African Journal of Pharmaceutical Research and Development

Vol. 18 No.1; pp 642-653 (2026)

Original Review Article

ISCHEMIC STROKE IN AFRICANS: EXPLORING PROTECTIVE MECHANISMS AND THERAPEUTIC STRATEGIES THROUGH GENETIC AND EPIGENETIC INSIGHTS

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ABSTRACT

Stroke constitutes a primary cause of mortality and disability globally, with populations in Africa experiencing higher incidence and worse outcomes relative to other demographic groups. Although genetic and epigenetic mechanisms are progressively elucidating the factors influencing stroke susceptibility and recovery, African populations are notably underrepresented, comprising less than 5% participants in Genome-Wide Association Studies (GWAS), thereby constraining the scope and application of precision medicine. This review highlights key genetic and epigenetic factors influencing ischemic stroke in people of African ancestry, with emphasis on receptor-mediated pathways and therapeutic opportunities. We summarize genetic determinants such as *APOL1, HDAC9, NOS3*, and *PDE4D*, along with epigenetic regulators, including histone modifications, DNA methylation, and non-coding RNAs. These factors interact with environmental influences such as hypertension, diet, infections, and pollution to shape stroke risk and outcomes. We also examine receptor-driven mechanisms, including NMDA, AMPA, GABA, P2X7, cannabinoid, and VEGF signaling, which regulate excitotoxicity, oxidative stress, inflammation, and angiogenesis. Current and emerging receptor-targeted strategies, such as NMDA antagonists, GABAergic modulators, and P2X7 blockers, are evaluated for their translational potential. This review integrates receptor-mediated mechanisms with genetic and epigenetic insights, emphasizing African-specific determinants of stroke. We propose receptor-focused and precision medicine strategies to address Africa's disproportionate stroke burden. Integrating African genetic and epigenetic data into stroke research is crucial for uncovering population-specific mechanisms and therapeutic targets. Advancing receptor-focused and precision medicine strategies could reduce the disproportionate stroke burden in Africa and improve global equity in stroke care.

ARTICLE INFO

Received 17 January, 2026
Accepted 26 April, 2026
Published 30 April, 2026

KEYWORDS

Ischemic stroke, gene-receptor interaction, africans, signaling pathways

INTRODUCTION

Stroke occurs when cerebral perfusion is disrupted, either through reduced blood supply to the brain (ischemic stroke) or bleeding into brain tissue (hemorrhagic stroke), leading to neuronal injury and death [1]. Africa appears to have the highest incidence, prevalence, and case fatality rates of stroke [2]. The incidence and prevalence of strokes among Africans are 2-3 times higher than those in western

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https://doi.org/10.59493/ajopred/2026.1.24 ISSN: 0794-800X (print); 1596-2431 (online)

Europe and the United States of America [2,3]. The rising stroke burden in Africans reflects complex interactions among genetic, infectious, and environmental factors [4-6].

The high prevalence of stroke among Africans is associated with a substantial burden of hypertension, primarily driven by salt sensitivity, which represents the most prominent and modifiable risk factor within this population [7]. Additionally, demographic-related infections such as malaria, sickle-cell disease, human immunodeficiency virus (HIV), and COVID-19 are significant contributors to the elevated stroke incidence in Africa [6,7]. Consequently, these factors elucidate the complexity of stroke etiology in the African context.

Several studies highlighted the survival mechanisms of stroke, which involve various metabolic pathways and signaling molecules [8,9]. Notably, most of the studies focused on cellular metabolism, revealing a close relationship between receptors, inflammation, and metabolic pathways among European participants with little or no focus on the high-risk population. This review explores receptor-mediated signaling mechanisms and epigenetic factors shaping ischemic stroke susceptibility and recovery in Africans. These pathways may explicitly enhance stroke prevention, treatment, and the post-recovery phase.

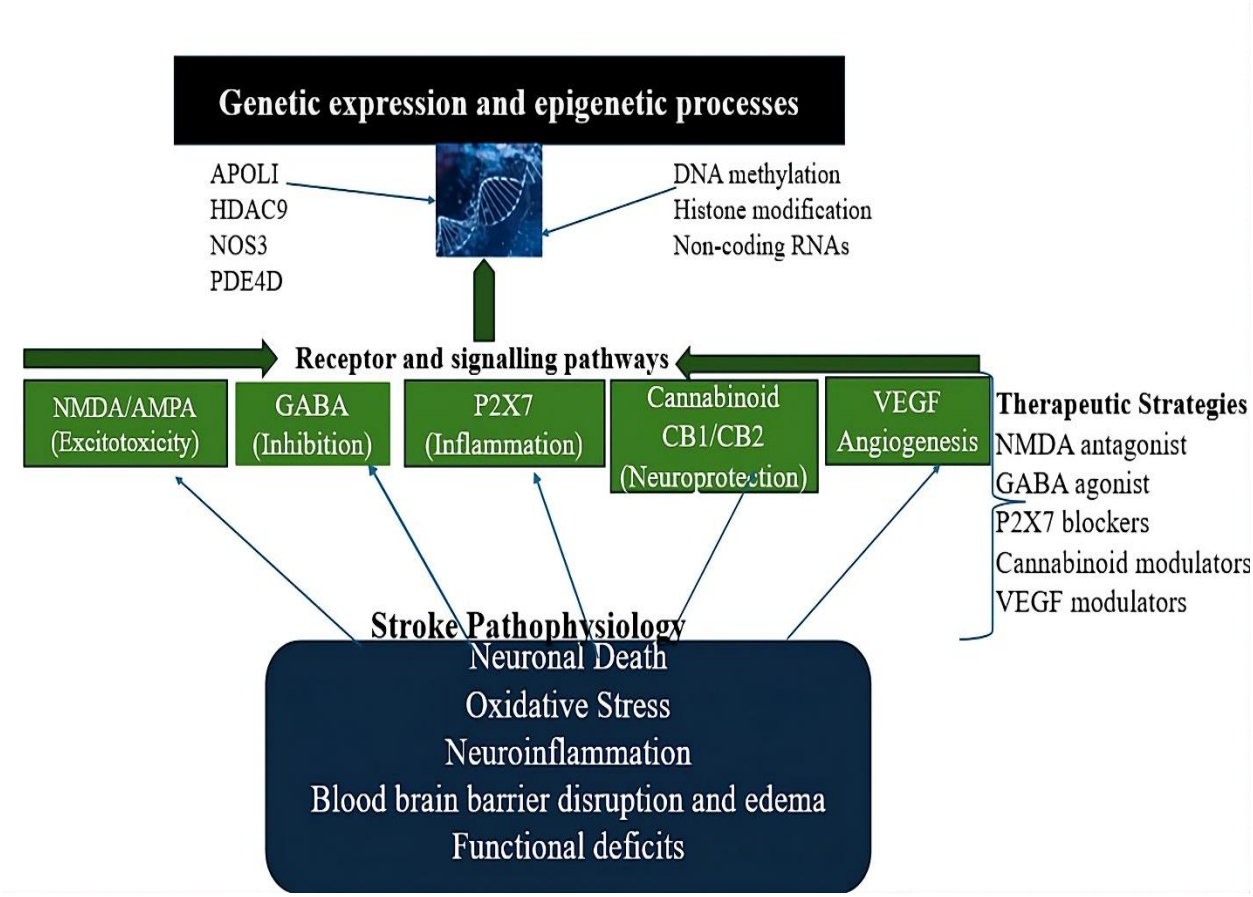

Figure 1: The mechanisms involved in ischemic stroke, the associated receptor-signaling pathways. And the potential therapeutic targets.

Genetic/epigenetic factors of stroke in Africans

Stroke in African ancestry populations is highly heritable and influenced by genetic and epigenetic determinants underlying cardiovascular risk factors [10-13]. Stroke subtypes may exhibit different heritability in Africans than in Europeans [11,12].

Genetic studies in populations of African ancestry have identified several loci associated with ischemic stroke risk. Variants in CDKN2A/CDKN2B and HDAC9 have been consistently linked to stroke susceptibility, particularly in relation to atherosclerotic and large artery stroke subtypes. In contrast, APOL1 risk variants have been implicated in stroke risk among individuals of African ancestry, likely mediated through hypertension and renal disease pathways; however, their specific association with small vessel disease remains under investigation. Findings from the Stroke Investigative Research and Education Network further identified candidate polymorphisms, including rs1800796 in IL6 and rs2383207 in CDKN2A/CDKN2B, which were associated with increased stroke risk in West African populations, with some sex-specific effects observed. Additionally, data from the Stroke Prevention in Young Women Study demonstrated that polymorphisms in NOS3 are associated with ischemic stroke risk in Black women, highlighting the role of endothelial dysfunction in disease pathogenesis [13,14]. In addition, SIREN also identified African-specific loci APOL1 and HBB (hemoglobin genes), which modulate stroke risk via hypertension and sickle cell disease, respectively [14].

HDAC9 is a common variant identified in a Genome-Wide Association study; the gene is associated with large artery stroke and has been replicated in some African-descended populations [14]. Histone acetylation/deacetylation can modulate the expression of genes involved in apoptosis and neuroprotection. Consequently, *HDAC* inhibitors are being investigated for their neuroprotective potential following ischemic injury. Additionally, studies have demonstrated the potential of *HDAC*s, including *SIRT6, HDAC9, and HDAC4*, in the treatment of vascular calcification, thereby offering new targets and intervention strategies for clinical prevention and management [15]. A comprehensive report focusing solely on the African population would be of considerable value in further establishing *HDAC*9 as a relevant gene variant in large vessel stroke.

Non-coding RNAs, particularly microRNAs such as miR-21, miR-124, and miR-210, play key roles in regulating inflammation and recovery following stroke [13,15]. However, data on their expression and function in African populations remain limited. Long non-coding RNAs (lncRNAs) also contribute to post-stroke processes by modulating angiogenesis and promoting neuronal survival [15,16]. Aberrant methylation patterns can influence the expression of genes relevant to stroke (e.g., those regulating inflammation, coagulation, and vascular tone). These genetic and epigenetic alterations converge on receptor-mediated signaling cascades that determine neuronal survival or death during ischemic stress.

Salt sensitivity and environmental stressors, such as infections, diet, pollution, and psychosocial stress, prevalent in certain African regions, may influence epigenetic marks [16-18]. Several African populations exhibit a high prevalence of salt-sensitive hypertension, which is linked to genetic factors, dietary habits, urbanization, and processed foods. Salt interacts with the renin–angiotensin system and endothelial pathways at the epigenetic level, modulating the expression of genes involved in sodium transport, oxidative stress, and nitric oxide signaling, thereby altering blood pressure regulation thresholds [19,20]. The signaling mechanisms similarly impact the translation of epigenetic changes into disease. Furthermore, high salt diets during pregnancy and childhood may modify DNA methylation and histone marks in renal and vascular genes, thereby increasing susceptibility to salt-sensitive hypertension.

Environmental exposures have the potential to alter epigenetic marks during sensitive developmental windows such as in utero, early childhood, and adolescence [20]. These modifications may result in enduring alterations in physiological functions, including metabolism, immune regulation, and vascular responsiveness. Some epigenetic marks can persist over the long term or potentially influence subsequent generations through transgenerational or parental effects. The majority of African regions continue to be exposed to lead, particularly within mining communities and through lead-containing products, although the extent of exposure in humans varies according to specific circumstances and outcomes [21].

Infectious diseases such as malaria, HIV, tuberculosis, and helminths repeatedly remodel the immune epigenome [18, 21-23]. This influences

immune training/exhaustion, vaccine response, and later risk of chronic inflammation and non-communicable diseases. Maternal infections can program the fetus epigenetically. Pollution such as indoor biomass smoke, urban air pollution, and heavy metals induces oxidative stress–linked epigenetic changes, increasing risks for asthma, cardiovascular disease, and neurodevelopmental impairment. Prenatal exposures are particularly harmful. Notably, hypomethylation of genes such as IL-6 or TNF-α may promote a pro-inflammatory response during post-stroke recovery [22].

Pathophysiology of Ischemic stroke and gene-receptor interaction

A sudden interruption of blood flow to a part of the brain, resulting in deprivation of oxygen and nutrients, initiates a complex cascade of cellular and molecular events that lead to neuronal injury and death. Endothelial cells lining cerebral blood vessels express NMDA receptors (comprising NR1 and NR2 subunits; encoded by the GRIN1 and GRIN2A-D genes) on adjacent neurons, which mediate excitotoxic calcium influx during ischemic events. Abundant AMPA receptors (GluA1–4; encoded by the GRIA1–4 genes) and voltage-gated calcium channels contribute to excitotoxic injury after a surge in glutamate levels. Purinergic receptors (P2X7 and P2Y12) present on microglia enhance the release of inflammatory cytokines. Endothelin receptors located in vascular smooth muscle cells regulate vasoconstriction and tissue perfusion. Microglia express Toll-like receptors (e.g., TLR4, gene: TLR4), which initiate inflammatory cascades through the NF-κB signaling pathway. In muscle cells, both vascular and cardiac, β-adrenergic receptors (ADRB1 and ADRB2) modulate cardiac output and blood pressure, thereby affecting the risk of stroke.

Post-stroke recovery

Interruption of cerebral blood flow results in cerebral ischemia, leading to impaired oxygen and glucose delivery and subsequent cellular energy failure [23]. This initiates a cascade of damaging processes, most importantly, mitochondrial dysfunction. Oxygen and glucose deprivation disrupt mitochondrial ATP synthesis, resulting in failure of ion homeostasis and increased accumulation of reactive oxygen species (ROS) [23-25]. Damaged mitochondria release pro-apoptotic factors like cytochrome c, leading to neuronal death. Energy failure impairs glutamate reuptake, leading to excessive extracellular glutamate and, consequently, excitotoxicity [25]. Mitochondrial repair controls glutamate signaling and receptor modulation (e.g., promoting neurotrophic receptor signaling) to support recovery.

The role of angiogenesis in post-stroke recovery

Angiogenesis, the process of forming new blood vessels from existing vasculature, is essential in post-stroke recovery, particularly within the penumbra, as it facilitates an increased supply of nutrients and oxygen [31]. In the adjacent penumbra, some cells sustain temporary survival, thereby providing an opportunity for therapeutic intervention. Angiogenesis is integral to stroke recuperation by supporting tissue repair and functional restoration through enhanced blood flow, as well as contributing to neural regeneration [31-33]. Additionally, the newly formed vessels foster neurogenesis and synaptic plasticity, ultimately aiding in functional recovery and the reestablishment of the blood-brain barrier over time.

During angiogenesis, several key mechanisms involving hypoxia-inducible factor 1-alpha (HIF-1α) are upregulated under hypoxic conditions, stimulating the transcription of angiogenic genes [34]. Vascular Endothelial Growth Factor (VEGF) also plays a central role by promoting endothelial cell proliferation, migration, and the formation of new capillaries [35]. Matrix Metalloproteinases (MMPs) facilitate angiogenesis by remodeling the extracellular matrix, allowing endothelial cells to invade surrounding tissues [36]. Additionally, endothelial progenitor cells (EPCs), mobilized from the bone marrow, contribute to vascular repair and neovascularization [37]. Signaling pathways, such as enhancing VEGF signaling or EPC recruitment, are potential therapeutic targets for stroke recovery. However, unregulated or excessive angiogenesis could lead to adverse effects, including cerebral edema or hemorrhagic transformation, highlighting the need for precise modulation of these processes.

Therapeutic and protective receptors in stroke management

Receptors are central to pathophysiology and potential treatment of stroke (Figure 1). Both neuronal and vascular receptors have interwoven signaling pathways; understanding their roles helps identify targets for neuroprotective therapies, especially in the acute and recovery phases. Studies have shown that certain vascular receptors are upregulated, inducing

transient angiogenesis in cerebral ischemia. Therapeutic strategies that modulate receptor activity are currently being investigated in preclinical and clinical trials. The following receptors and their roles in therapeutic interventions have been identified.

i. Excitatory Receptors: NMDARs containing the GluN2B subunit are associated with excitotoxicity and neuronal apoptosis during ischemic stroke [38]. NMDA Receptors mediate excitotoxicity due to excessive glutamate release during ischemia [25]. Its overactivation leads to calcium overload, mitochondrial dysfunction, oxidative stress, and neuronal death [38,39].

The receptor localization hypothesis proposes that the functional outcome of NMDA receptor activation depends on its subcellular distribution. Activation of synaptic NMDARs promotes neuronal survival by engaging intracellular signaling cascades such as the PI3K/Akt pathway and inducing CREB-mediated transcription of neuroprotective genes. In contrast, stimulation of extrasynaptic. NMDARs are linked to neurodegenerative signaling, characterized by suppression of survival pathways and activation of pro-apoptotic mechanisms [28,39]. This dichotomy underscores the critical role of spatial receptor signaling in determining neuronal fate during ischemic injury. Moreover, AMPA receptors also contribute to excitotoxicity by mediating rapid synaptic transmission in response to glutamate [26]. A subset of these receptors, the calcium-permeable AMPA receptors, is particularly implicated in neuronal injury during ischemia due to their ability to allow direct calcium entry into neurons, amplifying intracellular toxicity [26,27].

ii. Inhibitory Receptors: Gamma-aminobutyric acid (GABA) receptors are the primary mediators of inhibitory neurotransmission in the central nervous system. In the context of ischemic stroke, overactivation of excitatory neurotransmitters such as glutamate leads to excitotoxicity, which contributes significantly to neuronal injury [29]. Activation of GABA-A receptors helps to counteract this by dampening neuronal excitability and limiting further damage [40].

iii. Inflammatory Receptors. Toll-Like receptors (TLRs), particularly TLR4, recognize damage-associated molecular patterns (DAMPs) released by injured cells [41]. It initiates an innate immune response that releases cytokines and causes secondary brain injury. Hence, TLR antagonists are a potential therapeutic strategy. Interleukin Receptors (e.g., IL-1R), IL-1β binds to IL-1R, which triggers NF-κB signaling resulting in inflammatory gene expression [42]. Currently, IL-1 receptor antagonists (e.g., anakinra) are under study for stroke therapy.

iv. Vascular and Growth Factor Receptors: VEGF promotes angiogenesis, neuroprotection, and blood-brain barrier repair post-stroke [32,33]. Early activation may worsen edema, but later activation supports repair. Erythropoietin Receptors (EPOR) also act as anti-apoptotic and neuroprotective signaling. Notably, erythropoietin has shown potential in stroke models.

v. Dopamine and serotonin are key neuromodulators involved in mood regulation, motor function, cognitive processing, and neuroplasticity, which are critical in the aftermath of a stroke. Following a stroke incident, disruptions in these neurotransmitter systems can contribute to motor deficits, cognitive impairments, and post-stroke depression, potentially impeding recovery [43].

vi. Purinergic receptors: Following ischemic stroke, the release of extracellular ATP acts as a danger signal, activating purinergic receptors and initiating neuroinflammatory cascades [44-46]. Overactivation of P2X7 receptors amplifies inflammation and cell death, making them a target of interest for neuroprotective strategies [45]. P2X7 receptor antagonists are currently under investigation for their potential to limit inflammation, reduce brain tissue damage, and improve neurological outcomes after stroke [45-46]. Modulating purinergic signaling, especially through selective inhibition of P2X7 receptors [47], holds therapeutic promise in reducing secondary injury caused by inflammation and thrombosis in stroke [47]. However, achieving targeted effects without impairing physiological ATP signaling remains a key challenge in clinical translation.

vii. Cannabinoid receptors play a significant role in modulating the brain's response to injury. The two main subtypes, CB1 and CB2 receptors, have distinct distributions and functions relevant to stroke pathology [48,49]. CB1 receptors are primarily located on neurons within the central nervous system (CNS) and are involved in regulating neurotransmitter release, neuronal excitability, and synaptic plasticity. CB2 receptors are mainly expressed on immune cells, including microglia within the brain, where they modulate neuroinflammation and immune responses following ischemic injury [49]. Activation of

cannabinoid receptors, particularly CB2, has been shown to reduce inflammation, limit neuronal damage, and promote cell survival in preclinical models of stroke [50].

Genes and Receptors Associated with Stroke

The association of stroke-related receptors with genes is a critical area of study for understanding stroke pathogenesis, individual susceptibility, and therapeutic targets (Figure 1) [51]. Many receptors implicated in stroke are encoded by specific genes that regulate their expression, function, and interactions with signaling pathways [51]. Genetic polymorphisms or mutations in these genes can affect stroke risk, severity, and recovery. Table 1 links stroke-relevant receptors to their encoding genes and physiological roles.

Table 1: Summary of Genes and Receptors Associated with Stroke

Receptor Type	Receptor Name	Key Gene(s)	Role in Stroke
Excitatory	NMDA	*GRIN1*, *GRIN2A*–D	Excitotoxicity [52]
Excitatory	AMPA	*GRIA1–4*	Excitotoxicity, calcium overload [52,53]
Inhibitory	GABA-A	*GABRA1–6*, etc.	Neuroprotection [29, 54]
Inflammatory	TLR4	*TLR4*	Innate immune activation [55]
Inflammatory	IL-1R	*IL1R1*	Proinflammatory cytokine signaling [55]
Purinergic	P2X7	*P2RX7*	Inflammation, apoptosis [36]
Purinergic	P2Y12	*P2RY12*	Thrombosis [41], platelet aggregation [47]
Vascular	VEGF Receptors	*FLT1*, *KDR*	Angiogenesis [35], neurorepair [33]
Monoaminergic	Dopamine (D2)	*DRD2*	Cognitive recovery [43]
Monoaminergic	Serotonin (5-HT1A)	*HTR1A*, *HTR2A*	Mood, neuroplasticity [43]
Cannabinoid	CB1, CB2	*CNR1*, *CNR2*	Inflammation modulation [48-50]

Regulatory Pathways in Stroke

Following a stroke injury, multiple regulatory pathways activate to promote cellular survival, repair, and recovery (Table 2). The AMPK–SIRT1–PGC-1α signaling axis serves as a central regulator of mitochondrial biogenesis and cellular energy balance, particularly under metabolic stress. Activation of AMPK enhances SIRT1 activity, which in turn deacetylates and activates PGC-1α, promoting transcriptional programs that support mitochondrial function, antioxidant defense, and neuronal survival following ischemic injury [56]. Anti-inflammatory recovery pathways after ischemic stroke involve the coordinated activity of regulatory immune and glial mechanisms [57]. Regulatory T cells (Tregs), along with anti-inflammatory cytokines such as IL-10 and TGF-beta, as well as specialized pro-resolving mediators, contribute to the resolution of post-ischemic inflammation. In parallel, microglia undergo phenotypic polarization from a pro-inflammatory M1 state toward an anti-inflammatory, tissue-repairing M2 phenotype, thereby supporting neuronal repair and limiting secondary injury [58]. Oxidative stress generated during ischemia is counteracted by endogenous antioxidant defense systems, including superoxide dismutase, catalase, and glutathione peroxidase, which collectively reduce reactive oxygen species and protect neuronal and vascular integrity [59]. Under hypoxic conditions, the HIF-1α pathway is activated, enhancing angiogenesis, erythropoiesis, and glucose metabolism to support cell survival [ ]. The PI3K/Akt and MAPK/ERK pathways, triggered by growth factors and preconditioning, inhibit apoptosis and promote neuronal survival, proliferation, and differentiation [48]. Neurogenesis and synaptic plasticity, especially in the subventricular zone and dentate gyrus, are stimulated by BDNF, VEGF, EPO, and IGF-1, facilitating functional restoration [32-35,42]. The neurovascular unit, composed of neurons, astrocytes, endothelial cells, microglia, and the extracellular matrix, coordinates repair processes through glutamate buffering, ion regulation, and maintenance of blood-brain barrier integrity. Heat shock proteins, notably HSP70, mitigate ischemic damage by stabilizing proteins and preventing apoptosis [61]. Lastly, cerebral autoregulation and collateral circulation, including leptomeningeal anastomoses, maintain perfusion and redistribute blood flow to ischemic regions, thereby enhancing stroke recovery [62].

Table 2: Regulatory Pathways during stroke recovery and post-recovery

Pathway/Process	Key Molecules / Cells	Function / Outcome
Mitochondrial Biogenesis & Mitophagy	PGC-1α, AMPK, SIRT1	Promote recovery and removal of damaged mitochondria; restore energy balance [56].
Anti-inflammatory Resolution	Tregs, IL-10, TGF-β, SPMs, Microglia (M2 shift)	Resolves inflammation, shifts microglia from M1 to M2 for repair and healing [57, 60]
Antioxidant Defense Systems	SOD, catalase, glutathione peroxidase	Detoxifies ROS, protects neurons and vasculatures from oxidative damage [58]
HIF-1α Pathway	HIF-1α, VEGF, EPO, GLUT1	Enhance survival under hypoxia; promotes angiogenesis, erythropoiesis, and metabolism.
PI3K/Akt Pathway	IGF-1, BDNF, Bcl-2, Bad, Caspase-9	Inhibits apoptosis, promotes neuronal survival, and angiogenesis.
MAPK/ERK Pathway	Growth factors, ERK	Stimulates survival, proliferation, and differentiation, key in neuroplasticity.
Neurogenesis & Plasticity	BDNF, VEGF, EPO, IGF-1	Drives neural repair and synaptic remodeling that occur in the SVZ and dentate gyrus.
Neurovascular Unit Response	Neurons, astrocytes, endothelium, microglia, and ECM	Maintains BBB, regulates ion/glutamate levels, supports coordinated repair.
Heat Shock Proteins (HSPs)	HSP70, HSP27	Stabilize proteins, prevent aggregation, and inhibit apoptosis under stress [61]
Cerebral Autoregulation & Collaterals	Leptomeningeal vessels, cerebral arteries	Maintains perfusion through vasodilation and collateral circulation during ischemia [62]

Future directions

Several GWAS currently focus on some pathways mentioned earlier. However, despite more GWAS being conducted, less than 5% of participants are of African ancestry. Africans are underrepresented in GWAS related to stroke research. There are limited genomic datasets, biobank capacity, regulatory hurdles, and gaps in translating receptor-based therapeutics.

The first African genome-wide association study (GWAS) by Akinyemi and colleagues identified potential roles for regulatory microRNAs, intergenic non-coding DNA, and intronic non-coding RNAs in ischaemic stroke biology [15]. Their findings revealed novel molecular targets that may help address current gaps in accurate stroke risk prediction among individuals of African ancestry and support the development of targeted prevention and treatment strategies. However, the study did not establish an association between APOL1 and any stroke subtype. Notably, locus *APOL*1 plays a role in salt-sensitive/hypertension-stroke risk in the high-risk population. Further research is needed to confirm these initial results and to deepen our understanding of stroke genetics in people of African descent. Hence, community-based studies with a large number of African participants are essential to improve stroke management in Africa; integrating these efforts with precision medicine, biobanking, surveillance, and biomarkers, such as pilot targeted epigenetic biomarkers, is recommended as an early warning signal for high-risk groups.

Molecular insights into gene-receptors and protective signaling pathways are vital for identifying new drug targets or customizing existing therapies (Fig.1). Excitotoxicity and mitochondrial dysfunction are two primary factors contributing to ischemic brain injury. Synaptic NMDARs are believed to support neuronal survival, while extrasynaptic NMDARs promote neurodegeneration. Targeting excitatory receptors, especially through selective modulation of NMDA or AMPA receptors, offers a promising neuroprotective strategy during the acute phase of stroke. Therapeutic success depends on carefully balancing receptor inhibition to reduce damage while preserving essential neural communication and plasticity. However, limited data on the relationship between genes and NMDA receptors among people of African ancestry highlights the need for further research. Exploring the interaction between NMDA receptor signaling and mitochondrial dysfunction in stroke pathophysiology, along with evaluating the therapeutic potential of NMDA-gene receptor antagonists that target mitochondrial pathways, is crucial.

Furthermore, enhancing GABAergic signaling, either pharmacologically or via endogenous mechanisms, may decrease neuronal death, stabilize neural networks, and improve functional recovery after stroke. Nonetheless, the timing and degree of inhibition are vital, as excessive suppression of neural activity could impair neural plasticity and recovery during later stages of stroke rehabilitation. GABAergic drugs such as benzodiazepines have been studied for neuroprotection. P2X receptors, particularly P2X7, are known to facilitate microglial activation, pro-inflammatory cytokine release, and neuronal injury when excessively stimulated.

Over the years, cannabinoid receptor agonists have been investigated for their neuroprotective potential, as they may help mitigate the damaging inflammatory cascade and oxidative stress that follows cerebral ischemia. Additionally, modulation of CB1 receptors may help stabilize neuronal function and reduce excitotoxicity, though their psychoactive effects must be carefully managed in therapeutic contexts. Targeting the endocannabinoid system offers a promising therapeutic avenue for limiting secondary brain injury and enhancing recovery after stroke. However, further research is needed to optimize receptor selectivity, dosing, and timing to maximize benefit while minimizing side effects.

A review by Miras-Portugal et al [30] reported the novel contribution of nucleotide receptors to maintain cell homeostasis through the regulation of MAP kinases and phosphatases. Unraveling the various roles of nucleotide receptors in different models and cellular contexts may be crucial for delineating future therapeutic applications, thus, targeting these receptors for neuroprotection [30]. The purinergic receptor (*P2Y*13) plays a major role in HDL metabolism by facilitating reverse cholesterol transport and promoting the inhibition of atherosclerosis progression. Thus, it appears that the protectiveness of the novel locus near *AADACL2* against stroke may be associated with its epistatic interaction with the *P2RY*13 gene.

Interestingly, ongoing research by University College London, sponsored by a British Heart Foundation grant, is investigating ways to protect the brain from ischemia-reperfusion injury. The research programme specifically focuses on the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway. It investigates the neuroprotective effect of a novel, UCL-developed compound using an in vivo Middle Cerebral Artery Occlusion (MCAO) stroke model to identify pathways involved in the PI3K/AKT pathway in stroke. Hopefully, African genomic research will build equally effective and equitable preventive and therapeutic strategies.

This review highlights the importance of focusing on basic and translational research in stroke biology, particularly within African populations and communities. It is imperative to enhance awareness, attract, and engage researchers in this domain. Additionally, providing funding through reputable organizations such as the African Stroke Organization, the World Stroke Organization, and the World Health Organization can significantly impact progress. It is also essential to investigate the interactions between receptor-mediated survival signaling pathways and genetic or epigenetic factors, especially the treatment and prevention of ischemic stroke in African cohorts. Promising initiatives, such as African-led Genome-Wide Association Studies (GWAS), pharmacogenomic research, and receptor-targeted therapies tested among Africans, are strongly advocated. These efforts, conducted by neurologists, molecular biologists, and geneticists, in collaboration with entities such as SIREN (Stroke Investigative Research and Education Network) and the H3Africa consortium, are crucial. In addition, AI-based multi-omics modelling and network pharmacology approaches may offer transformative advances in the management of stroke among Africans.

CONCLUSION

The complex interaction between genetic variation, epigenetic mechanisms, and environmental exposures underscores the etiology of ischemic stroke in African populations. Despite evidence implicating genes such as APOL1 and HDAC9, and pathways involving histone modifications, DNA methylation, and non-coding RNAs, individuals of African descent remain markedly underrepresented in comprehensive genomic and epigenomic investigations. This gap in knowledge perpetuates health disparities and hampers progress toward personalized therapeutic approaches.

Receptor biology presents promising opportunities for intervention [63-65]. Dysregulated NMDA and AMPA signaling induce excitotoxicity, whereas impaired GABAergic function heightens neuronal susceptibility. P2X7 purinergic receptors exacerbate

neuroinflammation, and cannabinoid receptors influence neuroprotection and recovery. VEGF-mediated angiogenesis plays a dual role in both ischemia and repair processes. Targeting these receptors through pharmacological (Natural products) or gene-based strategies may improve therapeutic outcomes. Moving forward, it is crucial to prioritize African-led research in genetics, epigenetics, and receptor studies. Investment in biobanking, population-specific GWAS, and translational research will enhance global understanding of stroke biology and facilitate precision medicine tailored to African populations. By integrating molecular insights with culturally relevant health strategies, it is feasible to reduce Africa's disproportionate stroke burden and promote equitable prevention and treatment worldwide.

ACKNOWLEDGMENT

None

AUTHOR'S CONTRIBUTION

OAE drafted the manuscript. OAE and PIA were involved in revising it critically for intellectual content. The authors read and approved the final manuscript.

CONFLICTS OF INTEREST

No conflicts of interest to disclose.

FUNDING

This publication is self-funded.

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