The Science of Ischemic Stroke: Pathophysiology & Pharmacological Treatment

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ABSTRACT
Over the past two decades, research has heavily emphasized basic mechanisms that irreversibly damage brain cells after stroke. Much attention has focused on what makes neurons die easily and what strategies render neurons resistant to ischaemic injury. In the past few years, clinical experience with clot-lysing drugs has confirmed expectations that early reperfusion improves clinical outcome.Although great advances have been made in understanding the diverse mechanisms of neuronal cell death induced by ischemic stroke, clinically effective neuroprotective therapies are limited.Based on the accumulating evidence that ischemic cell death is a result of series of subsequent biochemical events, new concepts for prevention and treatment of ischemic stroke may eventually emerge without the hazard of severe complications**.**This review focuses on mechanisms and emerging concepts that drive the science of ischemic stroke in a therapeutic direction. Once considered exclusively a disorder of blood vessels, growing evidence has led to the realization that the biological processes underlying stroke are driven by the interaction of neurons, glia, vascular cells and matrix components, which actively participate in mechanisms of tissue injury and repair. As new targets are identified, new opportunities emerge that build on an appreciation of acute cellular events acting in a broader context of ongoing destructive, protective and reparative processes. This review then poses a number of fundamental questions, the answers to which may generate a number of treatment strategies and possibly new treatments that could reduce the impact of this enormous economic and societal burden.

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INTRODUCTION

Stroke is the second leading cause of death worldwide [1-4] and is the major cause of morbidity, particularly in the middle aged and elderly population [1,5-6]. Stroke, according to the American Heart Association (AHA) definition, is a sudden loss of brain function due to disturbance in the cerebral blood supply with symptoms lasting at least 24 hours or leading to death [7]. Stroke is defined as an acute neurologic dysfunction [8,9] of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of signs and symptoms [10,11]. Stroke is the rapid loss of brain function due to a disturbance in the blood supply to the brain [12]. Stroke is also the leading cause of adult long-term disability [3,8,9] and represents an enormous burden on society, which is likely to increase in future decades

as a result of demographic transitions in populations [2]. The ultimate result of ischemic cascade initiated by acute stroke is neuronal death along with an irreversible loss of neuronal function [9].
According to World Health Organization estimates, in 2002, 5.5 million people died of stroke in 2002 and roughly 20% of these deaths occurred in South Asian Countries (India, Pakistan, Bangladesh, and Sri Lanka) [3]. The incidence and mortality of stroke increase with age, and as the elderly population is rapidly growing in most developed countries ischemic stroke is a common societal burden with substantial economic costs [1,13]. According to the report from the Centers for Disease Control and Prevention, given in 2013 mortality from stroke was the fourth leading cause of

death in the United States in 2008, and stroke was a leading cause of long-term severe disability. Therefore, it is important to know the reason for this social burden so that safe and effective therapeutic treatment that could be given at medical services would improve the outcome of millions of acute stroke patients [12].

The two main types of stroke are ischemic and hemorrhagic, accounting for approximately 85% and 15%, respectively [4,9,10,12,14,15]. A third type of stroke, called as transient ischemic attack or TIA is a minor stroke that serves as awarning sign that a more serve stroke may occur [16]. Ischemic stroke is caused by focal cerebral ischemia due to arterial occlusion [1,4,9,10,14] or stenosis [17] whereas hemorrhagic stroke occurs when a blood vessel in the brain bursts, spilling blood into the spaces surrounding the brain cells or when a cerebral aneurysm ruptures[18]. Hemorrhagic stroke includes spontaneous intracerebral hemorrhage and subarachnoid hemorrhage [3,8] due to leakage or rupture of an artery [17]. Here our main concern is on ischemic stroke.

Ischemic Stroke

Ischemic stroke occurs when the blood supply to a part of the brain is suddenly interrupted by occlusion [15,18,25]. Ischemic cerebrovascular disease is mainly caused by thrombosis, embolism and focal hypoperfusion, all of which can lead to a reduction or an interruption in cerebral blood flow (CBF) that affect neurological function due to deprivation of the glucose and oxygen [6,8,10,19]. Approximately 45% of ischemic strokes are caused by small or large artery thrombus, 20% are embolic in origin, and others have an unknown cause [10]. Focal ischaemic stroke is caused by an interruption of the arterial blood flow to a dependent area of the brain parenchyma by a thrombus or an embolus [11]. In other words, Ischemic stroke is defined as acute onset, (minutes or hours), of a focal neurological deficit consistent with vascular lesion that persisted for more than 24 hour [9]. Ischemic stroke is a dynamic process whereby the longer the arterial occlusion persists the larger the infarct size becomes and the higher the risk of post-perfusion hemorrhage [20].

Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations [10,21]. Within 10 seconds after cerebral flow ceases, metabolic failure of brain tissue occurs. The EEG shows slowing of electrical activity and brain dysfunction becomes clinically manifest. If circulation is immediately restored, there is abrupt and complete recovery of brain function [22].

Ischemic stroke is more common in men than in women until advanced age, when a higher incidence is observed in women [3,23]. When younger patients are considered, females usually exceed males under 35, a period that coincides with the prime child-bearing years [23].

The three main pathology of ischemic strokes are:[3,6,12,16,17,22,24]

a) Thrombosis

b) Embolism and

c) Global ischemia (hypotensive) stroke

a) **Thrombosis:** Cerebral thrombosis refers to the formation of a thrombus (blood clot) inside an artery such as internal carotid artery, proximal and intracranial vertebral arteries which produce lacunes, small infarcts to typical locations include basal ganglia, thalamus, internal capsule, pons and cerebellum [25] that develops at the clogged part of the vessel. Atherosclerosis is one of the reasons for vascular obstruction resulting in thrombotic stroke [16]. Atherosclerotic plaques can undergo pathological changes such as thrombosis. Disruption of endothelium that can occur in the setting of thispathological change initiates a complicated process that activates many destructive vasoactive enzymes. Platelet adherence and aggregation to the vascular wall follow, forming small nidi of platelets and fibrin [15,26]. Thrombosis can form in the extracranial and intracranial arteries when the intima is roughened and plaque forms along the injured vessel. This permits platelets to adhere and aggregate, then coagulation is activated and thrombus develops at site of plaque. When the compensatory mechanism of collateral circulation fails, perfusion is compromised, leading to cell

death[10].Extracranial artery stenoses are prone to destabilization and plaque rupture leading to cerebral thromboembolism [4]. Thromboembolic occlusion of major or multiple smaller intracerebral arteries leads to focal impairment of the downstream blood flow, and to secondary thrombus formation within the cerebral microvasculature [4,14]. Thrombotic strokes occur without warning symptoms in 80-90% of patients. 10-20% is heralded by one or more transient Ischaemic attacks [22].

b) **Embolism:** Cerebral embolism refers generally to a blood clot that forms at another location in the circulatory system, usually the heart and large arteries of the upper chest and neck. Embolic stroke occurs when a clot breaks, loose and is carried by the blood stream and gets wedged in medium-sized branching arteries [10,25]. Microemboli can break away from a sclerosed plaque in the carotid artery or from cardiac sources such as atrial fibrillation, [16] or a hypokinetic left ventricle [10]. Embolism to the brain may be arterial or cardiac in origin. Commonly recognized cardiac sources for embolism include atrial fibrillation, sinoatrial disorder, recent acute myocardial infarction (AMI), subacute bacterial endocarditis, cardiac tumors, and valvular disorders, both native and artificial [17]. In approximately one-third of ischemic stroke patients, embolism to the brain originates from the heart, especially in atrial fibrillation [2,4,16]. Besides clot, fibrin, pieces of atheromatous plaque, materials known to embolize into the central circulation such as fat, air, tumor or metastasis, bacterial clumps, and foreign bodies contribute to this mechanism [10,16]. According to stroke databases from Western countries, cardioembolism is the most common cause of ischemic stroke [21]. Embolic strokes usually present with a neurologic deficit that is maximum at onset [22].

Global– Ischemic or Hypotensive stroke: A third mechanism of ischemic stroke is systemic hypoperfusion due to a generalized loss of arterial pressure [16,27]. Several processes can lead to systemic hypoperfusion, the most widely recognized and studied being cardiac arrest due to myocardial infarction and/or arrhythmia or severe hypotension (shock) [28,29]. The pyramidal cell layer of the hippocampus and the Purkinje cell layer of the cerebellar cortex areas are greatly effected [16].

Global ischemia is worse than hypoxia, hypoglycemia, and seizures because, in addition to causing energy failure, it results in accumulation of lactic acid and other toxic metabolites that are normally removed by the circulation [28]. Fatal strokes in elderly patients often appeared to be due to acute hypotension caused by extracranial events such as heart-failure, occult haemorrhage, or multiple pulmonary emboli [29].

Consequences after stroke: Active cell death mechanism

Within seconds to minutes after the loss of blood flow to a region of the brain, the ischemic cascade is rapidly initiated [30].Due to the disruption of blood flow to the area there is limitation of the delivery of oxygen and metabolic substrates to neurons which causes ATP reduction and energy depletion [8,31]. This comprises a series of subsequent biochemical events that eventually lead to disintegration of cell membranes and neuronal death at the core of the infarction [30]. These biochemical events include: ionic imbalance, the release of excessglutamate in the extracellular space which leads to excitotoxicity, a dramatic increase in intracellular calcium that in turn activates multiple intracellular death pathways such as mitochondrial dysfunction, blood-brain barrier dysfunction, oxidative and nitrosative stress and initiate post ischemic inflammation which leads ultimately to cell death of neurons, glia and endothelial cells[4,6,30,31]. In the penumbra region surrounding the infarct core, however, tissue is preserved for a certain time span depending on whether blood flow is restored [4].

In general, neurons and oligodendrocytes seem to be more vulnerable to cell death than astroglial or endothelial cells, and

among neurons, CA1 hippocampal pyramidal neurons, cortical projection neurons in layer 3, subsets of neurons in dorsolateral striatum and Purkinje cells of the cerebellum are particularly susceptible [26].
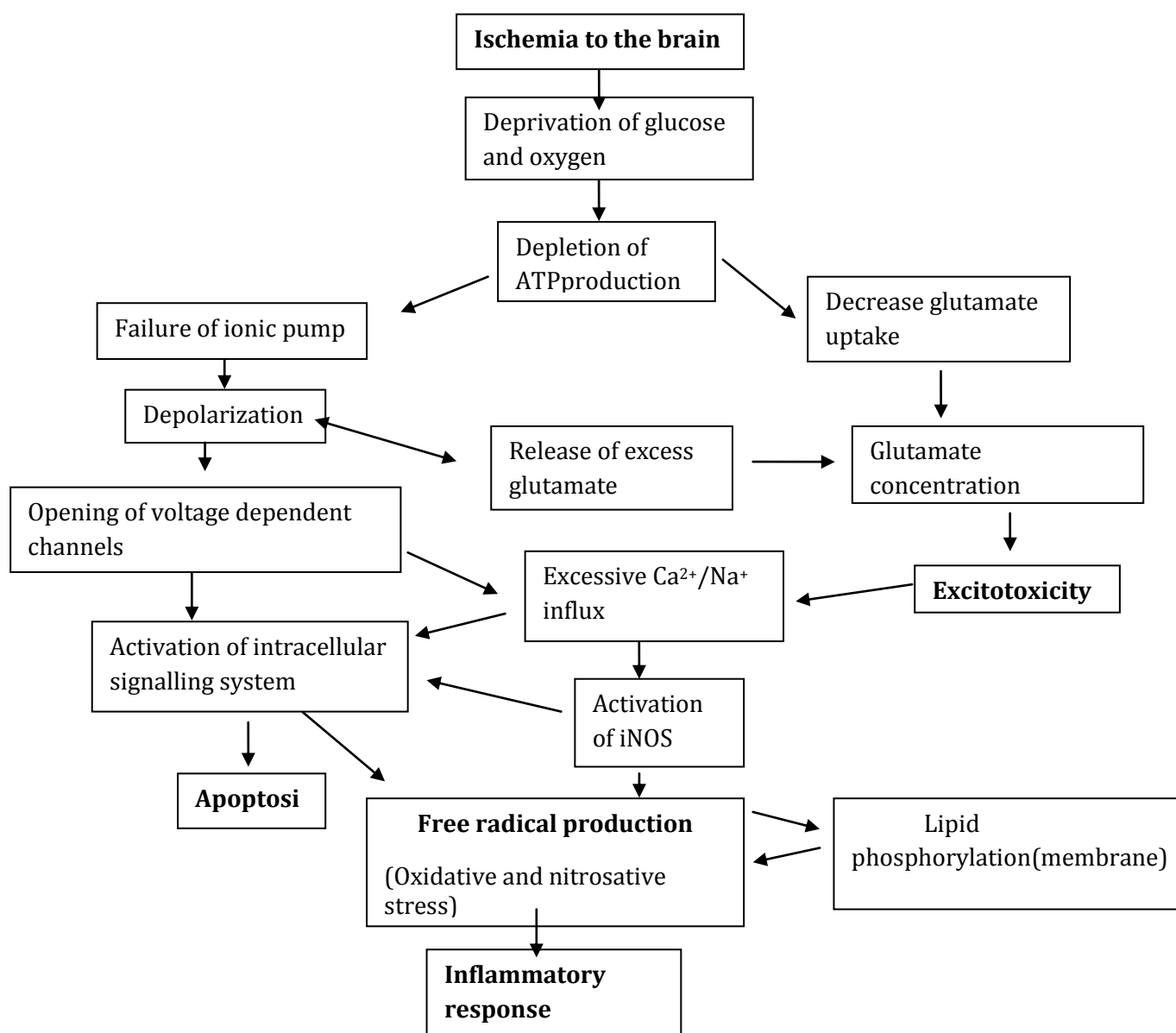
Figure 1: Schematic representation of active cell death mechanism

Ionic imbalance: The most common cause of stroke is the sudden occlusion of a blood vessel by a thrombus or embolism, resulting in an immediate loss of oxygen and glucose to the brain [25,32]. Large reserves of alternative substrates to glucose, such as glycogen, lactate and fatty acids, for both glycolysis and respiration are present in brain but oxygen is irreplaceable in mitochondrial oxidative phosphorylation, the main source of ATP in neurons. Reduced ATP stimulates the glycolytic metabolism of residual glucose and glycogen, which causes an accumulation of protons and lactate and therefore intracellular acidification[31].This result in further decline in ATP concentration due to cessation of the electron transport chain activity within mitochondria and leads to disruption of ionic pumps systems like Na^+-K^+-ATPase,[33]Ca^{2+}-H^+ ATPase, reversal of Na^+-Ca^{2+} transporter resulting in increase in intracellular Na^+, Ca^{2+}, Cl concentration and efflux of K^+ . This redistribution of ions across plasma membrane causes depolarization of neurons and astrocytes,

leading to excess release of neurotransmitters (particularly glutamate) that causes neuronal excitotoxicity [25,31].

Excitotoxicity: Excitotoxicity, the term coined by Olney in 1969, occurs due to excess release of excitatory amino acid glutamate and excessive activation of their receptors [25]. Excitotoxicity is an exaggeration of neuronal excitation mediated by sodium ions and that any source of excitation is potentially harmful. The first step toward excitotoxicity during an acute episode of stroke is the rapid elevation of glutamate levels in the ischemic region of the brain and this is due to dysfunction in the homeostasis of glutamate [33]. Under physiological condition release of glutamate into the synaptic space stimulates glutamate receptors of the NMDA subtype, [33-35] which causes depolarization of the postsynaptic neuron by an influx of calcium and sodium. NMDA receptors (NMDARs) revert to the inactive state as transporters sequester glutamate into cells. During acute and chronic ischemia, ATP depletion causes neuronal membrane depolarization, which opens voltage-gated Ca^{2+} and Na^+ channels and releases excitatory glutamate in the synaptic cleft and also impairs the clearance of glutamate due to transporter dysfunction [25,34]. NMDARs are complex, heterotetramer combinations of three major subfamilies of subunits: NR1, NR2, NR3. NR2 (GluN2AR-GluN2DR) subtypes appear to play a pivotal role in stroke. NR2A and NR2B are the predominant NR2 subunits in the adult forebrain, where stroke most frequently occur [31]. NMDAR subtypes can confer neuronal survival and neuronal death, synaptic GluN2AR protects neurons against excitotoxic neuronal death mediated by synaptic GluN2BR.Similarly, extrasynaptic GluN2AR is pro-survival and protects neurons against extrasynaptic GluN2BR-induced neuronal death [31,36]. Synaptic NMDAR conveys the synaptic activity-driven activation of the survival-signaling protein extracellular signal-regulated kinase (ERK) and triggers an increase in nuclear calcium via release from intracellular stores, leading to the activation of the transcription factor CREB and the production of the survival-promoting protein BDNF. In contrast, global or extrasynaptic NMDAR stimulation, when there is too much glutamate in the brain, such as during cerebral ischemia decreases ERK, CREB activation and BDNF production, while there is calcium-dependent activation of death-signaling proteins that triggers a plethora of signaling cascades that work synergistically to induce neuronal death. NMDAR-mediated dysfunction of sodium-calcium exchanger (NCX) [33] which regulate intracellular calcium level explains the subsequent calcium overload that occurs following an excitotoxic stimulus [35]. Mitochondria can recover intracellular calcium concentration by (i) itself taking up a huge amount of calcium [33] (ii) facilitating ATP dependent calcium extrusion, which results in the production of reactive oxygen species (ROS) [33,35,36] such as superoxide (O_2^-), and hydrogen peroxide (H_2O_2) as well as reactive nitrogen species (RNS)[35] such as nitric oxide (NO) and peroxinitrite ($ONOO^-$) [34,36]. High concentrations of intracellular calcium, ROS, and RNS induce cell death by: **1)** activating proteases that damage cellular architecture i.e. protein, DNA, lipid, [37,38] **2)**peroxidizing lipids,[35] which disrupt membrane integrity, **3)** stimulating microglia to produce cytotoxic factors, **4)** disrupting mitochondrial function, and **5)** inducing pyknosis (chromatin condensation) [31,33,34,39]. The opening of the permeability transition pore results in mitochondrial depolarization , induction of calcium deregulation and induction of neuronal death by damaging dendrites and synaptic connections [16,26,35].

Oxidative and nitrosative stress: Oxidative stress occurs when there is an imbalance between the production and quenching of free radicals by endogeneous antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione [40-42]. Compared to other tissues and organs in the body, the brain is particularly prone to oxidative damage [36] because of high consumption of oxygen under basal conditions, high concentrations of peroxidisable lipids, and high levels of iron that act as a pro-oxidant during stress. The primary sources of ROS in the brain are the mitochondrial respiratory chain (MRC), NAPDH oxidases, and xanthine oxidase [25].
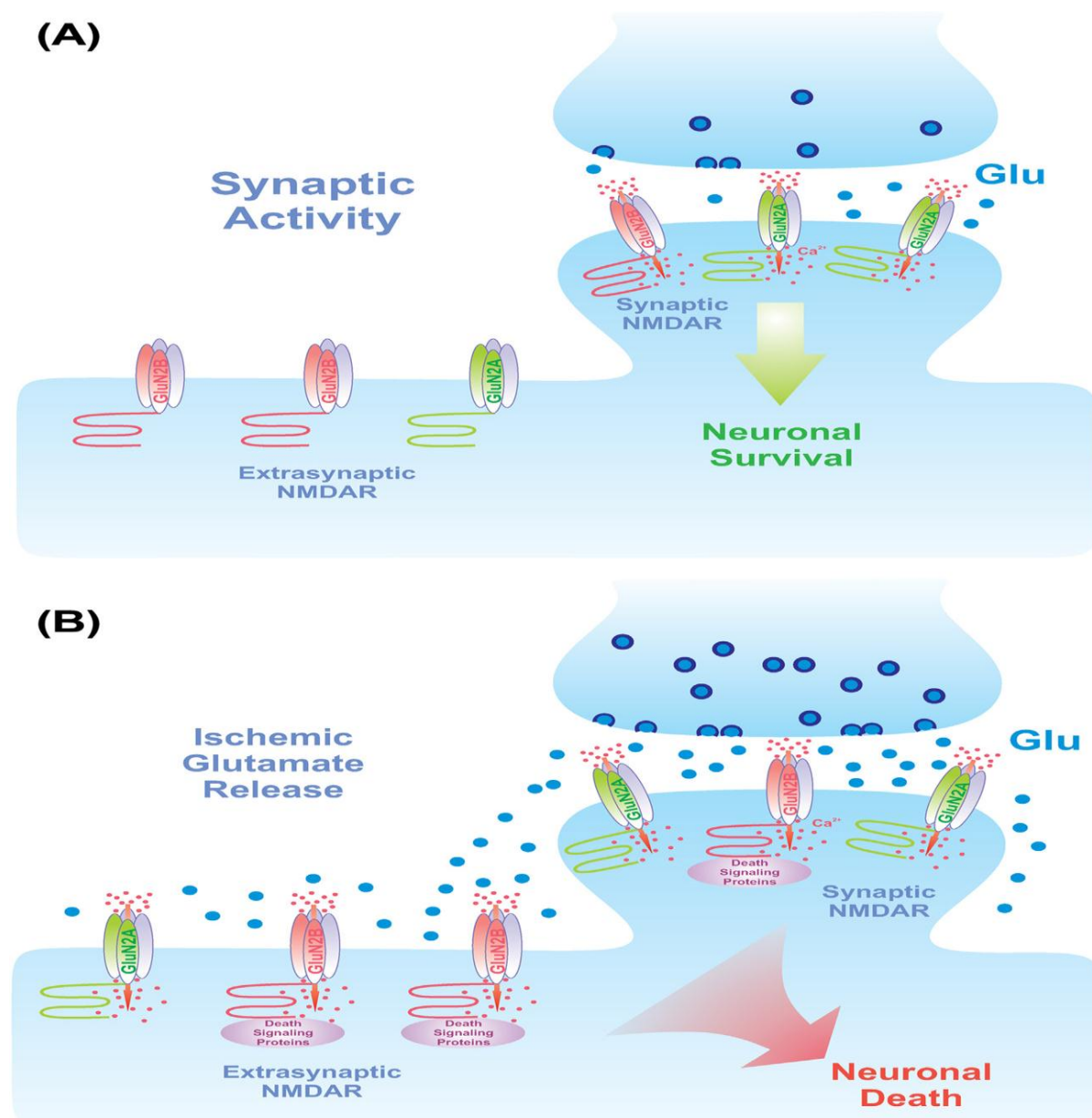
Figure 2: NMDA receptors with synaptic and extrasynaptic location and their role in neuronal survival and death [31]

Several oxygen free radicals (oxidants) and their derivatives are generated after stroke, including superoxide anions ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\cdot OH$). $O_2^{\cdot-}$ are formed within the mitochondria when oxygen acquires an additional electron, leaving the molecule with only one unpaired electron. Pro-oxidant enzymes such as xanthine oxidase and NADPH oxidase (NOX) also catalyze the generation of $O_2^{\cdot-}$[43]. Under normal cellular conditions, mitochondria produce superoxide as a by-product of their primary function i.e. ATP generation by oxidative phosphorylation through the MRC [25]. Superoxide concentration is regulated by enzymatic antioxidants by dismutation of superoxide to hydrogen peroxide by superoxidedismutase which is then converted to water (by peroxidases such as glutathione peroxidase and peroxiredoxin) or dismuted to water and oxygen (by Catalase)[25,43]before leaving the mitochondria to act as an intracellular messenger. In the ischaemic cell, O_2 levels are depleted before glucose, favouring a

switch to the glycolytic pathway of anaerobic ATP production.This results in lactic acid and H^+ production within the mitochondria and the subsequent reversal of the H^+uniporter on the mitochondrial membrane which causes excess cytosolic H^+ accumulation and acidosis [44]. Acidosis contributes to oxidative stress by providing H^+ for the conversion of $\bullet O_2^-$ into H_2O_2 or the more reactive hydroxyl radical ($\bullet OH$). The reperfusion after ischaemia leads to production of superoxide and hydroxyl radicals which overwhelms endogenous scavenging mechanism.Superoxide can cause oxidative damage of iron/sulfur clusters of aconitase, an important enzyme in the tricarboxylic acid cycle [25,26].

In addition, activation of nitric oxide synthase (NOS) during ischaemia might lead to excessive nitric oxide production which leads to nitrosative damage bynitrosylation of protein heme sites (e.g. cytochrome *c*) and by its reaction products with oxygen or other nitrogen oxides[25].$O_2^{\cdot-}$ can react with nitric oxide (NO) to produce peroxynitrite $ONOO^-$ which is a strong oxidative radical that causes protein nitration and dysfunction[25,43]. Hydroxyl radical, peroxynitrite and peroxynitrite-derived products (hydroxyl radical, carbonate radical and nitrogen dioxide) all have the potential to react and damage lipids, proteins and DNA. Activation of NMDA receptors (NMDARs) by glutamate also increases intracellular NO and subsequent $ONOO^-$ production in the ATP depleted post-synaptic cell [25].

Another source of ROS production is nicotinamide adenine dinucleotide phosphate-oxidases (NOXs) enzyme. Under normal physiological conditions NOX enzymes function as membrane bound enzymes which generate ROS for biological functions such as blood pressure regulation, microbial killing and otoconia formation but in pathological conditions NOXs are significant contributors to pathological damage by oxidative stress from $\bullet O_2^-$ overproduction and ROS imbalance[45].

Apoptosis Cell Death: Within minutes after a focal ischemic stroke, the core of brain tissue exposed to the most dramatic blood flow reduction is injured and subsequently undergoes necrotic cell death. This necrotic core is surrounded by a zone of less severely affected tissue which is rendered functionally silent by reduced blood flow but remains metabolically active. This region is known as "ischemic penumbra" and neurons in this area may undergo apoptosis after several hours or days, and therefore are potentially recoverable for some time after the onset of stroke [46]. The normal human brain expresses caspases 1, 3, 8 and 9, apoptotic protease-activating factor 1, death receptors, the transcription factor p53, DNA fragmentation factor (DFF45)**,** and a number of proteins(i.e.pro-apoptotic proteins) belonging to Bcl2 family and all these are implicated in apoptosis [47,48]. Proapoptotic protein are subdivided into (a) multidomainproapoptotics (eg, Bax [Bcl-2–associated X protein] and Bak [Bcl-2–antagonist/killer]) and (b) BH3-only proapoptotics (eg, Bid, Bad [Bcl-2-antagonist of cell death] etc [49,50].

There are two general pathways for activation of apoptosis: The Intrinsic and Extrinsic pathway

Intrinsic pathway- The intrinsic pathway is activated in response to a number of stressing conditions including DNA damage, oxidative stress and many others [50] Cerebral ischemia elevates cytosolic calcium levels through the stimulation of N-methyl-d-aspartate (NMDA) and D,L-α-amino-3-hydroxy-5-methyl-isoxazolpropionic acid (AMPA) receptors by glutamate. Increased intracellular calcium activates calpains and mediates cleavage of Bid to truncated Bid (tBid). This occur at the mitochondrial outer membrane (MOM) where the Bcl-2 protein family plays a pivotal role in the regulation of apoptosis, inhibit the antiapoptotic proteins and activate the pro-apoptotic proteins[49,51]. Either Bax or Bak is required for all instances of apoptosis mediated via the intrinsic pathway [49]. tBid interacts with apoptotic proteins such as Bad and Bax[49] at the mitochondrial membrane. After heterodimerization of proapoptotic proteins with tBid, mitochondrial transition pores (MTP) are open [50] and dissipates the proton motive force that is required for oxidative phosphorylation and ATP generation. Another mechanism is the result of the opening in the inner membrane of the

permeability transition pore complex (PTPC) that would require the Adenine Nucleotide Transporter (ANT) and the Voltage Dependent Anion Channel (VDAC) [50]. As a result, mitochondria release their constituents including apoptosis-related proteins within the inner and outer mitochondrial membranes [26,52]. The first group of apoptosis-related protein include cytochrome *c*,Smac/DIABLO, and the serine protease HtrA2/Omi[53]. After releasing into the cytosol, Cyt*c* binds with apoptotic protein-activating factor-1 (Apaf-1) and procaspase-9 to form an "apoptosome,"

which activates caspase-9 and subsequently caspase-3 [50,53,54]. Activated caspase-3 cleaves nDNA repair enzymes, such as poly (ADP-ribose) polymerase (PARP), which leads to nDNA damage and apoptosis [50,52]. The second group of pro-apoptotic proteins, apoptosis-inducing factor (AIF)[50,52]and endonuclease G[52] are released from the mitochondria during apoptosis, but this is a late event that occurs after the cell has committed to die [53]. It mediates large-scale DNA fragmentation and cell death in a caspase-independent manner [53].
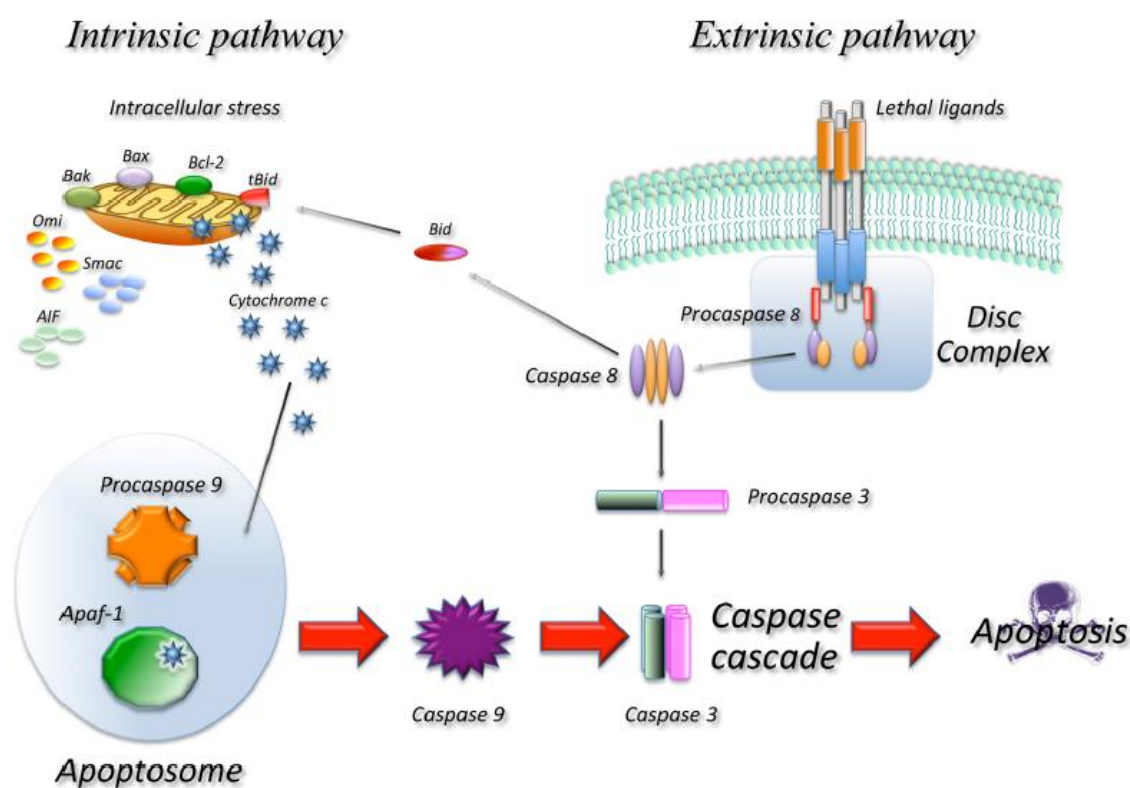
Figure 3: Schematic representation of the main molecular pathways leading to apoptosis [50]

Extrinsic pathway- The extrinsic pathway initiated extracellularly via activation of cell surface receptors CD95/FasR and DR4, DR by specific molecules known as lethal ligands or death ligand trimer [49,50,55,56]. The ligand may be an integral membrane protein on the surface of a second cell (eg, Fas [CD95/Apo-1] ligand) or a soluble extracellular protein (eg, tumor necrosis factor-α)[49].This pathway is also known as death receptor pathway [50] because these

receptors belong to the tumor necrosis factor receptor (TNFR) superfamily.

Upon ligand binding several receptor molecules are brought together and undergo conformational changes allowing the assembly of a large multi-protein complex known as Death Initiation Signalling Complex (DISC) that leads to activation of the caspase cascade [49,50,55]. Taking the example of Fas ligand- extracellular Fas ligand (FasL) binds to Fas death receptors

(FasR) and once activated, the death domains of these receptors recruits a highly conserved 80 amino acid domain, known as death domain (DD), an adaptor molecule Fas-associated protein with a DD (FADD) [49,50,55]. FADD, in turn, recruits procaspase-8 through death effector domains into the DISC this, in turn, results in procaspase-8 dimerization and activation. Once activated, caspase-8 cleaves and activates downstream procaspase-3 and Bid, a proapoptotic Bcl-2 protein, which links the extrinsic and intrinsic pathways [49,55,56]. Cleavage of Bid to truncated Bid (tBid), which integrates the different death pathways at the mitochondrial checkpoint of apoptosis. tBid binds to the mitochondrial membrane to facilitate the release of cytochrome c and initiate the intrinsic pathways. This allows "cross-talk" between the two main pathways and amplifies the apoptotic signaling from death receptors [46,55,56].

Post ischemic inflammation: Brain inflammation has been implicated as a secondary injury mechanism following ischemia and stroke [57-59]. Stroke triggers this inflammatory response as a result of several factors, such as hypoxia, shear stress,necrotic cells debris and reactive oxygen species (ROS)[59,60].The increase in oxygen free radicals triggers the expression of a number of pro-inflammatory genes by inducing the synthesis of transcription factors, eg. NF-κB,[57,61]hypoxia inducible factor 1, interferon regulator factor 1 and STAT3 [15]. These triggering factors lead to microglial(main immune cell in CNS) [57] activation, upregulation of chemokins and cytokines, expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecules (VCAMs), selectins (in particular, P-selectin and E-selectin), and integrins (Mac-1 and LFA-1) on the surface of endothelial cells, leukocytes, and platelets[59,60]. Activated Microglial transformed into phagocytes and are responsible for relase of various substances like pro-inflammatory cytokines (TNH-α,IL-1β,IL-6 cytotoxic molecules like NO, ROS, prostanoids) or cytoprotectives [15,26]. Chemokine upregulation stimulates inflammatory cell chemotaxis into ischemic brain, especially around the penumbra, or the infarct's border. Adhesion molecules mediate adhesion of leukocytes (especially neutrophils) to endothelia in the periphery of the infarct [15,60] causing microvascular occlusion [59,62,63] and alteration of permeability of BBB [60,62,64]. Altered BBB leads to infiltration of immune cells into the brain parenchyma, all within 24 hours of the ischemic insult [59,65]. As the ischemic cascade progresses, cell death leads to a new phase of the inflammatory response. Certain endogenous molecules are called danger-associated molecular patterns (DAMPs) such as nucleotides adenosine triphosphate (ATP), uridine triphosphate (UTP)[60] and high-mobility group protein B1 (HMGB1)[64] or alarm molecules released from the necrotic brain to activate infiltrating immune cells [60,62,63]. A result of these processes is a time-dependent infiltration of neutrophils, macrophages, dendritic cells, and T and B lymphocytes. This lead to granule exocytosis and release of a variety of pro-inflammatory molecules such as nitric oxide (NO) derived from inducible NO synthase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived ROS, and matrix metalloproteinases (MMPs). Both CD4+ and CD8+ T lymphocytes contribute to brain injury by producing pro-inflammatory mediators, such as the potent cytokines interferon-γ (IFN-γ), IL-1β,[32] interleukin-6 (IL-6),[32] IL-17, and tumor necrosis factor (TNF), which leads to disruption of the blood-brain barrier (BBB) and extracellular matrix [57,59,60,62].

Modifiable risk factors [66-70]

- **High blood pressure:** High BP is the single most important modifiable risk factor for stroke. Arterial hypertension (HTN) contributes to 60% of all strokes by several mechanism such as atheroma in carotids, vertebral arteries and aortic arch; friability of small cerebral arteries; left ventricular dysfunction and atrial fibrillation. Treatment is required if BP is >140/90mmHg. Meta-analyses of randomized controlled trials confirm an approximate 30% to 40% stroke risk reduction with BP lowering.

- **Diabetes Mellitus (DM):** Diabetes has been clearly established as a risk factor for first stroke but not as one for recurrent stroke. 11% of strokes and 9.1% of

recurrent strokes have been estimated to be attributable to diabetes. Patients with diabetes have higher mortality, more severe disability, and slower recovery after a stroke, as well as higher rates of stroke recurrence compared to nondiabetic stroke patients.

- **Abnormal lipid level**: Dyslipidemia is a well-established risk factor for stroke. Cholesterol levels represent an important and modifiable risk factor for coronary artery disease (CAD). However, the epidemiological association between cholesterol and stroke is controversial. An association between serum cholesterol levels and both incident and recurrent stroke rate has not been clearly demonstrated.
- **Tobacco/Cigarette smoking:** Smoking and exposure to passive smoke are established independent risk factors for primary ischemic stroke.Risk of stroke occurance may be double in smokersas compare to th non-smokers**.** The risk associated with smoking is present at all ages, in both sexes, and among different racial/ethnic groups. The pathological pathway contributing to increased risk includes changes in blood dynamicsand vascular stenosis.
- **Alcohol consumption:** Heavy alcohol use has been associated with an increased rate of stroke in patients with previous ischemic strokes. There is an association between alcohol and stroke, ranging from a definite independent effect to no effect. The deleterious risk mechanism for the same may include alcohol-induced hypertension, hypercoagulable state, reduced cerebral blood flow, and atrial fibrillation (AF).
- **Atrial fibrillation**: Patients with nonvalvular atrial fibrillation (AF) are at 4-5% annual risk of stroke particularly cardioembolicstroke . AF is present in 15–21% of patients affected by stroke.
- **Other risk factors** - Obesity,Physical activity, illicit drug use, and oral contraceptive use .

Treatment of acute ischemic stroke-
1. Thrombolytics
2. Antiplatelets
3. Anticoagulants
4. Glutamate and the NMDA receptor antagonists
5. GABA antagonists
6. Free radical scavengers
7. Apoptosis inhibitors

1.Thrombolytics: Thrombolytic drugs dissolve blood clot by activating plasminogen,which form plasmin . Plasmin is a proteolytic enzyme that break cross-links between fibrin molecules and restricts the damage caused by the blockage in the blood vessel.Because of this action it is also known as "plasminogen activator" and "fibrinolytic drugs"[71]. The primary aim of thrombolysis in acute ischemic stroke is recanalization of an occluded intracranial artery. Recanalization is an important predictor of stroke outcome as timely restoration of regional cerebral perfusion helps salvage threatened ischemic tissue [72].

At present, Intravenous tissue plasminogen activator (IV-TPA) i.e. streptokinase, alteplase, reteplase remains the only FDA-approved therapeutic agent for the treatment of ischemic stroke [71,73-77]. Intravenous recombinant tissue plasminogen activator (rt-PA,alteplase) in a dose of 0.9 mg/kg (maximum 90 mg) given over one hour has been licensed in the USA since 1996 was safe and effective when given within 3 hours from symptoms onset [77-79].

Intra-arterial(IA) thrombolysis has been shown effective until 6 hours after middle cerebral artery occlusion and basilar artery occlusion. It offers a higher concentrations of thrombolytic delivered to the clot with reduced systemic exposure and therefore higher rate of recanalization, compared with intravenous thrombolysis [73,78]. While there are currently no FDA-approved IA thrombolytic agents, several uncontrolled and anecdotal studies have evaluated IA thrombolysis in acute ischemic stroke.Desmoteplase is a fibrin-specific and nonneurotoxic protein derived from the saliva of vampire bat. At a dose of 125 μg/kg, Desmoteplase appeared to improve clinical outcome according to Dose Escalation of Desmoteplase in Acute Stroke (DEDAS) study in patients treated within 3 to 9 hour time window. Ancrod (Viprinex) is an

enzyme derived from pit viper venom with defibrinating properties is under study [73].

2.Antiplatelet drugs: Early antiplatelet treatment is recommended to treat most patients with acute ischemic stroke because few patients can be treated with thrombolysis due to the limit of strict indications, such as a time window[80].Two clinical trial studies, The Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST) showed a significant benefit of aspirin as to the reduction of morbidity and mortality rates. Therapy should be initiated with aspirin160-325mg daily within 48 hours of symptom onset provided contraindications such as allergy and gastrointestinal bleeding are absent, and the patient has or will not be treated with recombinant tissue-type plasminogen activator [71,76,78,80,81]. The benefit of aspirin when used in early phase of ischemic stroke is modest [76]. In patients who were allergic, non-responsive, or intolerant to aspirin, other antiplatelet agents may be used as an alternative. Another (CHANCE) trial, which compared clopidogrel (300 mg loading followed by 75 mg once daily for 90 days) plus aspirin (75 mg once daily for the first 21 days) versus aspirin monotherapy (75 mg once daily for 90 days) was conducted in 5170 patients with minor ischemic stroke. The rate of the primary endpoint of a recurrent stroke within 90 days was significantly lower for dual therapy than for aspirin monotherapy.Another study showed that early initiation of aspirin plus extended release dipyridamole leads to no or mild disability at 90 day compared with late initiation [80,82]. The superiority of combination therapy compared to monotherapy may be due to the synergy effects of different antiplatelet mechanisms in reducing vascular events. Thus, combined antiplatelet therapy, such as aspirin and clopidogrel, should be encouraged in the treatment of acute ischemic stroke [78].

Intravenous antiplatelet therapy with Glycoprotein (GP) IIb/IIIa receptor inhibitors for acute stroke appears promising. while oral GPIIb/IIIa receptor inhibitors appear hazardous [83]. GP IIb/IIIa receptors are found on the platelet surface for fibrinogen, through which agonists like collagen, thrombin, TXA2, etc. finally induce platelet aggregation [84-86]. Glycoprotein (GP) IIb-IIIa inhibitors act by antagonising GP IIb-IIIa receptors on the platelet surface and block the final common pathway to platelet aggregation by preventing the binding of fibrinogen molecules that form bridges between adjacent platelets[85,87]. GPIs in clinical use include Abciximab (ReoPro),Tirofiban (Aggrastat) and Eptifibatide (Integrillin) [71,85,86]. The data are insufficient at this time to recommend the use of any other platelet antiaggregant in the setting of acute ischemic stroke [81]. Use of ticlopidine, clopidogrel, dipyridamole, or other antiplatelet agents during ischemic stroke, whether alone or in combination, has yet to be assessed properly [88].

3.Anticoagulants: Routine anticoagulation with unfractionated or low-molecular-weight heparin is not recommended in acute ischemic stroke, particularly for patients with moderate to extensive cerebral infraction due to increased risk of severe intracranial hemorrhagic complications [90,91]. The use of fixed dose subcutaneous unfractionated heparin is not recommended for decreasing the risk of death or stroke-related morbidity or for preventing early stroke recurrence because of concomitant increase in the occurrence of hemorrhage. Dose-adjusted, unfractionated heparin is not recommended for reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke (i.e., in the first 48 hours) because the evidence indicates it is not efficacious and may be associated with increased bleeding complications [81]. However, anticoagulation continues to be recommended for some specific clinical situations. Indications currently proposed by many experts for early full-dose i.v. heparin after stroke [90].

4.Glutamate and the NMDA receptor antagonist: Since NMDA receptor over activation is implicated in excitotoxicity therefore NMDA receptor antagonists can be used for the treatment. Many NMDA receptors antagonist are presently in phase II and phase III clinical trials. Most clinical trials involving NMDA receptor antagonists have failed due to unwanted side effects of the drugs; since the receptors also play an important role in normal glutamatergic neurotransmission, blocking them causes

side-effects. These results have not yet been reproduced in humans, however [92]. Amonophospho-novalerate (APV) a selective NMDA receptor antagonist prevente the excitoxic action of L –glutamate on cortical neurons. A non –competetive NMDA receptor antagonist , MK 801 is use to prevent NMDA receptor dependent influx of calcium[93].BQ-869, a potent NMDA receptor antagonist, blocks the receptor in concentration-dependent in focal cerebral ischemia in rats and reduced stroke mortality. The neuroprotective effect of BQ-869 provide new insights with potential therapeutic applications for the treatment of stroke[94]. Memantine, an adamantane derivative, preferentially blocks excessive NMDA receptor activity without disrupting normal activity. Memantine does this through its action as an open-channel blocker and its off-rate is relatively fast so that it does not substantially accumulate in the channel to interfere with normal synaptic transmission [95].

5.GABA antagonist: Tonic neuronal inhibition is increased in the peri-infarct zone after a stroke. This increased tonic inhibition is mediated by extrasynaptic GABA-A receptors and is caused by an impairment in GABA (γ-aminobutyric acid) transporter (GAT-3/GAT-4) function. Benzodiazepine inverse agonist specific for a 5-subunit containing extrasynaptic GABA-A receptors can be used to counteract the heightened inhibition. This treatment produced an early and sustained recovery of motor function [96].

Cortical GABAergic signalling through GABA-A receptors is divided into synaptic (phasic) and extrasynaptic (tonic) components. Tonically active extrasynaptic GABA-A receptors set an excitability threshold for neurons[97]. Pharmacological andgenetic knockdown of a 5-GABA-A receptors enhance long term potentiationand improve performance on learning and memory tasks [98,99].

6.Free radical scavengers: Free radicals have been implicated in stroke pathophysiology as pivotal contributors to brain cell injury. The increased amount of free radicals in ischemic stroke condition damages all cellular components, including DNA, lipids, and proteins, leading to injuries

of neurons, glial cells, nerve fibers, and blood vessels [100,101]. Edaravone, a free radical scavenger, has been clinically available in Japan since 2001 and has been reported to improve clinical outcomes in patients exhibiting ischemic strokes. Experimental studies have revealed that the possible mechanisms of Edaravoneare decreasing oxidative stress, protecting neurovascular units, and reducing the activation of microglia after ischemic stress [102,103]. Tirilazadmesylate (U-74006F), an inhibitor of lipid peroxidation was studied extensively in pre-clinical models in the mid-1990s and was shown to reduce infarct size in rats following transient focal ischaemia. Across 19 publications, tirilazad was demonstrated to reduce lesion size by an average of 29% and improve neurological score by 48% [45]. Ebselen, an inhibitor of glutathione peroxidase-like activity, may be a promising neuroprotective agent and improve the outcome of acute ischemic stroke [104].

Mitoquinone (mitoQ) a derivative of ubiquinone, reduced to ubiquinol and has been found to be an effective antioxidant protecting mitochondria from oxidative damage and apoptosis caused by H_2O_2. The use of antioxidant vitamin (Vit.C and E) supplements is another choice [45].

7.Apoptosis inhibitor: Cell death in the penumbral region of the lesion can be suppressed by administering caspase inhibitors during and after vessel occlusion [105]. In fact, the therapeutic window seems to be temporally related to the onset of caspase activation, and caspase inhibitors attenuate ischaemic brain injury and neurological function when administered up to the point of protease activation. Strategies to silence caspases or suppress apoptosis-related gene products using antisense oligonucleotides or viral vector-mediated gene transfer substantiate these observations [106]. However, caspase inhibitors do not reduce infarct size in all brain ischaemia models.This might relate to the intensity and duration of ischaemia, robustness of caspase expression and cleavage, upregulation of caspase-independent or redundant cell death pathways and/or shortcomings of the administered agent [107].

Primary preventionof ischemic stroke-
The main aim of primary prevention is to reduce the risk of ischemic stroke (IS) in asymptomatic patients and focuses on managing known risk factors such as arterial hypertension (AH), diabetes mellitus (DM) and lipid metabolism disorders[108].In asymptomatic individuals, this value is determined by using nomograms from the Systematic Coronary Risk Evaluation (SCORE) project, which evaluates the age, gender, systolic blood pressure (SBP), smoking habits , total cholesterol levels and a value over 5% is considered a high risk . The risk is high (≥5%) for symptomatic individuals with manifested cardiovascular disease, type 2 diabetes or type 1 diabetes with microalbuminuria, or chronic kidney disease and very high (≥10%). if there are a combination of factors[109]. Here the area of focus is pharmacological treatment. Of all strokes, approximately 70% are first-time events, thus primary-care physicians have a great opportunity to identify patients who may benefit from risk factor modification. In these settings, initiation of primary prevention strategies may have the greatest impact on the disease and its enormous toll on the healthcare system [110].

1.Antihypertensive drugs- Elevated systolic pressure, with or without an accompanying elevation in diastolic pressure, has been shown to increase stroke risk. BP reduction was associated with a 32% risk reduction in stroke incidence[111]. In case of arterial hypertention the target for systolic blood pressure is under140mmHg, except for older patients (>160-150 mmHg) [109]. Although lowering blood pressure is clearly beneficial, the best drug regimen to achieve this is unclear. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that a thiazide diuretic was more effective at reducing the risk of cardiovascular events than angiotensin-converting enzyme (ACE) inhibitors or α-blockers. The Heart Outcomes Prevention Evaluation (HOPE) trial suggested the ACE inhibitor ramipril reduced the risk of stroke and myocardial infarction, with a 0.68 relative risk of stroke for ramipril versus placebo. A meta-analysis of 18 long-term randomized trials found that both β-blocker therapy and treatment with high-dose diuretics were effective in preventing stroke [111]. Angiotensin II receptor blockers (Losartan) may also have a beneficial effect on cardiovascular events and stroke [112]. The Systolic Hypertension in the Elderly Program (SHEP) trial demonstrated a 36% reduction in the incidence of total stroke with antihypertensive treatment (chlorthalidone or atenolol) [111]. The choice of an antihypertensive agent depends on the patient's age and comorbidities. To prevent stroke, it is necessary to treat older adults with hypertension should be treated aggressively to the same target blood pressures which is identified for younger patients. Thiazide diuretics and angiotensin-converting enzyme inhibitors are the drug of choice from which therapy may be initiated in older patients (over 80 years of age).Calcium channel blokers can be another choice [108,109,113].

2.Statins- Lipid management remains vital component of primary stroke prevention. The benefits of statins in stroke prevention in patients with coronary heart disease have been supported by several meta-analyses [111]. The Cholesterol and Recurrent Events (CARE) study found patients with average cholesterol levels treated with pravastatin after a myocardial infarction had a lower risk of stroke than patients receiving placebo. A large randomized prospective study involving over 20,000 patients followed for 5 years showed a benefit of simvastatin versus placebo in reducing mortality, stroke and myocardial infarction in high-risk vascular patients regardless of cholesterol levels. People with cholesterol levels above 200 mg/dl and cardiovascular risk factors should have a complete lipid analysis (total cholesterol, LDL, HDL and triglycerides) and most likely would benefit from cholesterol-lowering regimens, including statins [109,112,114]. The exact mechanism how statins provide stroke protection is uncertain. Although some of the stroke reduction may be due to lipoprotein alterations, other mechanisms unrelated to their lipid-lowering properties, are improved endothelial function, plaque stabilization, and antithrombotic, anti-inflammatory, and neuroprotective properties [111]. To date, the largest trials

suggest a beneficial effect of statins for stroke prevention in high-risk elderly subjects aged 82 years or younger [108].

3.Antidiabetic drugs- Type 1 diabetics have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, mainly obesity ,hypertension, and abnormal blood lipids. Syndrome X,a metabolic risk factor in some type 2 diabetics is charecterised by hyperinsulinemia and insulin resistance which results in hyperglycemia, increased very-low-density lipoprotein cholesterol, decreased HDL cholesterol, and hypertension. Both hyperglycemia and hypertension increase the frequency of diabetic complications, including stroke [111]. According to Primary stroke prevention guidelines rigorous control of BP among both type 1 and type 2 diabeticswith targets of <130/80 mm Hg, significantly lowers the risk of stroke [109,111-113]. The National Stroke Association and American Heart Association recommend rigorous comprehensive control of blood sugar levels for adherent patients with type 1 or type 2 diabetes to prevent microvascular complications. Intensive therapy to achieve tight control of hyperglycemia with ≥3 doses per day of insulin in patients with recent-onset insulin-dependent (type 1) diabetes mellitus was shown to reduce microvascular complications, nephropathy,retinopathy, and peripheral neuropathy [111]. Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists are recommended as first-choice medications for patients with DM.For hypercholesterolemia,statin are generally recommended [109,113].

4.Anticoagulants- Numerous large clinical trials have demonstrated the efficacy of warfarin for preventing stroke among patients with nonvalvular atrial fibrillation (AF). The relative risk reduction of thromboembolic strokes ranged from 42 to 86% for warfarin versus placebo [111,112,114]. However, the disadvantages of warfarin treatment, includes careful monitoring, dose adjustment,interaction with other drugs along with serious bleeding. This led to the quest for an alternative approach to prevention of ischemic stroke in patients with AF. An antithrombotic agent that might be used

(once it has been approved) instead of warfarin is the oral direct thrombin inhibitor, dabigatran [112,114].

Secondary prevention of ischemic stroke- Patients with an initial stroke are known to be at high risk for further stroke(s) compared to the general population, therefore secondary prevention is necessary [115]. Timing for initiation of secondary preventative treatment depends upon the clinical scenario. In minor stroke, most secondary preventative measures can be initiated almost immediately after presentation [78]. Treatment of risk factors such as hypertension, hyperlipidemia, atrial fibrillation, management of diabetes mellitus and carotid stenosis are important in secondary stroke prevention [116].

1.Antiplatelet treatment- Treatment with an antiplatelet agent is an essential part of secondary prevention of strokein Non-cardioembolics(atherothrombotic) patients, yet the relative effect is only modest [117]. Long term anti-platelet therapy should be prescribed to all people who are not prescribed anticoagulant therapy [118]. Evidence from randomized clinical studies suggests that aspirin (50–325 mg daily) monotherapy, clopidogrel (75mg daily) monotherapy, and Extended Release (ER) Dipyridamole (200mg twice daily) monotherapy provide comparable benefit for the prevention of recurrent stroke [119]. Six clinical trials have investigated the benefit of dipyridamole in the secondary prevention of ischaemic stroke. A meta-analysis based on individual patient data from five of the six trials confirmed the result from ESPS-II (the second European Stroke Prevention Study), finding that dipyridamole reduces the risk of stroke recurrence by 18% [83]. Clopidogrel is more effective, show 9% reduction in recurrent stroke and other atherothrombotic events as compare to aspirin [114] and may be considered over aspirin alone and it is reasonable for patients allergic to aspirin [90,108]. Ticlopidine's role in stroke prevention has been studied in two medium-sized trials, CATS (Canadian American Ticlopidine Study) which show a reduction of 30.2% in the risk of vascular events at two years and TASS (Ticlopidine Aspirin Stroke Study) show a 21% reduction in the risk of

fatal and non-fatal stroke as compared with aspirin at three years [83]. Ticlopidine may be more efficacious than aspirin in secondary stroke prevention; however its side effects limit its use [120].

One strategy that has been adopted in secondary prevention is the use of aspirin in combination with another antiplatelet agentbecause it is presumed that the individual effects on platelets will be additive [117]. Currently, the only therapy that has been shown to be better than aspirin alone is the combination of aspirin(25mg) plus Extended Release (ER) Dipyridamole (200 mg twice daily) [80,108,117,119,120] with 23% reduction of risk of recurrent stroke [78,114]. Current AHA/ASA (American Heart Association/ American Stroke Association) guidelines for secondary stroke prevention do not support the routine use of combination of clopidogrel + aspirin due to increase hemorrhagic complications [90,108,114,120]. However, the preliminary results of the CHANCE trial suggest that use of dual antiplatelet therapy in the acute post-ischemic period for a limited duration (short course i.e.21 days) may be of benefit [90,108]. Combination of aspirin (75mg/day), clopidogrel (75 mg/day), dipyridamole (modified release 200 mg twice daily) can also be used in patients who were resistant to single or dual antiplatelet therapy [117].

2.Anticoagulates—Oral Anticoagulant is not routinely recommended within 24 hrs for secondary prevention but is the therapy of choice and are significantly more effective than antiplatelets therapy in reducing the risk of recurrent ischemic stroke in patient with atrial fibrillation or cardioembolic stroke[90,108,114]. Warfarin is treatment of choice if the benefit outweighs the risk of hemorrhage,other generally used anticoagulant are unfractionated heparin,low molecular-weight heparin (Tinzaprin) and Danaparoid [108,114]. Warfarin significantly reduces risk of recurrent stroke, myocardial infarction, and systemic embolism after minor stroke [78]. Result from ACTIVE-A and the ACTIVE-W trials suggest that Unless all anticoagulant options are untenable, there is no compelling reason to treat patients with an antiplatelet agent for secondary prevention of

cardioembolic stroke [121]. Dabigatran, a direct thrombin inhibitor and rivaroxaban, apixaban, and edoxaban- direct Xa inhibitors were approved in the USA in 2012 and 2013 respectively. The advantage of NOAs over warfarin is their fixed dosage with no need for regular monitoringand lower quantity of clinically significant drug interactions. The short half-life and rapid onset and decrease in efficacy are important aspects that required careful compliance with treatment [109]. The definitive role of Dabigatran for secondary stroke prevention needs further evaluation [114].

3.Antihypertensive treatment—
Antihypertensive therapy is effective in reducing the risk of recurrent stroke. Careful identification of hypertensive patients with stroke and initiation of single or combination therapy, is essential for secondary stroke prevention [122,123]. Information on the use of specific antihypertensive agents is provided by the seventh report of the Joint National Committee (JNC7) guidelines. In the PROGRESS study, active treatment with perindopril, with or without the diuretic indapamide, reduced the risk of recurrent stroke by 28%. The PROGRESS and ACCESS trials suggest that ACE inhibitors or angiotensin II receptor blockers (ARBs) may be especially effective in secondary stroke prevention. The HOPE trial also confirmed a benefit of the ACE inhibitor ramipril in preventing strokes. The LIFE trial suggested that an ARB (losartan) was superior to a β-blocker (atenolol) for prevention of stroke [108]. The angiotensin converting enzyme (ACE) inhibitor ramipril significantly reduces the risk of stroke and acute coronary syndromes in patients with vascular disease and at least one recognised risk factor, irrespective of blood pressure and other treatments [78]. Data suggests that a diuretic or the combination of a diuretic and an ACEI are useful [113,120]. On the basis of PROGRESS study thiazide diuretic with or without an angiotensin-converting enzyme inhibitor is recommended. Other-CCBs or B-blokers.Drug selection should be based on patient specific factors and comorbities [114].

4.Statins— Treatment with statins reduces the risk of recurrent stroke among patients with coronary artery disease or those at risk for atherosclerotic disease[124-126].Treatment with atorvastatin 80 mg/day reduced recurrent stroke in patients with evidence of atherosclerosis and LDL-C level >100 mg/dl, with a target to reduce the LDL-C by half or to an LDL-C level of<70 mg/Dl [120]. Administration of statins after 48 hours of the occurrence of stroke is safe [127]. Pravastatin significantly reduces the incidence of stroke and other vascular end points in patients with a history of ischaemic heart disease, irrespective of initial cholesterol concentrations, and possibly independent of cholesterol lowering [78]. Simvastatin 40mg/day was shown to reduce the risk of stroke in patients with vascular diseases. Patients who are already on statins at the time of stroke onset should continue taking them [127].

CONCLUSION

Ischemic stroke is the leading cause of long-term disability and imposes significant financial burden on both the individual and society. Cerebral ischemia impairs the normal neurological functions which are triggered by a complex series of biochemical and molecular mechanism. Understanding of mechanisms of injury and neuroprotection in this disease is important to learn new target sites to treat ischemia. In this article, there is clear understanding of ischemic cascade followed by the mechanism of all damaging factors like energy failure, excitotoxicity, oxidative stress, neuro-inflammation, cell death modes: necrosis, apoptosis along with histological changes. Hence a good pharmacological management for the better treatment and recovery from stroke can be given. Great attention should be given on aspects like time of initiation and choice of drug therapy because this may have great impact on the disease and its recovery especially in acute condition. Drug selection should be based on patients specific factors i.e. age, contraindications with the use of drugs such as aspirin, warfarin etc. Careful indentification of stroke patient with modifiable risk factors like hypertension, hyperlipidemia, atrial fibrilation, diabetes etc are important in case of primary and secondary prevention.

Finally, aggressive stroke prevention employing several modalities is the best measure to improve outcomes and reduce stroke burden.

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