Review Article

Ischemic Stroke and Neuroprotection

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Abstract

Stroke is a major cause of morbidity and mortality in both developed and developing countries of the world. Greater understanding of the pathophysiology of neuronal damage in ischemic stroke has generated interest in neuroprotection as a management strategy. This paper aims to review the current concept and place of neuroprotection in ischemic stroke. An extensive search of all materials related to the topic was made using library sources including Pubmed and Medline searches. Current research findings were also included. The findings are as presented. Neuroprotection is an increasingly recognized management strategy in ischemic stroke that promises to assist clinicians in reducing stroke mortality rates and improving the quality of life of survivors.

Keywords: Neuroprotection, Review, Stroke ischemic

Introduction

Stroke or cerebrovascular accident is defined as an acute focal or global neurological deficit lasting longer than 24 h or leading to death and which is of no aetiology other than vascular.[1]

It is the third leading cause of death in Western countries.[2] In Africa it accounts for 4-9% of deaths and between 6.5% and 41% of neurological admissions in hospital based studies.[3] Findings from South West Nigeria show that the incidence of stroke rises with age reaching a peak in the 8th decade in males and 7th decade in females.[4]

Stroke is classified as being either hemorrhagic or ischemic in nature depending on the underlying pathological process responsible. Several studies have documented that the ischemic subtype accounts for the greater number of stroke cases.[5-8] An ischemic stroke occurs when a cerebral vessel occludes, obstructing blood flow to a portion of the brain.

The only currently approved medical stroke therapy, tissue plasminogen activator (tPA), is a thrombolytic that targets the thrombus within the blood vessel. Neuroprotective agents, another approach to stroke treatment, have generated as much interest as thrombolytic therapies.

Access this article online	
Quick Response Code:	Website: www.amhsr.org
	DOI: 10.4103/2141-9248.105669

Materials and Methods

An extensive search of all materials related to the topic was made using library sources including Pubmed and Medline searches. Current research findings were also included. Key words used in the search include stroke ischemia, neuroprotection.

Pathogenesis and pathophysiology of ischemic stroke

The pattern of pathological damage from cerebral vascular occlusion varies depending on the degree and duration of the impaired blood flow.[9]

Ischemia causes loss of membrane potentials (anoxic depolarisation) and in its mildest form (brief focal ischemia) kills uniquely vulnerable neurones such as the pyramidal neurons in the CA1 and CA4 zones of the hippocampus while sparing other neurons and all glial cells. However, about 1 h of focal ischemia causes cerebral infarction characterized by the death of neurons, glial, and other supportive cells within the affected vascular bed. When ischemia lasts more than 1 h, this zone of infarction beginning in the central zone of lowest blood flow progressively enlarges in a circumferential fashion towards its maximum volume over 6-7 h in primates and an undetermined time in humans.[10]

Deprivation of oxygen supply to the brain tissue leads to activation of the ischemic cascade with a series of molecular mechanisms being activated. There is depletion of adenosine

triphosphate and consequent high levels of lactate and unbuffered hydrogen ions. These hydrogen ions facilitate the generation of ferrous iron-mediated free radicals that result in astroglial injury.

Failure of energy dependent mechanisms including ion pumps leads to deterioration of membrane ion gradients, opening of selective and unselective ion channels, and equilibration of most intracellular and extracellular ions (anoxic depolarisation). Thus potassium ions leave the cell, sodium, chlorine and calcium enter and many excitatory neurotransmitters (glutamate, aspartate) are released in potentially toxic concentrations.[11]

There is evidence that raised intracellular calcium accelerates many potentially injurious processes.[12] Calcium activates phospholipases which hydrolyse membrane-bound glycerophospholipids to free fatty acids and these in turn facilitate free radical peroxidation of other membrane bound lipids. Calcium similarly activates both proteases that lyse structural proteins as well as nitric oxide synthase that initiates free radical mechanism.[13]

The intracellular entry of calcium is made largely possible by the activation of two types of receptors: Voltage gated (L-type) and/or several *N*-methyl-D-aspartate (NMDA) and quisqualate (Q) post synaptic receptor/channel complexes (named after their most potent agonist molecule) by glutamate. Blockade of either receptors leads to a reduction in infarct volume in laboratory animals with focal brain ischemia.[9]

Outside these mechanisms, a role in the ischemic cascade for inflammatory cells has been demonstrated. Despite the good outcome generally associated with reopening a blood vessel, additional brain injury may result when reperfusion occurs. When white blood cells reenter a previously hypoperfused region via returning blood, they can occlude small vessels, producing additional ischemia. Leukocytes release toxic products that can lead to free radical and cytokine formation.

Agents that prevent white blood cells from adhering to vessel walls, limit formation of free radicals, or promote neuronal repair may protect the brain from additional injury during reperfusion. Neuroprotective agents that work primarily during reperfusion may have a longer window of therapeutic effect than drugs that work earlier in the ischemic cascade.

Implications for therapeutic neuroprotection

By preventing excitatory neurotransmitter release, neuroprotective agents may reduce deleterious effects of ischemia on cells. A recent review of this topic by Lutzep and Clark provides us further insight into various agents that have come under the searchlight:[14]

Modulating the *N*-methyl-D-aspartate receptors

The most commonly studied neuroprotective agents for acute stroke block the N-methyl-D-aspartate (NMDA) receptor. Dextromethorphan, a noncompetitive NMDA antagonist and metabolite of cough suppressant, was the first NMDA antagonist studied in human stroke patients. Unfortunately, dextromethorphan caused hallucinations and agitation; it also produced hypotension, which limited use.

To avoid these unpleasant side effects indirect NMDA receptor antagonists that work at the glycine site of the receptor were developed. These agents prevent glycine from binding, which in turn prevents glutamate from activating the receptor. A large, 1367-patient, efficacy trial with the agent GV150526 was completed in 2000. Although the drug was reported to be safe and well tolerated, no improvement was observed in any of the 3-month outcome measures.

Magnesium is another agent with actions on the NMDA receptor and a low incidence of side effects. It may reduce ischemic injury by increasing regional blood flow, antagonizing voltage-sensitive calcium channels, and blocking the NMDA receptor. The benefit is the subject of the ongoing Field Administration of Stroke Therapy—Magnesium Phase III (FAST-MAG) Trial.

Modulating the non NMDA receptors

Modulating other non-NMDA receptors and channels also can reduce excitatory neurotransmitter release. Nalmefene (Cervene) is a narcotic receptor antagonist that reduces levels of excitatory neurotransmitters contributing to cellular injury in early ischemia. Unlike NMDA receptor antagonists, this drug causes minimal side effects. Post hoc analyses of early studies suggest that the drug may have more benefit in patients younger than 70 years. However, a later clinical trial in which the drug was administered intravenously (IV) within 6 h of symptom onset showed no benefit.

The exact mechanism of action of lubeluzole, a drug effective in animal models, is unclear. The drug may block sodium channels in cells. In addition, it may reduce the release of nitric oxide, a neurotransmitter generated by activation of the NMDA receptor. Although stroke severity and patient age appeared to influence outcome in early studies, a later trial was unable to confirm that lubeluzole was efficacious in these subsets of acute stroke patients.

Clomethiazole, a g-aminobutyric acid agonist, decreases excitatory neurotransmission by increasing activity of inhibitory pathways. In Europe, clomethiazole's central nervous system inhibitory properties have been used for anticonvulsant and sedative effects. The potential efficacy of clomethiazole as a neuroprotective agent in ischemia was first investigated in Europe as part of the Clomethiazole Acute Stroke Study. Patients received a 24-h IV infusion of clomethiazole or placebo within 12 h of symptom onset. As predicted by the drug's inhibitory effects, its primary side effect was sedation. Overall, the study was negative.

Calcium channel blockers were extensively evaluated in acute stroke with the hope that stemming excessive cellular calcium influx caused by ischemia may prevent neuronal injury. Studies of calcium channel blockers did not show efficacy in stroke treatment. However nimodipine is of value in preventing secondary ischemic infarction as a result of vasospasm following subarachnoid haemorrhage.

Several drugs with novel mechanisms to modulate neurotransmission or ion channels have recently completed clinical trials. These treatments included an a-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid antagonist developed by Yamanouchi, USA, Inc; a serotonin agonist, repinotan, developed by Bayer Corporation; and a transmembrane potassium channel modulator developed by Bristol-Myers Squibb. Unfortunately, none of the clinical trials showed efficacy for the investigational treatment. ONO 2506, a novel neuroprotectant developed by Ono Pharmaceutical Co. Ltd, that inhibits astrocyte activation, was administered within 6 hours of stroke onset. A futility analysis performed in May 2005 led to discontinuation of the trial in the United States.

Another target of neuroprotective therapy in acute ischemic stroke is free-radical generation, which leads to further release of calcium and excitatory neurotransmitters. The free-radical scavenger tirilazad did not show benefit in an acute stroke trial. The drug also was investigated in subarachnoid hemorrhage and in traumatic brain injury, without convincing evidence of benefit. The free-radical trapping agent NXY-059 is currently being investigated in stroke efficacy trials (see below).

Phase 3 trials are still ongoing for certain agents. In addition to assessments of NXY-059, a trial is investigating albumin within 5 h of symptom onset. In preclinical studies, albumin appears to have both antioxidant properties and the ability to increase blood flow to the penumbra. Hypothermia is also being evaluated for its neuroprotective capabilities. One study is evaluating hypothermia (treatment within 300 min) in conjunction with a combination of caffeine and ethanol (caffeinol) (treatment within 240 min).

Agents in earlier acute stroke trials include SUN N4057 or piclozotan, a serotonin agonist (Daiichi, Asubio Pharmaceuticals); TS-011 (Taisho Pharmaceutical Co. Ltd), which blocks the synthesis of 20-hydroxyeicosatetraenoic acid (20-HETE), a potent vasoconstrictor; lovastatin, a statin agent; and normobaric oxygen.

The free-radical trapping agent NXY-059 is the first neuroprotectant to show efficacy in an acute stroke treatment trial. The trial, called Stroke-Acute Ischemic NXY Treatment (SAINT I), was the first of two efficacy trials. The drug was delivered intravenously over 72 h in patients within 6 h of stroke symptom onset.

Patients who received treatment had significantly better outcomes ($P = 0.038$) on the primary endpoint, the distribution of scores on the modified Rankin scale that assessed disability at 90 days. The co-primary endpoint did not show a difference between treatment groups. Of interest, post hoc analyses in patients treated with tPA showed that patients who received NXY-059 and tPA had significantly fewer hemorrhagic transformations than those who received placebo and tPA ($P = 0.001$) and symptomatic hemorrhagic transformations also occurred less frequently in this group ($P = 0.036$).

The second efficacy trial, SAINT II, completed enrollment in the summer of 2006. The results which came in by early 2007 proved to be disappointing. Nevertheless more studies are being planned to further assess this novel drug.

Anti-adhesion antibodies

Monoclonal antibodies can block an intercellular adhesion molecule (ICAM) on the endothelium to prevent adhesion of white blood cells to the vessel wall. Because anti-ICAM antibodies appear to block an early step in reperfusion-related injury, they present a hopeful mechanism for preserving neuronal function.

A large multicenter trial assessed clinical efficacy of anti-ICAM-1. More than 600 patients received either IV boluses of murine monoclonal antibody to ICAM-1 (enlimomab) or placebo for 5 days, beginning within 6 h after symptom onset. Treated subjects were found to have higher mortality rates and worse outcomes than subjects in the placebo group.

A phase III trial was then done by using a human antileukocytic antibody, Hu23F2G, developed by ICOS Corporation. Because the antibody is humanized and not murine, this agent hopefully avoids the unwanted effects of enlimomab. This agent did not appear to produce the immune response seen with enlimomab. However, no clinical benefit was seen with Hu23F26 on any of the planned measures.

Another antiadhesion monoclonal antibody strategy targets platelets. These antibodies inhibit platelet aggregation, potentially preventing additional ischemic injury during reperfusion as well as promoting thrombolytic action. Such an antiplatelet drug, abciximab (ReoPro), was in phase three clinical stroke treatment trials, but an increased rate of intracranial hemorrhage led to discontinuation of all trials.

Membrane stabilization

Citicoline is an exogenous form of cytidine-5'-diphosphocholine (CDP-choline) used in membrane biosynthesis. Citicoline may reduce ischemic injury by stabilizing membranes and decreasing free radical formation. A phase II trial showed improved outcome in stroke patients treated with either a 500- or 2000-mg/d dose of citicoline. A post hoc subgroup analysis of the phase III trial suggested that patients with more

severe strokes (National Institutes of Health Stroke Scale >8) had better functional outcome with citicoline.

Another phase 3 trial assessed infarct size on magnetic resonance imaging (MRI) in patients with mild, moderate, and severe strokes. Although this study also failed to show a significant difference between treated and untreated groups, there was a trend toward smaller infarct volumes in treated patients. A large international trial, ICTUS Study: International Citicoline Trial on acUte Stroke is enrolling patients within 24 h of stroke onset.

Neuronal healing

Fiblast, a basic fibroblast growth factor, could help regulate neuronal healing after ischemia. In a phase II safety trial, Fiblast was administered IV for up to 24 h in acute stroke patients. Although it was associated with transient leukocytosis, the drug otherwise appeared to be well tolerated and safe. A large trial was begun to evaluate the efficacy of Fiblast in stroke patients presenting within 6 hours of symptom onset. However, the trial was terminated because of poor risk-to-benefit ratios.

Optimal care of acute ischemic stroke

The concept of optimal care of the acute ischemic stroke patient includes the use of stroke units, adequate supportive therapies to reduce risk of complications and necessary measures to maintain acute physiologic parameters that may exacerbate ischemia, hypoxia or the ischemic cascade.[15] The level of hypertension necessitating intervention has been debated with some advocating use of SBP 220 mmHg and DBP of 120 mmHg while others prefer the use of the MABP.[16,17] Attention to the effects of oxygen, fluid balance, and temperature regulation in acute stroke have all been stressed.[18-22]

The failure of many proposed neuroprotectants in phase III trials to demonstrate convincing therapeutic benefits despite promising phase II trials is multifactorial.[15] A failure to provide optimal stroke care to prevent secondary brain insult may override any beneficial effect of a neuroprotectant. Many animal trials are carried out in strictly controlled settings which do not obtain in clinical practice. Also due to commercial pressure certain therapies are not comprehensively evaluated in phase III trials. Equally notable is that stroke trial subjects are heterogeneous.

Hypothermia

Hypothermia reduces brain damage from ischemia by preventing disruption of the brain-blood barrier. It also lowers the basal metabolic rate and counteracts the ischemic cascade in the penumbra.[23] Hypothermia might enhance the effects of neuroprotective drugs.[24,25]

Hypothermia is neuroprotective in animal models of stroke. It extends the therapeutic window for systemic thrombolysis or endovascular reperfusion techniques.[15]

High-dose human albumin treatment

In animal models of focal cerebral ischemia, albumin infusion at the doses ranging from 0.6-2.5 g/kg are neuroprotective. Albumin therapy for acute cerebral ischemia has received renewed attention.[26] Apart from functioning as a haemodiluent, albumin induces systemic mobilization of n-3 polyunsaturated fatty acids and help to replenish polyunsaturated fatty acids lost from neural membranes.[27-32]

Hyperacute magnesium therapy

Magnesium may act as a neuroprotective agent in brain ischemia via several mechanisms. It acts as an endogenous calcium channel antagonist. It inhibits the release of excitatory neurotransmitters such as glutamate. Magnesium antagonizes the NMDA receptor and has a direct vascular smooth muscle relaxant effect. The use of hyperacute magnesium therapy to provide neuroprotection is still under investigation.[33]

Conclusion

The rather large number of therapeutic agents that have undergone clinical trials for possible neuroprotective benefits in acute stroke is a pointer to the fact that translating better understanding of the pathogenesis and pathophysiology of ischemic stroke to clearly beneficial treatment strategies remains a daunting task.

The ischemic cascade appears to be so complex that targeting a single pathway may be ineffective. Nevertheless the window of opportunity is still open and it probably is a matter of time before scientific research yields a breakthrough. Such an optimal therapy may be achieved by combining neuroprotective agents with complementary mechanisms in a "stroke cocktail."

Physicians must strive to achieve better functional recovery in stroke patients in order to reduce the shattering societal impact.

References

1. Odusote KO. Management of stroke. Niger Med Pract 1996;32:54-61.
2. Gorelick PB. Stroke prevention. Arch Neurol 1995;52:347-55.
3. Osuntokun BO. Epidemiology of stroke in blacks. Hypertens Res 1994;17 Suppl 1:S1-10.
4. Osuntokun BO. Stroke in the African. Afr J Med Sci 1997;6:39-53.
5. Onwuekwe IO, Onyedum CC, Ekenze O, Nwabueze AC. Handedness in stroke: A review of 450 cases at Enugu, South East Nigeria. J Coll of Med 2006;11:136-9.
6. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular diseases in the community: The Oxfordshire Community Stroke Project-1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhages. J Neurol Neurosurg Psychiatry 1990;53:16-22.

7. Osuntokun BO, Bademosi O, Akinkugbe OO, Oyediran AB, Carlisle R. Incidence of stroke in an African City: Results from the Stroke Rregistry at Ibadan, Nigeria, 1973-1975. Stroke 1979;10:205-7.
8. Bwala SA. Stroke in a subsaharan Nigerian hospital-a retrospective study. Trop Doct 1989;19:11-4.
9. Pulsinelli W. The pathophysiology of acute ischemic stroke. Lancet 1992;339:533-6.
10. Jones TH, Morawetz RB, Crowell RM, Marcoux FW, FitzGibbon SJ, DeGirolami U, *et al*. Thresholds of focal cerebral ischemic in awake monkeys. J Neurosurg 1981;54:773-82.
11. Obrenovitch T, Sarna G, Symon L. Ionic homeostasis and neurotransmitter changes in ischemic. In; Krieglstein J, Oberpichler H, editors. Pharmacology of cerebral ischemic. Stuttgart: WVS; 1990. p. 97-112.
12. Choi DW. Ionic dependence of glutamate neurotoxicity. J Neurosci 1987;7:369-79.
13. Garthwaite J. Glutamate, nitric oxide and cell-cell signaling in the nervous system. Trends Neurosci 1991;14:60-67.
14. Lutzep HL, Clark WN. Neuroprotective agents in stroke. Available from: http://www.medscape, eMedicine journal; 2006;3-6.
15. De Keyser J, Uyttenboogaart M, Koch MW, Elting JW, Sulter G, Vroomen PC, *et al*. Neuroprotection in acute ischemic stroke. Acta Neurol Belg 2005;105:144-8.
16. Sulter G, De Keyser J. From stroke unit care to stroke care unit. J Neurol Sci 1999;162:1-5.
17. Klinjn CJ, Hankey GJ. Management of acute ischemic stroke: New guidelines from the American Stroke Association and European Stroke Initiative. Lancet Neurol 2003;2:698-701.
18. Sulter G, Elting JW, Stewart R, den Arend A, De Keyser J. Continuous pulse oximetry in acute hemiparetic stroke. J Neurol Sci 2000;179:65-9.
19. Reith J, Jorgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, *et al*. Body temperature in acute stroke: Relation to stroke severity, infarct size, mortality and outcome. Lancet 1996;347:422-5.
20. De Keyser J. Antipyretics in acute ischemic stroke. Lancet 1998;352:6-7.
21. Sulter G, Elting JW, Maurits N, Luijckx GJ, De Keyser J. Acetylsalicylic acid and acetaminophen to combat elevated body temperature in acute ischemic stroke. Cerebrovasc Dis 2004;17:118-22.
22. Gerriets T, Stolz E, Walberer M, Kaps M, Bachmann G, Fisher M. Neuroprotective effects of MK-801 in different rat stroke models for permanent middle cerebral artery occlusion: Adverse effects of hypothalamic damage and strategies for its avoidance. Stroke 2003;34:2234-9.
23. Olsen TS, Weber UJ, Kammersgaard LP. Therapeutic hypothermia for acute stroke. Lancet Neurol 2003;2:410-6.
24. Berger C, Schabitz WR, Wolf M, Mueller H, Sommer C, Schwab S. Hypothermia and brain-derived neurotrophic factor reduce glutamate synergistically in acute stroke. Exp Neurol 2004;185:305-12.
25. Nito C. Kamiya T, Ueda M, Arii T, Katayama Y. Mild hypothermia enhances the neuroprotective effects of FK506 and expands its therapeutic window following transient focal ischaemia in rats. Brain Res 2004;1008:179-85.
26. Koch S, Concha M, Wazzan T, Romano JG, Forteza A. High dose human serum albumin for the treatment of acute ischemic stroke: A safety study. Neurocrit Care 2004;1:335-41.
27. Huh PW, Belayev L, Zhao W, Busto R, Saul I, Ginsberg MD. The effect of high-dose albumin therapy on local cerebral perfusion after transient focal cerebral ischaemia in rats. Brain Res 1998;804:105-13.
28. Liu Y, Belayev L, Zhao W, Busto R, Belayev A, Ginsberg MD. Neuroprotective effect of treatment with human albumin in permanent focal cerebral ischaemia: Histopathology and cortical perfusion studies. Eur J Pharmacol 2001;428:193-201.
29. Belayev L, Alonso OF, Huh PW, Zhao W, Busto R, Ginsberg MD. Posttreatment with high-dose albumin reduces histopathological damage and improves neurological deficit following fluid percussion brain injury in rats. J Neurotrauma 1999;16:445-53.
30. Belayev L, Saul I, Huh PW, Finotti N, Zhao W, Busto R, Ginsberg MD. Neuroprotective effect of high-dose albumin therapy against global ischemic brain injury in rats. Brain Res 1999;845:107-11.
31. Rodriguez de Turco EB, Belayev L, Liu Y, Busto R, Parkins N, Bazan NG, *et al*. Systemic fatty acid responses to transient focal cerebral ischemia: Influence of neuroprotectant therapy with human albumin. J Neurochem 2002;83:515-24.
32. Belayev L, Marcheselli VL, Khoutorova L, Rodriguez de Turco EB, Busto R, Ginsberg MD, *et al*. Docosahexaenoic acid complexed to albumin elicits high-grade ischemic neuroprotection. Stroke 2005;36:118-23.
33. Jaworski N, Brambrink A. Electrolyte and metabolic derangements. In: Bhardwaj A, Mirski MA, editors. Handbook of Neurocritical Care. 2nd ed. Springer Sciences+Business Media, LLC 2011. p. 13-35.

How to cite this article: Onwuekwe IO, Ezeala-Adikaibe B. Ischemic stroke and neuroprotection. Ann Med Health Sci Res 2012;2:186-90.

Source of Support: Nil. **Conflict of Interest:** None declared.