lipids, proteins, and DNA, triggering inflammation, programmed cell death (apoptosis), and breakdown of the blood-brain barrier (BBB). As a result, injury in the surrounding brain tissue, known as the penumbra, worsens. This damage occurs even in the presence of natural antioxidants, such as glutathione (GSH) and superoxide dismutase (SOD), which are insufficient to counteract the overwhelming oxidative stress.[24] In stroke, reactive oxygen species (ROS) activate matrix metalloproteinases (MMPs), enzymes that break down the tight junctions between cells. This disruption of the blood-brain barrier (BBB) allows harmful substances to enter the brain, leading to lipid peroxidation, death of endothelial cells, inflammation, and brain swelling (edema). These processes increase the risk of hemorrhage and contribute to long-term brain injury.[25]

ENDOTHELIN SYSTEM IN BRAIN:

The endothelin system consists of three peptides, two peptidases, and two G-protein-coupled receptors (GPCRs). It is widely expressed in brain cells and tumors and regulates both short-term and long-term cellular responses. In conditions such as stroke, trauma, Alzheimer's disease, and inflammation, reactive astrocytes show altered levels of endothelins (ETs), highlighting the system's role in disease-related cellular changes.[26] The G-protein-coupled endothelin receptors ETA and ETB bind the endothelins (ET-1, ET-2, and ET-3). ETA receptors, which are highly expressed on vascular smooth muscle, promote vasoconstriction and cell proliferation through Gq, Gi, and G12 signaling pathways. In contrast, ETB receptors, which are equally present on endothelial cells, support vasodilation, stimulate the release of nitric oxide (NO), and help clear endothelins from circulation.[27] Endothelin-2 (ET-2), which is less abundant in neurons, causes only mild blood vessel constriction. Endothelin-3 (ET-3), found in brain stem cells, activates endothelin-B (ETB) receptors to support cell growth and protection. In contrast, endothelin-1 (ET-1), the most abundant isoform, worsens stroke-related injury by constricting cerebral blood vessels through

endothelin-A (ETA) receptors.[28] High levels of endothelins (ETs) in the brain contribute to stroke by causing vasospasm through endothelin-A (ETA) receptors and promoting brain swelling (edema) via endothelin-B (ETB) receptors, partly through the actions of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF). At the same time, ETs activate ETB receptors to stimulate the proliferation of neural progenitor cells, release neurotrophic factors, and trigger reactive astrogliosis. These dual effects make the brain endothelin system an attractive target for strategies aimed at neuroprotection.[29]

SOVATELTIVE PHARMACOLOGICAL PROFILE:

Endothelial cells, which make up the inner lining of blood arteries, have receptors that are activated by sovateltide, a highly specific peptide agonist of endothelin-B receptors. The blood supply of tumors is different from that of healthy tissues because the blood arteries in actively growing tumors are mostly made of endothelial cells and have little smooth muscle support.[30]

- **MECHANISM OF ACTION:** Sovateltide is a synthetic version of endothelin-1 and a selective agonist of the endothelin-B receptor (ET-B). It affects many of the central nervous system's (CNS) receptors. By increasing antioxidant activity, decreasing apoptosis, maintaining mitochondrial function, boosting angiogenesis, and increasing cerebral blood flow, it has neuroprotective benefits. Following a cerebral ischemic stroke, these combined actions promote healing.[31–34]
- **DOSE:** Three intravenous (IV) bolus injections, each administered at a concentration of 0.3 micrograms per kilogram (µg/kg), are the standard dosing schedule in clinical trials. The intervals between dosages are roughly three hours, and each dose is given over the course of one minute. On days 1, 3, and 6 of therapy, this schedule is adhered to, yielding a daily dosage of 0.9 µg/kg.[31,32]
- **PHARMACOKINETIC PARAMETER:** In terms of pharmacokinetics (PK), sovateltide has a brief half-life in humans, roughly five minutes. It has not been linked to any notable negative effects on hemodynamic (HD) measures or metabolic indicators, and it is generally well tolerated.[31,32]
- **SAFETY AND EFFICACY:** Phase I through Phase III trials and other clinical research have demonstrated that sovateltide greatly enhances neurological outcomes. Standard metrics such the Barthel Index (BI), National Institutes of Health Stroke Scale (NIHSS), and modified Rankin Scale (mRS) are used to evaluate these advantages. In general, sovateltide-treated patients show higher rates of recovery than placebo-treated individuals.[33,34]
- **SIDE EFFECTS:** Sovateltide is generally well tolerated, with minimal side effects and no reported drug-related adverse events (AEs). The incidence of intracranial hemorrhage (ICH) is comparable between the sovateltide and control groups, further supporting its favorable safety profile.[34]

TOXICOLOGICAL PROFILE:

Sovateltide has demonstrated an excellent safety profile in animal studies, causing no mortality or major organ toxicity, including cardiovascular effects, even at repeated intravenous (IV) doses. It showed no allergic, reproductive, or teratogenic effects and was non-mutagenic and non-clastogenic. Notably, when combined with chemotherapy, sovateltide contributed to complete tumor regression, highlighting its safety and therapeutic potential.[35]

MECHANISMS OF NEURAL REPAIR BY SOVATELTIDE:

Sovateltide, a highly selective endothelin-B receptor (ETBR) agonist, promotes neuroprotection and brain repair through multiple mechanisms. By activating ETBRs, it enhances cerebral blood flow, reduces oxidative stress, and limits apoptosis by increasing pro-survival signals, such as phosphorylated Akt (phospho-Akt) and B-cell lymphoma 2 (Bcl-2), while decreasing pro-apoptotic markers like Bax. It also stimulates neural progenitor cells to mature into neurons and boosts mitochondrial function, including fusion and biogenesis, supporting neurogenesis and tissue recovery. Blocking ETBRs abolishes these effects, confirming that sovateltide's benefits are specifically mediated through ETBR activation.[35]

Sovateltide promotes neural repair by encouraging neural progenitor cells to differentiate into mature neurons, as indicated by increased expression of HuC/HuD and NeuroD1. It also improves mitochondrial function by enhancing fusion and biogenesis while reducing harmful mitochondrial fission. Together, these effects support better neurological and motor recovery following stroke.[36]

PRECLINICAL STUDIES OF SOVATELTIDE:

1. Sovateltide significantly reduced amyloid-beta (Aβ) plaque accumulation in 6- and 12-month-old APP/PS1 transgenic mice and improved learning and memory. It also lowered oxidative stress by decreasing malondialdehyde (MDA) and lipid peroxidation while boosting antioxidant defenses, including superoxide dismutase (SOD) and glutathione (GSH). In addition, sovateltide enhanced mitochondrial health and promoted differentiation of neural progenitor cells. No significant effects were observed at three months of age.[37]
2. Sovateltide markedly improved motor function and locomotor recovery in rats with spinal cord injury, reducing neurological deficits and pain sensitivity. Treated animals showed sustained recovery, approaching pre-injury performance levels, whereas control animals did not. These findings highlight sovateltide's neuroprotective, anti-inflammatory, and pain-relieving (antinociceptive) effects, supporting its potential as a therapeutic option for spinal cord injury. Further clinical studies are needed to confirm these benefits in humans.[38]

CLINCAL STUDIES AND EVIDENCE:

1. In preclinical models of middle cerebral artery occlusion (MCAO), the endothelin-B receptor (ETBR) agonist sovateltide reduced infarct size by 40–60% by protecting the blood-brain barrier (BBB) and enhancing cerebral blood flow within a six-hour therapeutic window. Phase I clinical studies confirmed its safety, and the Phase II RAISE trial showed significant improvements in neurological outcomes, including the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores.[39]
2. In a Phase II clinical trial (n=148), sovateltide combined with standard care produced significantly better outcomes than placebo. At 90 days, 54% of patients showed a ≥2-point improvement on the National Institutes of Health Stroke Scale (NIHSS) compared with 32% in the placebo group (p=0.024). Similarly, 49% achieved a favorable outcome on the modified Rankin Scale (mRS 0–2) versus 28% with placebo (p=0.027). The treatment was well tolerated and did not increase the risk of bleeding, supporting its favorable safety profile.[40]
3. In patients with acute ischemic stroke, sovateltide substantially improved functional and neurological recovery. At 90 days, a greater proportion of patients achieved favorable outcomes on the modified Rankin Scale (mRS) and the National Institutes of Health Stroke Scale (NIHSS) compared with controls. Sovateltide also increased the rates of complete recovery, was well tolerated, and caused only minor, transient side effects without increasing serious adverse events. While larger international trials are needed to confirm its global applicability, the data support sovateltide as a safe and effective addition to standard care.[34]

LIMITATIONS AND CHALLLENGES

- Most of the clinical data on sovateltide come from a single country (India) and a limited number of centers, which may restrict the generalizability of the findings to more diverse populations and healthcare systems.[34]
- Longer-term and larger global data are still awaited, such as from the RESPECT-ET trial. Current evidence of sovateltide's effectiveness comes from a small Phase II trial (n=40) and a larger Phase III trial (n=158).[32,34]
- The findings cannot be generalized to patients with hemorrhagic stroke, those treated with endovascular procedures, or individuals with recurrent stroke, as the trials to date have focused.[32]
- Most trial participants were younger adults (18–70/78 years), meaning that older and frailer patients who represent the majority of real-world stroke cases are underrepresented.[32]
- Laboratory and hemodynamic parameters remained unaffected, and Phase I, II, and III studies including healthy volunteers reported no clinically significant drug-related adverse effects.[32,34]

FUTURE PERSPECTIVE:

- Need for large-scale, multicenter, and globally diverse clinical trials to validate current findings.
- Optimization of treatment protocols with further research should focusing on the ideal therapeutic window, dosing regimen, and timing of administration, especially in relation to existing treatments such as intravenous thrombolysis and mechanical thrombectomy.
- Long term outcome studies are necessary to evaluate sustained neurological recovery, cognitive function, quality of life, and functional independence.
- Advancements in precision medicine and biomarker driven approaches may help to identify patients most likely to benefit from sovateltide therapy. Integration with neuroimaging techniques and molecular markers could enable personalized treatment strategies.

CONCLUSION:

Sovateltide, a highly selective endothelin-B receptor (ETBR) agonist, offers a promising approach for acute ischemic stroke by addressing the critical need for therapies that promote brain regeneration and functional recovery beyond reperfusion. It exerts multiple beneficial effects, including enhancing cerebral blood flow, reducing oxidative stress, limiting apoptosis, promoting neural progenitor cell differentiation into mature neurons, and improving mitochondrial function—mechanisms essential for long-term tissue repair and neurological recovery. Clinical evidence from Phase II and III trials shows that, whether used alone or alongside standard care, sovateltide significantly improves neurological and functional outcomes, as measured by the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores. The therapy is well tolerated, demonstrating a strong safety profile with no significant adverse effects or systemic toxicity. While current data are largely limited to specific populations, highlighting the need for larger, international studies, sovateltide appears to be a safe and effective addition to conventional stroke treatment, offering a unique neuroprotective and regenerative strategy with the potential to reduce the global burden of ischemic stroke-related disability.

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