Novel Roles for Arginase in Cell Survival, Regeneration, and Translation in the Central Nervous System\textsuperscript{1,2}

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ABSTRACT In this review the current knowledge about the arginine-degrading enzyme arginase and its unexpected roles in survival and regeneration in the central nervous system will be discussed. Recent data suggest the neuroprotective effects of extracellularly applied arginase can be attributed to an activation of the endoplasmic reticulum stress response with a consequent change of the pro-survival gene expression profile. However, the activation of neural regeneration pathways caused by an upregulation of endogenous arginase I is mediated by polyamines, a group of arginase downstream products with widespread biological effects. In light of these new discoveries, there is heightened interest in the regulation of arginase I gene expression within the central nervous system. A number of transcription factors such as Sp1, C/EBP (CCAAT/enhancer-binding protein), and CREB seem to be involved in the transcriptional control of arginase I and may contribute to the complex expression pattern of arginase I in distinct brain regions and during development. Beyond molecular mechanisms, this review will also include relevant clinical findings in patients with neurodegenerative diseases. J. Nutr. 134: 2812S–2817S, 2004.

KEY WORDS: • arginase • arginine • neurodegeneration

Apoptosis plays a pivotal role in physiological and pathophysiological processes. Recent insights into the molecular mechanisms of apoptosis have provided fresh perspectives for the development of therapeutic strategies in the treatment of neurodegenerative diseases. In this context, the arginine-degrading enzyme, arginase, is the focus of increasing attention. This short review aims to highlight the emerging knowledge about arginase, its regulation, its products, and the effector pathways regulated by arginase products in the survival and regeneration of the central nervous system.

L-arginine is a key metabolite in the urea and the citrulline-nitric oxide (NO)\textsuperscript{4}cycles (1). As a part of the urea cycle, arginase catalyzes the degradation of l-arginine to urea and ornithine. The generation of urea is an essential pathway for the disposal of nitrogen from the body. By contrast, ornithine, which can be decarboxylated to putrescine by the enzyme ornithine decarboxylase, serves as a precursor for the synthesis of polyamines (2–4). Alternatively, in the citrulline-NO cycle, arginine can also be metabolized by nitric oxide synthase to produce l-citrulline and nitric oxide.

Arginase is the only enzyme of the urea cycle that exists in 2 distinct isoforms (1). The 2 isoenzymes are encoded by different genes and show distinct tissue, cell type, and subcellular patterns of distribution. Arginase I (also designated the “liver-type”) is highly expressed as a cytosolic enzyme in the liver as a component of the urea cycle. It is also expressed in different regions of the brain, but at a lower level. Arginase I has recently been found to be highly induced in many tissues and cell types following exposure to a variety of cytokines and other agents. Arginase II (“kidney-type”) is ubiquitously expressed the eukaryotic translation initiation factor 2; GCN, general control protein; \(\gamma\)-GCS, \(\gamma\)-glutaryl cysteine synthetase; \(\gamma\)-arg-3,4- \(\gamma\)-arginyl-3,4-spermidine; NO, nitric oxide; INOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MAG, myelin-associated glycoprotein; ODC, ornithine decarboxylase; PERK, PKR-like endoplasmic reticulum kinase; PKR, RNA-dependent protein kinase-like endoplasmic reticulum eIF2\(\alpha\) kinase; ROS, reactive oxygen species; uORF, upstream open reading frame.

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\textsuperscript{4} Abbreviations used: ATF4, activating transcription factor 4; BDNF, brain-derived nerve growth factor; BIP, luminal binding protein; cAMP, cyclic adenosine monophosphate; C/EBP, CCAAT/enhancer-binding protein; CNS, central nervous system; dbcAMP, dibutyryl cyclic adenosine monophosphate; DG, dentate gyrus; DRG, dorsal root ganglion; ER, endoplasmic reticulum; eIF2\(\alpha\), a subunit of eIF2\(\alpha\); GCN, general control protein; GCS, \(\gamma\)-glutaryl cysteine synthetase; HSPA5, heat shock protein 90kDa alpha (1B); iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MAG, myelin-associated glycoprotein; ODC, ornithine decarboxylase; PERK, PKR-like endoplasmic reticulum kinase; PKR, RNA-dependent protein kinase-like endoplasmic reticulum eIF2\(\alpha\) kinase; ROS, reactive oxygen species; uORF, upstream open reading frame.

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pressed at a low level within the mitochondria, but can also be induced by cytokines.

**Extracellularly applied arginase is neuroprotective**

Using an in vitro model of neuronal oxidative stress, our laboratory was the first to demonstrate that arginase has neuroprotective properties (5). In this model, high concentrations of glutamate competitively inhibit transport of cystine into the cell at the plasma membrane. Cystine transport is required for synthesis of the cysteine containing antioxidant, glutathione. Agents that inhibit cystine transport thus lead to depletion of glutathione and oxidative stress-induced death. We hypothesized that the reactive oxygen species hydrogen peroxide is a critical mediator of neuronal death induced by glutathione depletion. Hydrogen peroxide is noncharged and diffuses readily through membranes; it can be degraded by catalase to generate peroxide and water. Catalase was therefore added to the extracellular bathing medium of neurons induced to die by depletion of glutathione to reduce ambient and intracellular peroxide concentrations. As expected, catalase had a strong neuroprotective effect. Interestingly, this neuroprotective effect was still present when catalase activity was chemically inhibited. Finally, the neuroprotective activity was found to be due to a contaminant of the catalase preparation, which was identified as arginase I. Recombinant arginase I confirmed that arginase was sufficient to protect the neurons against several apoptosis-inducing stimuli. Furthermore, the protective effect was due to the decrease of arginine, because adding ornithine or urea had no protective effect. Moreover, depletion of asparagine also caused a significantly higher viability of the neurons when they were exposed to oxidative stress. The findings are consistent with a model in which amino acid depletion leads to inhibition of macromolecular synthesis, suppressed translation of “death proteins,” and neuroprotection. Moreover, arginase acted as a nitric-oxide independent inhibitor of neuronal apoptosis because a broad array of nitric oxide synthase inhibitors had neither a pro- nor an antiprotective effect.

**Arginase and the regeneration pathway**

Investigations of arginine and arginase in the central nervous system (CNS) were further stimulated by studies of neural regeneration. It has been known for some time that axons of the adult mammalian CNS fail to regenerate after injury (6–9). However, significant progress has been made in identifying the factors that are responsible for the inhibition of regeneration. The major obstacle appears to be the inhibitory environment of the mature CNS, which is composed of 2 major components: the myelin-associated inhibits and the formation of the glial scar. Despite the inhibitory environment of the mature CNS, several studies indicate that regeneration, albeit limited, is still possible. Progress has been made in identifying the factors that provide a more permissive environment. A breakthrough was the finding that axons show regeneration when they are exposed to several neurotrophic factors [brain-derived nerve growth factor (BDNF) or neurotrophin-3] (10,11) but only if these factors are applied for a certain period of time prior to exposing them to the inhibitory environment, suggesting that the cells must be “primed” to resist the effects of myelin inhibitors. The attempt to characterize the downstream events that are responsible for this effect led to the discovery that the cyclic AMP (cAMP) analogue dibutyryl cAMP (dbcAMP) was able to mimic the neurotrophin effect without requiring a “priming period.” The latter finding led to the proposal that cAMP is a central downstream component of the neurotrophin-induced “regeneration” pathway (12,13). Of note, endogenous levels of cAMP are greatly elevated in young neurons and suddenly decline after birth (12). Moreover, the time course of this change parallels the neurons’ ability to regenerate; embryonic and, to a lesser extent, perinatal neurons will spontaneously regenerate, whereas postnatal neurons will not.

What are the downstream targets of a raised cAMP that mediate these effects? The systematic search of crucial targets that act downstream of the regeneration pathway concentrated on genes that are known to be upregulated in response to cAMP in other cell types. The arginase I gene became the focus of attention because it was known that 1) arginase I is upregulated in response to an elevation of cAMP in macrophages (14) and hepatocytes (15); and 2) polyamines have been implicated in neuronal growth and development (16,17), axonal regeneration after injury (18–20), and in wound healing of the CNS (21). As published in 2002 by Cai et al. (12) provided several lines of evidence that the arginase I gene plays a central role in this context: 1) Arginase I is upregulated and polyamine synthesis increases in neurons in response to either dbcAMP or BDNF; 2) overexpression of arginase I using an adenoviral construct carrying the arginase I cDNA is capable of blocking myelin-associated glycoprotein (MAG)/myelin-induced inhibition of regeneration; 3) the ability of arginase I to block the MAG/myelin induced inhibition of regeneration is abrogated when inhibitors of the polyamine synthesis pathway are added; and 4) “priming” with polyamines is capable of blocking inhibition by MAG and myelin. Finally, the data of this study (12) provided a possible explanation for the phenomenon that dorsal root ganglion (DRG) neurons switch their response to MAG and myelin with age; younger neurons up to a postnatal age of 4 days are promoted by MAG and will extend neurites, whereas their older counterparts are inhibited by MAG and myelin. Interestingly, Cai et al. demonstrated in their study that between the postnatal age of 3 and 5 d, the expression level of arginase I in DRG neurons drops spontaneously and remains at a low level. The authors attributed the downregulation of arginase I to a decrease of cAMP, which is also known to occur during this developmental window.

**Polyamines and neurodegeneration**

Given arginase’s role in the regeneration/protection pathway, what are the effects of these biological effects? Polyamines have been known for some time to be important for neural growth, development, and regeneration. A number of reports indicate that polyamines play a crucial role in the development of the brain (17,22–27). For example, even a short-term inhibition of ornithine decarboxylase (ODC), an enzyme involved in polyamine synthesis, has widespread effects on growth and development of the brain. With respect to cell survival or cell death, it is believed that polyamines act as bivalent regulators of cellular function, promoting cell growth or cell death depending on other environmental signals (28). Packham and Cleveland demonstrated that an increase in ODC activity and polyamines is coupled to apoptosis in fibroblasts (29,30). By contrast, several reports also implicate a protective role for polyamines. In rat cerebellar granule neurons, all 3 polyamines (i.e., putrescine, spermine, and spermidine) prevented cell death induced by high potassium chloride concentrations (31). Another report again found protective effects of exogenous spermine (32). DNA stabilization (33), protection of DNA from oxidative damage (34), and increases in the expression of antiapoptotic genes (35) have also been associated with polyamines in vitro.
stress (34), as well as inhibition of endonucleases (35) have been discussed as possible mechanisms of the protective effects of polyamines. Strong evidence for the protective role of spermine was recently published when Morrison and co-workers found that 1-arginyl-3,4-spermidine (L-arg-3,4) is neuroprotective in several models of neurodegeneration (36). The authors showed that L-arg-3,4 significantly reduced cell death in the hippocampal subregion CA1 when administered prior to, or immediately after, global ischemia in vivo. L-arg-3,4 also reduced cell death in excitotoxicity models as well as in superoxide-mediated cell injury.

**Regulation of arginase in the nervous system**

Arginase I expression is highly regulated in different cell types in response to cytokines, glucocorticoids, catecholamines, and cAMP analogues (1). In astrocytes, arginase I is upregulated in response to either cAMP or interferon-γ but not by their combination (37). Moreover, as mentioned above, in young DRG neurons, arginase I is strongly downregulated when intraneuronal cAMP levels decrease (9,12).

To date, little is known about the detailed brain-specific transcriptional or translational regulation of arginase. Early investigations focused on the characterization of regulatory domains in the arginase promoter region in the liver specific environment. Because the 5′ flanking regions of the rat and human arginase genes are well conserved up to about −100 base pairs, investigations have focused on this region because it is likely that this region contains a requisite transcriptional control element (1). In the original study by Takiguchi and Mori (38), the authors used a promoter/reporter system and subsequent deletion constructs. As expected from the in vivo tissue specificity, the arginase I promoter was transcribed more efficiently in the liver nuclear extracts than in the brain extracts. Analysis of the deletion mutants of the 5′ flanking region revealed a positive regulatory region spanning nucleotides −90 to −51 relative to the transcription start site. Two regulatory elements were identified within this region, one more upstream that is recognized by a factor related to C/EBP (CCAAT/enhancer-binding protein) and one more downstream that is recognized by 2 transcription factors, each related to CCAAT-box binding transcription factor / nuclear factor I and Sp1. For the Sp1 site, it has been demonstrated more recently (1) that it is required for the response to LPS but not to cAMP. Further studies revealed that the 5′ flanking region of the murine arginase I gene also contains elements involved in transcriptional responses to IL-4, cAMP, tumor growth factor β, dexamethasone, and LPS (1). Given the results obtained in DRG neurons, it is likely that at least the cAMP-response element binding proteins and/or C/EBP may also play an important role in neuronal specific arginase gene regulation.

**Structural and histochemical findings**

In light of the new discoveries of the complex gene regulation of arginase I, some recently published reports highlighted age-related changes and regional variations of arginase I activity and arginase I expression in several subregions of the hippocampus (39–41). As expected, the authors found arginase I to be expressed at a very low level in the brain (the whole hippocampus) as compared with the liver. There was no regional variation in arginase I protein expression across the subregions of the hippocampus, although the authors found significant differences in the arginase activity between 3 subregions of the hippocampus, with the highest level of arginase activity in the dentate gyrus (DG) region of the hippocampus as compared with the CA1 and CA2/3 subregions. When comparing young and aged rats, arginase activity was significantly decreased in CA1 and CA2/3, but not in DG in the aged rats. However, the changes in arginase activity were not reflected by corresponding changes in protein expression, and the study failed to detect significant changes in arginase I expression between young and aged groups in the 3 subregions of the hippocampus. These results suggest that factors other than protein levels may regulate arginase I activity in aged rats.

**Changes in arginine mediate changes in gene expression**

Beyond the salubrious effects of arginase mediated by the cAMP/polyamine pathway, increasing attention has been directed to the modulation of gene expression by changes in cellular arginine concentration (42–44). Because arginine depletion is neuroprotective (5), it is interesting to consider how arginine depletion leads to neuroprotection. In general, different mechanisms of gene regulation have been identified, which play a role in gene expression induced by arginine depletion: 1) transcriptional control; 2) a post-transcriptional component involving stabilization of mRNA and 3) a translational control.

How is amino acid starvation recognized by the cell? One important pathway involved in amino acid regulation of gene and protein expression is the “amino acid general control response.” It is assumed that amino acid depletion causes an increase in cytosolic concentration of uncharged tRNAs (i.e., tRNAs that are not coupled with an amino acid). The uncharged tRNAs activate the “general control” kinase GCN2. GCN2 contains a regulatory domain homologous to histidyl-tRNA synthetase, which can bind to various uncharged tRNA and act as a sensor for amino acid depletion. Once activated, GCN2 phosphorylates the α-subunit of the eukaryotic translation initiation factor eIF2 at serine 51.

As an adaptive response, the phosphorylation of eIF2α by GCN2 in response to amino acid depletion is phylogenetically conserved from yeast to humans. Moreover, eIF2α phosphorylation occurs not only in response to amino acid starvation. Several other cellular stress events converge at the phosphorylation of the α-subunit of the translation initiation factor eIF2. Therefore, an “integrated” stress response is mediated by changes in gene expression caused by eIF2α (45). To date, 4 different kinases are known that phosphorylate the α-subunit of the translation initiation factor eIF2α. Each kinase seems to be specific for a stress event: the PERK kinase (PKR-like endoplasmic reticulum kinase), which mediates endoplasmic reticulum stress (ER stress); GCN2, which is activated by amino acid depletion; HRI (heme-regulated eukaryotic initiation factor eIF2α kinase), which couples protein synthesis to heme availability in erythrocytes; and PKR (RNA-dependent protein kinase-like ER eIF2α kinase), which mediates an interferon-induced stress response against viral infections.

One form of the ER stress reaction is the unfolded protein response, which is the result of a disproportion between ER protein load and the ER’s capacity to properly run folding reactions and post-translational modifications of the nascent client proteins (46). The unfolded protein stress is recognized by the protein kinase PERK (47,48). Its N-terminal luminal domain is capable of binding the ER chaperone BiP (luminal binding protein), whereas the C-terminal cytoplasmic domain directly phosphorylates the α-subunit of the translation initiation factor eIF2. Under ER stress conditions, the increased ER protein load leads to an increased BiP binding to the
luminal nascent proteins, thus promoting the dissociation from PERK. Loss of BiP binding is associated with oligomerization and transautophosphorylation of PERK and causes the phosphorylation of eIF2α (49).

What are the consequences of eIF2α phosphorylation? eIF2α phosphorylation causes a repression of cap-dependent protein synthesis (50). This effect is the result of an influence on the translation initiation mechanism. As a part of the ternary complex, eIF2α and GTP mediate the Met-tRNA, binding to the ribosomal 40S subunit. When an AUG start codon is recognized, the bound GTP is hydrolyzed to GDP by eIF2α as the nonactive eIF2/GDP complex is released. For the regeneration of eIF2/GDP, an exchange factor is necessary (eIF2B) to cause GDP release so that a new GTP molecule can bind and eIF2α can be reused. The reuse of eIF2α is inhibited when it is phosphorylated at serine 51; the phosphorylated eIF2α binds to eIF2B unusually tightly, thus causing an inhibition of protein translation.

In a publication from our lab (37), the specific inhibition of protein synthesis as a consequence of arginine depletion and consecutive eIF2α phosphorylation was also shown for cells of the CNS: in astrocytes, arginine depletion leads to eIF2α phosphorylation by GCN2 and an altered translation of the iNOS gene. Astrocytes express the iNOS gene upon cytokine stimulation. Using adenovirus mediated gene transfer, overexpression of arginase I in astrocytes decreased cytokine-induced NO production by decreasing the iNOS protein levels. Additionally, switching the astrocytes to medium containing various concentrations of arginine, the level of iNOS protein induction was dependent on the level of extracellular arginine. Moreover, in this publication (37) we showed that either overexpressing arginase I or treatment with arginine depleted medium caused a phosphorylation of eIF2α. The increase of eIF2α phosphorylation directly correlated with the decrease in iNOS expression. iNOS promoter activity in astrocytes cultured in the absence of arginine did not differ from the activity in the presence of arginine, and varying the concentration of extracellular arginine also did not affect iNOS mRNA levels. Furthermore, we were able to demonstrate that adenoviral infection with a phosphomimetic mutant of eIF2α significantly decreased expression of iNOS, whereas overexpression of a form of eIF2α that cannot be phosphorylated resulted in increased expression of iNOS, suggesting that the eIF2α phosphorylation inhibits iNOS expression at the translational level.

Even though the eIF2α phosphorylation leads to a general inhibition of cap-dependent translation machinery, the translation of some specific mRNAs is upregulated in a paradoxical manner (45,51). This intriguing pathway of activation of gene expression was first elucidated in yeast. Under conditions of amino acid starvation and consequent eIF2α phosphorylation, the transcription factor GCN4 is translated (52). The 5’ UTR of the GCN4 mRNA contains four 5’ upstream open reading frames (uORFs). In normal physiological conditions, ribosomes synthesize short peptides encoded by these uORFs. The ribosomes then slow down and dissociate from the mRNA before reaching the actual GCN4 start codon. In the case where eIF2α/GTP is limiting, no new initiations are possible and the ribosomes continue scanning the mRNA, thus reaching the GCN4 start codon. In this way, GCN4 is paradoxically synthesized.

Higher eukaryotes use a similar mechanism for the translational upregulation of mRNA under the conditions of cellular stress. Similar to GCN4 in yeast, the ATF4 (activating transcription factor 4) coding mRNA contains multiple 5’ upstream open reading frames (uORFs), which cause an increase in ATF4 expression under the conditions of eIF2α phosphorylation (45,50). Target genes of the transcription factor ATF4 may be part of an integrated stress response of the higher eukaryotic cell. New experimental data indicate that these ATF4 target genes are not only involved in amino acid metabolism and transport but also cell redox control (see below).

The intimate link between the cell’s redox control and eIF2α phosphorylation was demonstrated in a neuronal cell line when Tan and co-workers used a genetic screen to identify genes whose expression is involved in oxidative-stress induced cell death and the regulation of intracellular glutathione (53). They found that downregulation or phosphorylation of eIF2α protects the hippocampal cell line HT22 from oxidative-stress induced cell death by inhibiting glutathione depletion and the increase in both reactive oxygen species (ROS) and intracellular calcium that are normally seen in cells exposed to oxidative stress. The authors provided additional evidence that the inactivation of eIF2α upregulates the expression of the γ-glutamylcysteine synthetase (γGCS), the rate-limiting enzyme for glutathione synthesis by a translational mechanism, resulting in significantly higher levels of glutathione. The observation that eIF2α expression as well as its activity can directly modulate γGCS proves again the close relationship between amino acid depletion and neuroprotection against oxidative stress.

Harding and co-workers have provided elegant logic for coupling the activating antioxidant and amino acid metabolism pathways during ER stress by phospho-eIF2α (45,51). Protein secretion can be seen as an irreversible loss of amino acids, but also affects the net loss of reducing equivalents from the cell. The oxidative folding of proteins is accompanied by a transfer of electrons from the nascent protein to the FAD-dependent oxidoreductase Ero1p. Ero1p, in turn, is oxidized by molecular oxygen, which acts as the terminal electron acceptor. Thus, electrons removed from nascent proteins are lost to oxygen. As is the case of amino acid supply, the greater the secretory burden of the cell, the greater the anticipated loss of reducing equivalents. Therefore, the activation of genes whose products are involved in the redox status control and amino acid metabolism by ATF4 provides an effective means of stress response. This hypothesis is supported by experimental findings in PERK knockout cells. Harding and co-workers found that in these cells induction of ER stress causes a rapid accumulation of reactive oxygen species, possibly due to the impaired ability to activate ATF4 and its downstream antioxidant target genes. Similarly, cells lacking ATF4 are less resistant to ER stress, ROS, and amino acid starvation. ATF4 knockout and PERK knockout cells require supplementation with both extra amino acids and cysteine, the former presumably to replenish amino acids lost to secretion and the latter likely to stimulate the synthesis of glutathione, of which cysteine is a precursor.

Despite this compelling transcriptional pathway of protection, many different mechanisms could contribute to the protective effects of eIF2α phosphorylation that accompany amino acid starvation (53–55). First, as it has been demonstrated in a host of publications, the shutdown of protein synthesis has neuroprotective effects, especially because translation inhibitors like cyclohexamide are clearly protective. Moreover, one should keep in mind that apoptosis itself is a process that requires new protein synthesis. Second, the upregulation of protective genes like ATF4 or other transcription factors may play an important role as well. However, it still needs to be clarified whether the protection by eIF2α phosphorylation is due to decreased pro-apoptotic effector gene expression or the upregulation of putative pro-survival factors,
such as ATF4, or both. Third, as suggested by Tan and co-workers, the direct regulation of glutathione synthesis by translational regulation of its key enzyme may play an important role. Interestingly, they found that their selected HT22 cells with a downregulated eIF2α do not display a reduced protein synthesis compared to control cells. This latter finding suggests the possibility that the amount of eIF2α phosphorylation after all determines which effect predominates in this complex pattern of altered gene expression and protein synthesis. Additionally, one should also keep in mind that the ER stress response itself is a complicated balance between survival and apoptosis; while translational attenuation and new synthesis of stress-induced proteins such as chaperones and components of the ER associated degradation aim at remodeling and restoring ER function, a persistence of severe ER stress can lead to an activation of apoptosis signaling pathways, including induction of C/EBP homologous protein (46, 56). However, the pathways that shift this balance either towards protection/survival or towards apoptosis still need to be characterized in detail.

Clinical findings

Independent of the recent findings of the effects of arginine and arginase in preclinical models, we are only beginning to understand amino acid metabolism and its role in neurodegenerative diseases. Indeed, there are few clinical studies that have scrutinized the connection with arginine/amino acid metabolism and neurodegeneration. For example, Kuper et al. found no differences in the levels of l-arginine in patients with Parkinson’s disease, multiple system atrophy, and Alzheimer’s disease compared to healthy subjects (57). Reilmann and co-workers also failed to find a significant difference in the arginine levels in the plasma of patients with Huntington’s disease (58), whereas plasma alanine and isoleucine levels were decreased. However, local changes in cellular amino acid levels are not well understood and are a topic for further study. The study of signaling pathways that are activated downstream of arginine deprivation in tissue culture and animal models has identified useful markers of arginine dysmetabolism (e.g., eIF2α, ATF4) and may be useful in the study of human systemic and tissue.

LITERATURE CITED


