

MINI-REVIEW

Role of arginase in hypoxic–ischemic brain injury in infants: An update

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Abstract

Hypoxic–ischemic (HI) brain injury is a major cause of neurological impairment in newborns worldwide and can lead to severe short- and long-term neurodevelopmental dysfunction. Adult neuroprotective interventions, on the other hand, may have a major influence on children's developing nervous systems. The detailed aetiology of HI in the developing brain needs to be discovered to establish new pathways for successful therapies. The exact mechanism of newborn HI brain damage is still not completely known. However, mitochondria play a huge part not only because of their central position in metabolism, but also because certain enzymes are involved in the mitochondrial urea cycle. Arginase is responsible for two key physiological functions: the production of proline and polyamines, and the detoxification of ammonium ions. The arginase enzyme catalyses the final phase of the urea cycle by removing extra nitrogen from the amino acid. The release of nitrogen is a key feature of both neuronal and vascular cell signalling and is crucial for ensuring adequate blood supply to the central nervous system. In this mini-review, arginine and ornithine were used to evaluate their roles in regulating arginase activity under HI conditions.

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1. Introduction

Hypoxic–ischemic (HI) brain injury causes a significant amount of death and long-term disabilities in children, impacting between 0.5 and 1.5 million neonates per year.¹ Although advancements in respiratory and intensive care technologies have enhanced recovery rates significantly, the prevalence of motor and cognitive disabilities due to perinatal and early post-natal brain injury has risen over the last two decades.² Despite the substantial socioeconomic impact of neonatal HI, there are currently few preventative and/or preventive treatments accessible for patients who have experienced brain damage as a result of HI, with only hypothermia becoming approved for use.³ The aetiology of HI is complicated, with a simple primary-insult process accompanied by a more delayed, secondary-injury phase that may last for years. Although the original, main insult plays a role in neuronal cell death, the severity of secondary damage caused by inflammation and oxidative stress may be a more important factor in neuronal survival.³

Arginase (ARG), a manganese-dependent ureohydrolase, catalyses the final step of the urea cycle to discard harmful ammonia by converting it to *L*-ornithine and urea

from *L*-arginine. More recent research, however, shows that ARG plays a series of roles in both desirable and undesirable ways, especially in numerous disease states.³ As ARG is one of the most acutely overregulated enzymes in ischemic injury (heart, liver, and retina) and an essential regulatory enzyme in several inflammatory states, it is possible to create more efficient treatments to enhance outcomes by clarifying the molecular mechanisms of the ARG route.³ Ultimately, we conjecture that the dynamic interaction between the physical characteristics of ARG isoenzymes and their relations with other co-regulators and their temporary manifestations determines the particular consequences following HI injury of the ARG central nervous system (CNS). Recent investigation indicates that hypoxia-related pathways, notably those involving vascular dysfunction, inflammation, and metabolic dysregulation, that are linked to neonatal HI damage, also overlap with those seen in juvenile stroke and traumatic brain injury (TBI).^{4,5}

2. Arginase

The role of ARG, a manganese-dependent enzyme that catalyses the conversion of *L*-arginine into *L*-ornithine and urea, in the urea cycle was elucidated following the discovery of the Krebs–Henseleit urea cycle in 1932 (Figure 1). The manganese-containing ARG ureohydrolase

catalyses the final step of the urea cycle to discard harmful ammonia by converting it to *L*-ornithine, urea.⁶ ARG exists as two isoforms, arginase 1 (ARG1) and arginase 2 (ARG2), which are encoded by separate genes and differ in their subcellular localisation, tissue distribution, immunological cross-reactivity, and molecular regulation. In humans, ARG1 (105 kDa) and ARG2 (129 kDa) exist primarily as homotrimeric metalloenzymes,^{7,8} with ARG1 comprising 322 amino acids⁶ and ARG2 having 354.⁹ Each isoform is encoded separately, and both genes are located on individual chromosomes. The two isoforms have identical action pathways, and they deliver the same metabolites.¹⁰ ARG1 and ARG2 are constrained mainly to the kidney, brain, prostate, intestine, and pancreas.^{3,9,11–13} They contain more than 60% homology in amino acids, and the sections crucial to enzyme function are 100% homologous.⁶ This suggests that overlapping metabolites have functional capacities within their isoforms, but their influence is quite unique to cell and organ groups.

3. Arginase and nitric oxide pathway

An omnipresent gaseous nitric oxide (NO) plays a vital role in numerous neurobiological processes. ARG, which also generates NO, plays a crucial role in the synthesis of proline and polyamines. The degree of production of NO is regulated by the enzyme nitric oxide synthase (NOS).

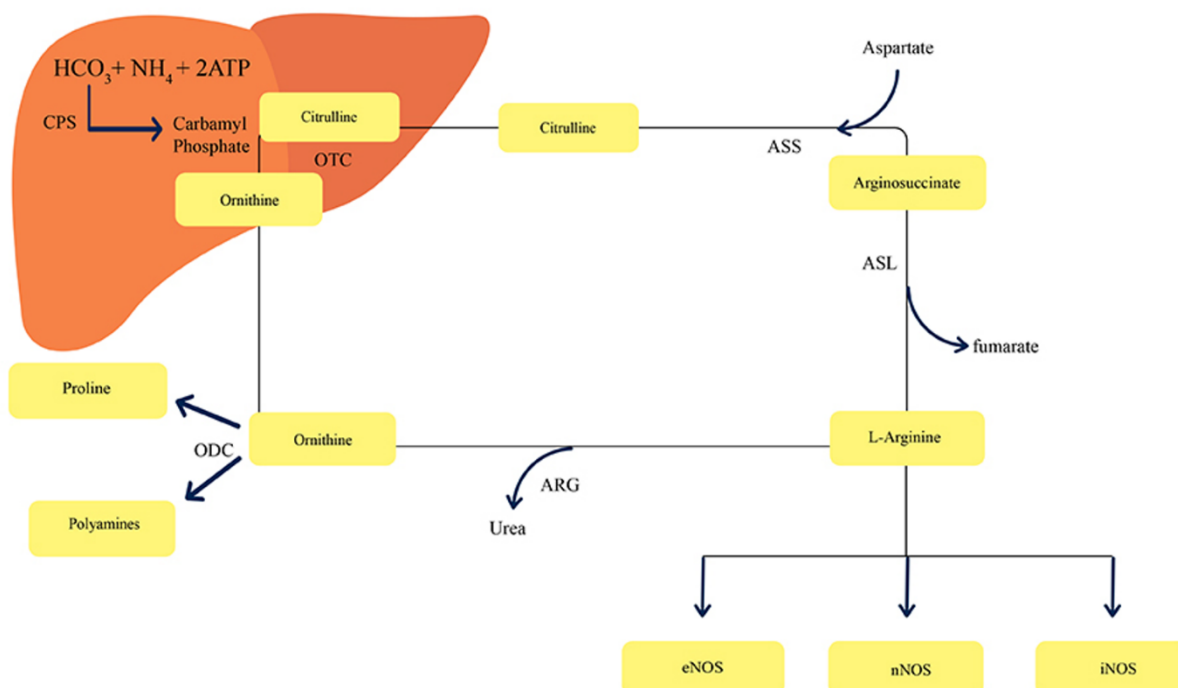


Figure 1. Different steps of the urea cycle structure, overall articulation of *L*-arginine, ARG, and *L*-ornithine

Abbreviations: ARG: Arginase; ASL: Argininosuccinate lyase; ASS: Argininosuccinate synthase; CPS: Carbamoyl phosphate synthetase; NOS: Nitric oxide synthase; OAT: Ornithine aminotransferase; ODC: Ornithine decarboxylase; OTC: Ornithine carbamoyltransferase.

There are three isoforms of NOS: neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3). Two of these, NOS1 and NOS3, are constitutively expressed and need activation. In comparison, transcriptional and posttranscriptional pathways control mainly the inducible NOS2 at the expression stage.^{3,14-17} It implies that the restriction and hence physiological functioning of NO output by ARG depends on the on the conjunction of ARG and NOS isoforms. of ARG isoform with NOS isoform. Upregulation of ARG1 or ARG2 essentially restricts NO iNOS activity, but because nNOS uses a much lower rate of *L*-arginine than iNOS, the result cannot be presumed to be equivalent for nNOS.¹⁸

However, it is crucial to note that ARG does not produce NO. Instead, it acts competitively with NOS because they share the common substrate *L*-arginine. High levels of ARG lead to low levels of available substrate for NOS, and hence, the formation of NO is inhibited.

Nitric oxide acts as a gaseous neurotransmitter in the CNS, where it is an excitatory amino acid, glutamate. Cyclic guanosine-monophosphate (cGMP), a soluble NO receptor-mediated signalling cascade, communicates its modulatory effects as either a post- or a pre-synaptic retrograde messenger.¹⁸ NO is linked with guanylyl cyclase.¹⁹

4. Arginase and proline pathway

Arginase is responsible for the production of urea and the conversion of arginine to ornithine. ARG exists as two isoforms, ARG1 and ARG2, which are encoded by separate genes. ARG1 is a cytosolic enzyme that is highly expressed in the liver. In contrast, ARG2 is a mitochondrial enzyme²⁰ when ARG1 co-localisation with ornithine decarboxylase (ODC) in the cytosol forms polyamine.³ In comparison, mitochondrial ARG2 co-localisation with ornithine aminotransferase (OAT) begins with proline.²⁰ Ornithine is a mediator of two neurotransmitters, glutamate and γ -aminobutyric acid.^{3,14} These two synapses could play a huge part in resulting injury processes. There are a number of activities that putrescine, spermidine, and spermine may perform, including cell survival, proliferation, maturation, and neurite development.¹⁹⁻²² Overactivation of the *N*-methyl-*D*-aspartate receptor results in excitotoxicity, which damages neurons.²³

5. Role of arginase

5.1. Localisation on central nervous system

In situ hybridisation and immunolocalisation strategies revealed that both ARG isoforms, ARG1 and ARG2, were

expressed in CNS.¹² In the brains of chickens²⁴ and rodents,¹³ ARG1 and ARG2 were both present, but ARG1 expressed a higher level than ARG2. As in humans, ARG1 and ARG2 are found in the brainstem and spinal cord of rats, as well as in the cortex, limbic system, and hippocampus.^{3,11,13,25-27} Early studies suggested that ARG expression was restricted to neurons¹³ and noted that both are found in the glia, i.e., oligodendrocytes and microglia,^{11,25,27} and in astrocytes.¹³ ARG articulation in both excitatory and inhibitory neurons situated in the hippocampus,²⁸ whereas in the cerebellum, ARG articulation was reported in the basket, stellate, Golgi, and Purkinje cells.²⁵ It is as yet unclear which cells are required as essential drivers of ARG in HI states of the cerebrum and what changes happen in ARG expression and movement as the injury progresses.

5.2. In the neurodevelopment process

The severe transient observation of the articulation of neuronal ARG will, in general, affect the axon development of early neurons. In refined DRG neurons, the levels of ARG in youthful neurons were initially elevated, which corresponds with the development of axons, as myelin is formed early. However, with the predictable decline in ARG activity at P4, myelin's effect quickly changed to inhibit axon formation. Neurotrophins also suggest elevated cAMP levels, which trigger ARG1 transcripts, which indirectly increase polyamine levels and promote axon growth by eliminating myelin-inhibitory signals. If cAMP fell precipitously at age P4, this atomic pathway was downregulated, and inhibitory myelin signalling flagged further axon improvement. ARG1, therefore, is thought to play a fundamental role in supporting axon formation and improving the capacity of axons to withstand injury, particularly during late post-natal neural development and even after CNS injury, by determining inhibitor factors, for example, myelin-related glycoprotein. The overexpression of ARG1 and polyamines also stimulated axon growth in cultured myelin neurons, while ARG and ODC inhibitors supposedly suppressed axon expansion by blocking the alteration from ornithine to ARG or polyamines from ornithine, respectively.³

Arginase is considered the most significant activity at the highest protein and polyamine synthesis cycles, meaning that it plays a crucial function in this early developmental enzyme.²⁹⁻⁶² According to the anatomical improvements found in the unforeseeable gradation of defects dependent, the dendritic complication, intrinsic excitability, synapse numbers, and functional synaptic deficiencies of the ARG knockout animals are reduced with the loss of arg1 single- or double-copy. Gene therapy treatment of ARG1 rescues every one of these defects at the neonatal levels.³

In neurodevelopment, neurogenesis and axonal pathways, ARG plays a direct and vital role. Therefore, it is essential to consider the developmental patterns and modulation of this trajectory following damage, particularly after HI, to establish effective treatment strategies.

5.3. In hypoxic-ischemic conditions

Hypoxia-ischemia provides a molecular environment that leads to long-term injuries, such as vascular dysregulation, oxidative stress, inflammation and excitotoxicity.⁴⁰ This injury is a vital factor for irreversible neuronal dysfunction and adverse clinical results. Different pathways triggered by neonatal brain HI alter ARG metabolism.

The hypoxic state causes ARG expression and action.⁴¹ Hypoxia-inducible factor 2 α (HIF-2 α) activates ARG2.⁴² One of the most prevalent reactions to severe cerebral hypoxia after a stroke is HIF-2 α .⁴³ Hypoxic-induced upregulation of ARG2 expression has been associated with activation of AMP-activated kinase α 1.³⁸ regulation by microRNAs,⁴⁴ and phosphoinositide 3-kinase/protein kinase B signaling,⁴⁵ and activation of ARG2 by ARG1 and activation of the extracellular signal-regulated kinase or epidermal growth factor tyrosine kinase, all of which promote the expression of ARG1 and ARG2 mRNA.⁴⁶⁻⁴⁸

The three phases after neonatal brain HI were described: acute due to HI insult; secondary, sub-acute phase due to re-oxygenation and reperfusion; and a tertiary, chronic phase in which previous events could become worse, and inflammation could become chronic. ARG appears to respond through shifts in its behaviour and speech in all phases.⁴⁹

The same pathways regulated by hypoxia have been seen in pediatric patients with ischemic stroke, wherein there is blockage of blood vessels and reduced blood supply to the brain, causing secondary inflammation and oxidative damage to neurons. This shared pathophysiology between the two disorders indicates the possible involvement of ARG pathways in influencing blood vessel and neuron function in both conditions.⁴

5.4. In neuroinflammation

Neuroinflammation plays a fundamental role in physical issues and post-injury in the cerebrum. It may be possible that the controllers of neuroinflammation may reconcile both injury and post-injury. Various mediators are implicated in neuroinflammation and have been shown to regulate ARG, a prominent characteristic of HI. It has been shown that interleukin (IL)-13 and IL-4 promote ARG1 through cAMP and activation of the Janus kinase/signal transducer and activator of transcription (JAK/

STAT).^{50,51} IL-13 induces ARG2 via STAT6, but not its STAT6-mediated effect on IL-13Ra2.⁵² On the other hand, IL-10 stimulates ARG1 to a lower level than other.⁵³ Many studies have revealed that IFN- γ suppresses the activity of both isoforms.⁵³⁻⁵⁵ Lingyun⁵⁶ reported that 2(S)-amino-6-bronohexanoic (ABH) acid inhibits ARG to decrease the production of IFN- γ . Apart from HI injury, there is an overlap between mechanisms such as neuroinflammation, oxidative stress, and blood-brain barrier damage involved in TBI in children. This is because these mechanisms can cause secondary injury, affect neurotransmission, and cause behavioural deficits, which means ARG pathways may also play a role in TBI-induced neurodegeneration.⁵

According to findings in the multiple sclerosis experimental autoimmune encephalomyelitis rat model, both brain and spinal cord expression and activation are increased. There has also been increased development of reactive oxygen species and increased expression of NOS2.^{57,58} The studies have also shown an improvement in ARG levels in the cerebrospinal fluid of MS patients. These findings affirm the roles of ARG and NO in acute neuroinflammatory pathogenesis and indicate that they may be useful as biomarkers for disease progression.

Deletion of the ARG2 gene prevented neuronal and vascular cell death and increased retinal function in mice with oxygen-induced retinopathy (OIR).^{59,60} Increased expression of A2 in horizontal retinal cells and photoreceptor cells of hyperoxic mice was observed.⁶⁰ In earlier studies, ARG activity has been indicated in the retina. Injury reduction may have a protective effect in this model. The authors observed a reduction of retinal cell death and increased survival of astrocytes in tumour necrosis factor alpha (TNF- α)-deficient mice.⁶¹ TNF- α -retina mice exposed to OIR had lowered NOS2 with increasing ARG and Arg2 mRNA expression compared to the wild-type mice exposed to OIR.

The regulation of ARG through cytokines appears to be a more complicated mechanism, where suppressors of cytokine signalling (SOCs) show via inhibition of negative input on the JAK/STAT signal pathway.⁶² Both SOCS1 and SOCS3 are communicated in microglia⁶² and control the activation⁶³ and polarisation of the microglia. Interestingly, this control is linked to variations in the ARG/iNOS ratio: SOCS1 results in a strong ARG/iNOS ratio and initiation of M2.⁶⁴ Knockdown of SOCs1 reduces the expression and behaviour of M2-induced ARG1 and reciprocally improves iNOS activity. Expression of SOCS3 has been associated with M1 activation,⁶⁴ whereas reduced ARG1 activity⁶⁵ may influenced inflammatory polarisation. Because microglia are one of the first recipients of neonatal brain injury and have both positive and negative impacts, these

results are essential for awareness of post-injury processes. Prostaglandin E1, E2, and E3,⁶⁶ as well as transforming growth factor β 1⁶⁷ were also shown to modulate ARG expression.

5.5. In oxidative stress

Reactive oxygen species can be produced aerobically or by free radicals. Oxidative stress and ARG have a prominent relationship. Chandra *et al.*⁶⁸ revealed that free radicals increase the ARG expression by proteinase-C and RhoA/Rho-associated kinase activation. These ARG activations lead to suppressing the availability of NOS. L-arginine is a substrate for NOS. These three analog NOS1, NOS2, NOS3. Reduction of NO by eNOS or nNOS is slightly lower compared to iNOS. The NO produced by iNOS is needed for alternative signalling mechanisms and microbial defence. NO-produced eNOS interacts with soluble guanylate cyclase (sGS) in vascular smooth muscle cells, activating it soluble guanylate cyclase (sGS). The activation of sGC resulted in the production of cGMP, K⁺ efflux, and smooth muscle relaxation.¹⁰ Thus, eNOS maintain the adequate blood flow by inhibiting leukocyte adhesion to vascular endothelium and inhibiting platelet aggregation. L-ARG is considered as a semi-essential amino acid,¹⁰ but some studies revealed that the over-expression of L-arginine increases ARG expression and competes with NOS for L-arginine and NOS uncoupled. The elevation of ARG activity by reducing L-arginine availability to NOS can decrease NO production, causing more superoxide (O₂⁻), which quickly responds with NO to produce another powerful oxidant peroxynitrite (ONOO⁻). ARG also suppresses L-citrulline production, which has been shown to have antioxidant properties,⁶⁹ attenuates eNOS and nNOS expression after ischemic injury,^{70,71} reestablish No levels, increase eNOS and downstream iNOS later glutamate toxicity.²⁸ This finding elucidates the ARG-mediated oxidative stress and the ensuing mechanism.

5.6. In blood–brain barrier regulation

The vascular pathophysiological characteristics of HI and reperfusion injury of the cerebrum include disruption of the blood–brain barrier, compromised cerebral autoregulation, and regional differences in perfusion. The relevance of ARG in vascular regulation and endothelial maturation has been broadly contemplated in various peripheral organs, and at least a portion of these discoveries are probably going to be summed up in the cerebrum. Although ARG1 and ARG2 have been revealed in the cerebral microvasculature, it is assumed that ARG has an influence on cerebral microcirculation, blood–brain barrier integrity, and endothelial function.⁷² The major isoform in endothelial cells is ARG2, which, as previously

indicated, interacts with eNOS to regulate NO generation. As ARG reduces the supply of L-arginine to eNOS, it causes eNOS uncoupling, thereby facilitating oxidative stress. Endothelial senescence, eNOS uncoupling,⁷³ increased adhesion molecule expression, and improved monocyte-endothelial cell connectivity are induced when ARG is upregulated. ARG2 has these effects through S6K1 activation, while ARG1 does not. At the site of vascular injury, many vascular causes function as ARG inducers. In an experimental model of rat TBI, ARG1 expression increased in the mesenteric arteries, and L-arginine supplementation or ARG suppression with N ω -hydroxynor-L-arginine (nor-NOHA) reversed the ARG impact. The therapeutic relevance of structural improvements in ARG articulation after cerebrum harm, On the contrary, is contradictory.

Despite the numerous studies that have linked the increase in ARG levels to HI brain injury, it is not clear what the function of ARG might be, and even then, it may depend on the particular circumstances. For instance, when ARG levels rise, there could be a decrease in NO production and impairment of blood vessel function, but in other studies, it appears to offer protection by promoting repair.

5.7. Biomarkers

Earlier, we discussed that several pathophysiologies may involve ARG expression, disrupting homeostasis and functionality of the organism. The upregulation of ARG is associated with several pathophysiological processes ranging from cardiovascular, immune-mediated, and tumorigenic to neurodegenerative diseases.⁶ We have also discussed that mammals have two isoforms of ARG, ARG1 and ARG2. ARG1, which is mainly expressed in the liver, plays a primary role in L-ornithine's urea cycle and biosynthesis. ARG2 is expressed in all tissues, i.e., kidney, prostate, gastrointestinal tract, and endocrine tissue.⁶⁶ It regulates the biosynthesis of L-ornithine, proline, and glutamate, which are essential for collagen synthesis, tissue repair, cell proliferation, neurodegenerative and regulate the immune response.⁶ Previous studies revealed that both the gene and serum activity of ARG1 have increased with ischemic stroke in adult.³ It might be slightly different in neonatal because neutrophils show different patterns after the stroke. It suggests that the expression of ARG1 may correlate with peripheral neutrophil count and the severity of the stroke, which has been associated with poor neurological outcomes in neonates.³

5.8. Therapy

The early ARG inhibitors exhibit a range of side effects because of their low effectiveness and nonspecific actions.

The weak ARG inhibitor alfa-difluoromethylornithine (DFMO) acts non-specifically to block ODC.⁶⁶ While DFMO increased NO levels in an experimental model with elevated ARG activity, this impact may be influenced by its ability to promote ornithine aggregation, which is reported to suppress ARG.⁷⁴ Restraint of ODC would likewise restrict polyamine arrangement, which could decrease oxidative pressure by anticipating the reversion of spermine and spermidine incorporation through polyamine oxidases. NOHA is a powerful ARG inhibitor, but at the same time it is a result of NOS's digestion of *L*-arginine to create NO. Nor-NOHA, an analogue of NOHA, is a successful ARG inhibitor, yet it has a longer half-life than NOHA. Likewise, in its role in the formation of urea, the action of ARG is likewise associated with advancing the amalgamation of polyamines, *L*-glutamine, *L*-proline, and *L*-ornithine. A few amino acids, including *L*-ornithine, *L*-leucine, *L*-valine, *L*-lysine, *L*-isoleucine, and *L*-norvaline, suppress the ARG. *L*-citrulline enhances NO output while still acting as an allosteric regulator of ARG.⁶⁷ Numerous competitive ARG inhibitors are currently accessible that have high specificity and do not hinder NOS at the focuses that are exceptionally viable in restraining ARG.

Kanyo *et al.*⁶⁹ established numerous competitive ARG inhibitors based on the crystal structure of human ARG1 and ARG2. They identified the whole structure of both isoforms and reported that their catalytic activity relies on a binuclear manganese cluster at the active site.^{7,69} Two highly selective ARG inhibitors, BEC(S-(2-boronoethyl)-*L*-cysteine] and ABH,⁷⁵ both have a boronic acid or *N*-hydroxy guanidinium head and are boronic acid analogues of *L*-arginine. Although this boronic head attaches to the manganese cluster at ARG's active catalytic region, it inhibits the enzyme's activity strongly.⁷² A variety of synthetic ARG inhibitors, such as analogues of boronic acid, *N*-hydroxide-*L*-arginine, *N*-hydroxy-nor *L*-arginine and the newer (R)-2-amino-6-borono-2-(2(piperidine-1-yl) ethyl) hexanoic acid, have been produced.⁷³ Currently, while approximately 27 ARG inhibitors have been patented and tested,⁷⁶ tests have shown that several of these inhibitors lack specificity.

Although knockout models may provide some insights into ARG inhibition effects, the results must be carefully assessed because of unknown compensatory pathways that can hide ARG effects. The limited lifespan of ARG1 knockout is a significant drawback. Since there are no isoform-specific ARG inhibitors, RNA knockdown techniques have been used to downregulate A1 or A2 expression. An experimental analysis of a mouse model reveals the positive outcomes in asthma,⁷⁷ erectile

dysfunction⁶⁷ and diabetes.⁶⁸ On the other hand, ARG antagonists have also been the target of clinical trials in patients with cardiovascular disorders, i.e., coronary artery disease, pulmonary hypertension, atherosclerosis, cardiac failure, vascular instability in diabetes mellitus, and hypertension, which have shown promising outcomes.^{75,78-79}

Following brain HI, the role of ARG inhibition is unclear. While many studies focus on the benefits of ARG inhibition, others (such as the ones mentioned above) focus on ARG's function as a neuroprotective enzyme. The number of trials focusing on various brain pathologies and the variety of injection times were small, making it difficult to compare the results of ARG's inhibition.

The use of ARG-targeted treatments in clinical settings is still restricted, despite encouraging preclinical results. Isoform-specific targeting, possible off-target metabolic consequences, and variations between animal models and human newborn physiology are some of the difficulties. Additionally, ARG's dual function in damage and repair makes therapeutic modulation more difficult, requiring precise temporal and cell-specific intervention techniques.

6. Conclusion

In animal models and human disease conditions, the role of the excessive ARG/ornithine pathway in neurovascular disease is well established. Treatments targeting various elements of the ARG/ornithine pathway have significant potential. Two ARG isoforms are shown to be 100% homologous in the activity-critical area. Furthermore, both isoforms are associated with the dysregulation of the NOS system. ARG1 and ARG2 are determined by independent genes and are found in different intracellular compartments. However, there is much evidence that ARG is involved in cell proliferation, collagen production, tissue repair, and the regulation of smooth muscle contraction. As a result, prolonged global inhibition of ARG production may be harmful. ARG function is being investigated at the subcellular and molecular levels. The results will help develop new approaches to reduce the pathophysiological impact of overactive ARG. More studies are needed to fully understand the activities of the two ARG isoforms and their downstream targets in health and disease, to develop new therapeutic approaches. Even with these drawbacks, greater knowledge of the impact of ARG on HI brain damage in newborns may lead to the development of novel neuroprotective therapies. In addition to developing selective modulators that can balance ARG's dual functions in neurotoxicity and repair, future research should focus on elucidating the temporal and cell-specific roles of ARG isoforms in neonatal HI injury.

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Conflict of interest

The authors declare that they have no conflicts of interest regarding this paper.

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Ethical approval and consent to participate

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