Review

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Autophagy in Post-Ischemic Brain Neurodegeneration: Friend, Foe, or Both?

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Ischemic stroke in humans imposes a substantial burden on health care organizations and personal care providers due to the absence of effective therapy that can prevent or halt the development of post-ischemic dementia. As a result, many patients become bedridden and require 24-hour care. Thus, the progressive and irreversible neurodegeneration following ischemia leads to severe long-term outcomes. For this reason, there is great emphasis on better understanding the neuropathogenesis of the post-ischemic brain. Experimental and clinical studies have shown that ischemia leads to progressive neurodegeneration of the brain, which results in impaired cognitive functions and the development of full-blown Alzheimer's disease-type dementia. Elevated levels of tau protein and amyloid have been found in post-ischemic brains, which transform into amyloid plaques and neurofibrillary tangles, respectively. Furthermore, other pathological phenomena have been identified, such as calcium accumulation, decreased acetylcholine levels, excitotoxicity, blood-brain barrier permeability and inflammation. These processes lead to massive neuronal cell death and brain atrophy. Moreover, it has been noted that post-ischemic neurodegenerative processes continue well beyond the acute stage and are irreversible. Previous studies indicate that protein misfolding, aggregation, and damage to multiple organelles are the main pathological phenomena in neurons after ischemia. Autophagy is a key process for the large-scale degradation of protein aggregates and damaged organelles, and existing data indicate that autophagy plays a dual role after ischemia (pro-survival and pro-death). In this review, we focus on the importance of autophagy and mitophagy gene expression at the onset of clinical symptoms (acute phase), during disease progression, and at lesion maturation (chronic phase) after cerebral ischemia. We present the current knowledge on alterations in autophagy genes and the function of autophagy in post-ischemic cerebral neurodegeneration.

Keywords: brain ischemia; neurons; endothelial cells; microglia; astrocytes; amyloid; tau protein; neuroinflammation; genes

Introduction

Cerebral ischemia in humans, as well as in experimental models, causes severe, life-threatening post-ischemic brain neurodegeneration. Currently, it is estimated that cerebral ischemia affects approximately 17 million individuals per year, with mortality of around 5.5 million, making it the second cause of death in the globe [1–3]. People who survive cerebral ischemia eventually suffer from cognitive impairment, which has a significant impact on their quality of life [2,4,5]. Evidence shows that the incidence of cognitive impairment in patients following cerebral ischemia is 5–8 times higher than in healthy individuals [2]. Forty percent of ischemia survivors develop mild cognitive impairment, which eventually progresses to full-blown dementia [2,5,6]. The chance of developing dementia in patients who have experienced brain ischemia is twice as high as in those who have not [6]. It has also been shown that ischemic brain damage can trigger the onset of dementia within about ten years [3,7]. It is projected that after the first cerebral ischemia, dementia develops in 8–13% of patients, should a second ischemia episode occur, over 40% of these patients develop dementia, and 25-years post-ischemia, this rate is approximately 48% [8]. Following brain ischemia, neurodegeneration is estimated to be the second most frequent cause of dementia worldwide after Alzheimer's disease, and the third leading cause of disability [5,9]. In fact, ischemic brain injury in humans poses a huge burden on the health care system and caregivers due to the absence of therapeutic approaches that could prevent or slow the progress of the subsequent neurodegeneration and the advancement to dementia [4,5,10].

Notably, only several years after the onset of brain ischemia and the progression of neurodegenerative changes do patients observe disturbing hallmarks such as memory loss and dementia [9]. These symptoms appear gradually with the progressive loss of neuronal cells in the hippocampus accountable for memory, learning and thinking [11,12]. As neurodegeneration progresses following ischemia, neurons in the thalamus, basal ganglia, and brain cortex also die [12]. These processes ultimately lead to mass neuronal cell death and brain atrophy [11] leading to patients requir-

ing 24-hour care. Moreover, it has been noted that neurodegenerative processes following ischemia persist in a chronic form long after the initial acute phase and are irreversible [11,13–15]. As a consequence, progressive and irreversible neurodegeneration of the brain caused by ischemia is fatal in the long term [11,13–15]. For this reason, there has been a recent emphasis on better understanding the neuropathogenesis of the brain following ischemia.

The progress of post-ischemic neurodegeneration is influenced by a cascade of damaging events, including neuronal cell loss in selectively vulnerable and resistant regions, free radicals, excitotoxicity, necrosis, apoptosis, persistent opening of the blood-brain barrier (BBB), chronic inflammation, protein folding, autophagy and mitophagy [16–19]. These can initiate cerebral injury and result in a positive feedback loop that, eventually, triggers intense injury to neurons, neuroglial and endothelial cells and their interconnections. Recent investigations have revealed amyloid plaques and neurofibrillary tangles following brain ischemia, mainly in cerebral areas responsible for learning and memory as key neuropathological changes [12,17,18, 20–24].

Amyloid deposition following brain ischemia has also been found in the walls of cerebral blood vessels. This phenomenon is called cerebral amyloid angiopathy (CAA) [10,11,25]. CAA is associated with vascular dysfunction, causing vasoconstriction, and this promotes recurrent ischemia, persistent blood-brain barrier (BBB) leakage, and chronic neuroinflammation, which are key elements in the progression towards neurodegeneration [3,26,27].

Furthermore, amyloid accumulation exacerbates chronic neuroinflammation through continuous activation of glial cells, which causes secondary neuronal damage and death and further accelerates the progression of post-ischemic brain neurodegeneration [3,27,28]. Amyloid-induced neuroinflammation affects its generation and aggregation, contributing to progressive post-ischemic brain neurodegeneration through a vicious cycle [3,27]. Neuroinflammation further damages the blood-brain barrier, facilitating the migration of immune cells from the blood, such as platelets, lymphocytes, and neutrophils, into the ischemic brain parenchyma [26,29,30]. For example, translocation of circulating platelets and β-amyloid peptides through the damaged BBB, on the one hand, promotes vasoconstriction and recurrent ischemia; on the other hand, enhances amyloid accumulation in the brain parenchyma, which plays a key role in the neuropathogenesis of dementia after ischemia [26,31]. Moreover, neuroinflammation causes the loss of ischemic neurons which survived the initial ischemic episode [19]. Prolonged neuroinflammation causes further damage to neurons by accelerating the development and deposition of amyloid plaques [3,27,32–34]. Amyloid generation causes hyperphosphorylation and aggregation of tau protein in the form of neurofibrillary tangles [20–23] and loss of neuronal and synaptic integrity [26,35]. In addition, oxidative stress promotes the accumulation of amyloid and hyperphosphorylated tau protein, which in turn increases oxidative damage [36]. The soluble form of tau protein acts as a transmission agent, spreading the pathology between different cells and areas of the brain [37].

Moreover, it has been shown that following cerebral ischemic injury with survival up to two years, and the coexistence of behavioral problems and progressive dementia, alterations in the expression of genes for amyloid precursor protein and its metabolizing enzymes, tau protein, apolipoproteins, receptor for advanced glycation end products (RAGE), low-density lipoprotein receptor-related protein-1 (LRP1) and alpha-synuclein occur [13–15,19,31, 38,39]. Gene expression in the temporal cortical neurons and CA1 region suggests amyloidogenic metabolism of amyloid precursor protein following ischemia [19,40]. However, tau protein expression was transient throughout the observation period [41]. Gene expression in CA3 neurons over a period of 2–30 days also indicates amyloidogenic metabolism of amyloid precursor protein after ischemia [42]. However, after 1–2 years of ischemia, the data indicate non-amyloidogenic processing of amyloid precursor protein [19]. Tau protein gene expression systematically increased, with a peak observed one year after ischemia [42]. An increase in alpha-synuclein gene expression in the CA3 region was also observed one year after ischemia [13]. Increased LPR1 gene expression in this region reached peak values 1.5 years after the ischemic episode, and there was no increase in RAGE expression throughout the observation period (2–30 days, 1–2 years) [31]. Apolipoprotein A1 gene expression in the CA3 region was variable throughout the observation period. However, apolipoproteins E and J genes reached their maximum values 1–2 years after ischemia [14]. In the frontal cortex, expression of genes metabolizing amyloid precursor protein into the nonamyloidogenic pathway was observed after ischemia [39]. Furthermore, results showed increased expression of tau protein and α-synuclein genes 12–18 months after ischemia [39]. These observations suggest that following brain ischemia, neurodegeneration is triggered by a series of genetic alterations that induce neuronal loss through tau protein, amyloid-, and alpha-synuclein-dependent mechanism [12,24,31,36,40–42]. Ultimately, these result in acetylcholine deficiency [43], chronic neuroinflammation [3,10,27,44], and brain atrophy [3,7,8], culminating in the development of Alzheimer's disease-like dementia in animals and humans [5,6,10,45–47].

Recently, studies have progressively revealed the significant role of autophagy in the pathological processes of post-ischemic cerebral neurodegeneration [2,8,48,49]. Autophagy selectively targets dysfunctional organelles and toxic proteins, and dysregulation in this mechanism may lead to disorder progression. Furthermore, existing data indicate a dual role of autophagy after ischemia (pro-survival

and pro-death). In this article, we review the history of autophagy from the perspective of elucidating and potentially reversing post-ischemic alterations in individual cerebral cells and in the brain as a whole. Research indicates that misfolding and aggregation of amyloid and tau protein are significant problems in the occurrence of neurodegeneration after brain ischemia. In neurodegenerative disorders, such as brain ischemia, autophagy is disrupted, for example, as a consequence of the extreme buildup of proteins relative to Alzheimer's disease and their structural alterations. It is also known that autophagy activity increases after excitatory neuronal damage [50] and after exposure to prooxidant factors [51], leading to neuronal death due to autophagy, in addition to neuronal cell death due to apoptosis [8,11]. Data also indicate that should ischemia be severe and followed by recirculation, it results in autophagic neuronal death. In this review, we focus on the importance of autophagy and mitophagy gene expression and their role at the onset of clinical symptoms (acute phase), during disease progression and ultimately lesion maturation (chronic phase) following cerebral ischemia.

Autophagy in the Post-Ischemic Brain

Autophagy, a cellular mechanism that maintains stability and supervises the properties of proteins in the cytoplasm, has been shown to be faulty and/or deficient in the post-ischemic brain [2,3,27]. It is an intracellular disintegration mechanism essential to maintaining proteostasis by eliminating non-native proteins. Mitophagy, a specialized form of autophagy, targets injured mitochondria, facilitating their removal and preventing cellular dysfunction. Autophagy is the major cellular pathway responsible for cytoplasmic purification, mainly from aberrantly conformed or accumulated proteins and run-down organelles resulting from aging-related disintegration and neurodegenerative diseases [52]. This process ensures that proteins with abnormal primary, secondary, or tertiary configurations, as well as aggregated materials such as amyloid and tau protein are eliminated from the cell or accurately reassembled [8,19,52]. Dysfunction of autophagy, characterized by impaired clearance and biogenesis, increases accumulation of tau protein and amyloid in neurodegenerative diseases [8,19,52]. In addition, raised levels of tau protein and amyloid have been documented to worsen autophagy and mitochondrial activity, causing disorder progression [8,53]. These processes are related to the formation and collection of folded proteins and autophagy-dependent neuronal cell loss in the brain [8].

Autophagy Genes in the Post-Ischemic Brain

Autophagy (*BECN1*) gene expression in the CA1 region of the hippocampus 2–30 days after ischemia has been shown to fluctuate around control values. Mitophagy (*BNIP3*) gene expression, on the other hand, was increased in the CA1 area 2 days post-ischemia and fluctuated around control values after 7–30 days (Table 1, Ref. [15,38,54–56]) [54]. *BECN1* expression in the CA3 area of the hippocampus also fluctuated around control values at 2 days, 0.5 year, and 1.5 years after ischemia. Seven days following ischemia, *BECN1* expression was found to be below control values, while 30 days, 1 year and 2 years later it was found above control values. *BNIP3* expression in the CA3 region of the hippocampus at 2 and 30 days and 0.5 and 1.5 years following ischemia varied around control values. Seven days following ischemia, *BNIP3* expression was lower than control values, whereas after one and two years it was higher than control values (Table 1) [38,55]. *BECN1* expression was increased in the temporal cortex at 2 days following ischemia and fluctuated around control values at 7–30 days. *BNIP3* expression in the temporal cortex following ischemia was below control values after 2 days, increased after 7 days and oscillated around control values after 30 days (Table 1) [56]. Another study reported that *BECN1* expression in the frontal cortex following ischemia increased after 2 days and at 0.5–1 and 2 years, and after 7–30 days and 1.5 years it fluctuated around control values. *BNIP3* expression in the frontal cortex remained around control values 2–30 days and 1.5 years after ischemia, and increased after 0.5–1 and 2 years (Table 1) [15].

Autophagy in Neurons in the Post-Ischemic Brain

The presence of membrane-bound vacuoles containing intracellular cytoplasmic components in neuronal cells in the CA1 area of the hippocampus post-ischemia was first reported in 1995 [57]. It was subsequently revealed that cortical neurons also possess cytoplasmic vacuoles associated with post-ischemic changes [58–60]. Post-mortem examination of the human brain following ischemia also revealed an increased presence of autophagic vesicles in cortical neurons [61]. These studies demonstrate that alterations in autophagy occur in human and animal brain parenchyma after ischemic injury, suggesting that modulation of autophagy following an ischemic episode may have clinical relevance.

Under normal conditions, autophagy in neurons remains at a relatively low level. Some studies have shown that inhibition of autophagy in neurons has a positive effect on the response to ischemic brain injury [62–64]. This was confirmed by another study where a gene related to autophagy was selectively deleted in neurons, leading to the prevention of autophagy induced by hypoxia and ischemia and limitation of neuronal death [65]. Furthermore, intracerebroventricular injection of an IL-17A-neutralizing monoclonal antibody revised functional outcome in mice after cerebral ischemia by inhibiting neuronal autophagy [66]. While several investigations have confirmed the harmful effects of neuronal autophagy in post-ischemic brain damage

Table 1. Changes in the expression of autophagy, mitophagy and apoptosis genes in the hippocampus, temporal and frontal cortex during different periods of brain neurodegeneration in female rats after ischemia [15,38,54–56].

Survival Genes	2 days	7 days	30 days	0.5 year	1 year	1.5 year	2 years
			Hippocampal CA1 area				
BECN1	↔	↔	↔	N.D.	N.D.	N.D.	N.D.
BNIP3	↑	↔	↔	N.D.	N.D.	N.D.	N.D.
CASP3	↑↑↑	↔	↔	N.D.	N.D.	N.D.	N.D.
			Hippocampal CA3 area				
BECN1	↔	↓	↑	↔	↑↑↑	↔	↑↑
BNIP3	↔	↓	↔	↔	↑↑↑	↔	↑
CASP3	↔	↔	↔	↑↑	↑↑↑	↔	↑↑
			Temporal cortex				
BECN1	↑	↔	↔	N.D.	N.D.	N.D.	N.D.
BNIP3	↓↓	↑↑↑	↔	N.D.	N.D.	N.D.	N.D.
CASP3	↔	↔	↔	N.D.	N.D.	N.D.	N.D.
			Frontal cortex				
BECN1	↑↑↑	↔	↔	↑	↑↑↑	↔	↑
BNIP3	↔	↔	↔	↑	↑↑↑	↔	↑
CASP3	↑↑	↔	↔	↑	↑↑↑	↔	↑

Expression: ↑, 0.5-fold increase; ↑↑, 1-fold increase; ↑↑↑, 2-fold increase; ↓, –0.5-fold decrease; ↓↓, –1-fold decrease; ↔, fluctuation around control values. Genes: *BECN1*-autophagy; *BINP3*-mitophagy; *CASP3*-apoptosis; N.D., No data.

[67–72], others have revealed that inhibition of autophagy increased ischemia-stimulated cytochrome c release and enhanced post-ischemic neuronal death [59,73].

Moreover, therapy with rapamycin, an mTOR inhibitor, enhanced autophagy and decreased neuronal cell loss and cerebral damage in hypoxic-ischemic injury [74, 75]. These data were confirmed by studies on models of focal cerebral ischemia [76–79]. Sphingosine kinase 2 protects neuronal cells from ischemic damage by interacting with Bcl-2 via its BH3 domain, thereby dissociating it from the beclin 1 complex and activating autophagy [80]. The neuroprotective role of neuronal autophagy by reducing neuronal apoptosis and improving functional outcomes after ischemia has also been confirmed in other studies [81–83]. Autophagy is therefore considered a double-edged sword in neuronal cells after cerebral ischemia [8,84].

Autophagy in Endothelial Cells and Blood-Brain Barrier in the Post-Ischemic Brain

The BBB, formed by endothelial cells, pericytes, perivascular astrocytes, and neurons controls the inflow and outflow of substances, which helps maintain normal brain activity. Among them, brain capillary endothelial cells, tied by tight junctions, play an important role in maintaining the integrity of the BBB [85,86]. Acute and chronic disruption of the blood-brain barrier integrity has been shown to be a significant pathological feature after cerebral ischemia [26], with subsequent development of cerebral edema and exacerbation of neuronal damage [87,88]. The positive effect of autophagy on blood-brain barrier after local cerebral ischemia has been demonstrated [89]. It was found that increasing autophagy by rapamycin attenuated the apoptosis of brain microvascular endothelial cells in an *in vitro* ischemic model [90]. Furthermore, rapamycin- and lithium carbonate-induced autophagy promoted the normal distribution of ZO-1, a tight junction protein, on cell membranes, indicating a beneficial effect of brain capillary endothelial cell autophagy on the integrity of the BBB [91]. This was also confirmed in a study where rapamycin treatment increased the viability of human umbilical vein endothelial cells in an *in vitro* model of ischemia, meanwhile reducing beclin-1 expression by siRNA impaired autophagy and reduced endothelial cell viability [90]. Furthermore, Netrin-1, an axon guidance molecule, has been shown to increase autophagy activity via the UNC5H2 receptor-dependent PI3K pathway and reduce blood-brain barrier dysfunction after ischemia by improving tight junction activity and endothelial cells survival [92]. Other investigations have also shown that endothelial autophagy may contribute to the protection of the BBB post-ischemia [93–95].

On the other hand, studies have also indicated a detrimental role of endothelial autophagy in BBB function post-ischemia. Following local brain ischemic injury, increased autophagic cell death of capillary endothelial cells and neurons and blood-brain barrier disruption were noted in NF-κB p50 knockout mice, which could be reversed by inhibiting autophagy [96]. Increased autophagy in hyperglycemic rats was noted to contribute to autophagy-mediated ZO-1 degradation and was at least partially responsible for blood-brain barrier permeability after local brain ischemia [97]. Similar changes were observed in an *in vitro* model

of ischemia in mouse cerebral microvascular endothelial cells where the inhibition of autophagy or autophagosome-lysosome fusion blocked claudin-5 degradation, which successively attenuated the disruption of the endothelial cells [98]. Collectively, these results demonstrated that endothelial autophagy plays a dual, context-dependent role at the blood-brain barrier after brain ischemia [99]. Intensified autophagy-like cell loss was revealed in cerebral microvascular endothelial cells of p50 knockout mice following cerebral ischemic injury [96]. Furthermore, rapamycin has been shown to increase autophagy in ischemic cerebral microvascular endothelial cells, while inhibition of autophagy by 3-methyladenine increases the apoptosis of these cells [100]. This indicates a protective effect of autophagy on cerebral microvascular endothelium and BBB integrity following cerebral ischemia. Another study confirmed that autophagy protects capillary endothelial cells during ischemia, while inhibition of autophagy with chloroquine intensifies the permeability of the BBB and exacerbates brain edema [89].

Cerebral ischemia, which induces oxidative stress, stimulates autophagy in cerebral endothelial cells, thereby affecting the integrity of the blood-brain barrier [94,95,101,102]. Increased permeability of the BBB post-ischemia is strongly related to the loss of tight junctions and damage to the basement membrane [103]. In response to the generation of reactive oxygen species, histone deacetylase inhibitors promote autophagy and eliminate injured organelles to keep the integrity of the blood-brain barrier [93,104–106]. Abnormal autophagy causes degradation of endothelial tight junctions, leading to loss of BBB integrity. In principle, autophagy is a key process for maintaining the integrity of the blood-brain barrier; however, impaired autophagy results in opening of the BBB and exacerbation of post-ischemic cerebral damage. These observations show that ischemia-stimulated autophagy in the cerebral microvasculature endothelial cells may influence post-ischemia outcomes.

Autophagy and neuroinflammation in the Post-Ischemic Brain

Microglia

Microglial cells have been shown to activate the autophagy mechanism in hypoperfusion and local cerebral ischemia [107,108]. In mice exposed to persistent focal brain ischemia, autophagy activation was investigated in the microglia in the brain cortex. Western blot analysis revealed an increase in the autophagy marker LC3-II in these cells post-ischemia. Furthermore, flow cytometry showed that the ratio of LC3-II to CD11b-positive microglia increased after the ischemic episode. Also, focal cerebral ischemia-induced autophagy was demonstrated in microglia by using an antibody against the marker CD11b to label microglia and an antibody against the marker LC3-II to label autophagosomes. CD11b was shown to colocalize with LC3-II in microglia, ultimately indicating the activation of autophagy in microglia after focal brain ischemia [108]. Data indicate that the initiation of microglial autophagy is connected with the severity of ischemia-induced neurons damage [109]. Moreover, it has been shown that the intensity of microglial autophagy activation is reliant on the time of ischemia and recirculation [110].

Recently, there is growing evidence that autophagy, particularly microglial autophagy, plays a significant role in the inflammatory reaction following cerebral ischemia. Furthermore, it has been revealed that excessive autophagy induced by cathepsin B in microglia plays an important role in the neurotoxic polarization of microglia/macrophages after hypoxic-ischemic damage [109]. Using a mouse model of permanent focal brain ischemia, autophagy was induced in microglial cells, accompanied by an enhanced neuroinflammatory response [77,108]. Treatment with 3-methyladenine reduced microglial autophagy and neuroinflammatory response, which consequently reduced infarct volume and edema development and improved functional recovery [77]. Current research shows that baicalein ameliorates neurobehavioral deficits and reduces infarct size by stopping M1 transformation of microglial cells/macrophages and inflammation [105]. In this case, baicalein was shown to inhibit autophagy via the PI3K/Akt/mTOR signaling pathway [105]. Additional investigation showed that local cerebral ischemia activated autophagy signaling in the penumbra and reduced CX3CL1 expression on autophagic neuronal cells, ultimately aggravating microglial inflammatory injury [111]. The autophagy inhibitor 3-methyladenine has been presented to reverse microglia inflammation caused by cerebral ischemia. During treatment with the autophagy-inducing peptide Tat-Beclin 1, microglial inflammation and brain edema were exacerbated [111]. Numerous latest studies have also reported that inhibition of microglial autophagy may be a potential curative approach for cerebral ischemia [112–114]. Other studies showed that the microglial protein PGC-1α protects neurological changes after ischemia by suppressing neuroinflammation due to the activation of autophagy [115] which was induced in the early phase after ischemia *in vitro* (12–48 hours), and inhibited in the latter phase (72 hours) [110]. Other reports have also demonstrated a neuroprotective role of microglial autophagy following ischemia [116,117].

Astrocytes

Additionally, in the post-ischemic brain, accumulation of vacuoles in astrocytes resembling autophagy has been observed [118]. A study reported that autophagy was triggered in post-ischemic astrocytes, resulting in their survival being limited. However, inhibition of autophagy with 3-methyladenine significantly reduced astrocyte loss [119]. In another study, the autophagy inhibitor 3-methyladenine

augmented astrocyte mortality after hypoxia [120]. Recently, a bidirectional autophagy activity in astrocytes following ischemic brain damage have been reported [121].

Astrocytes constitute a major cell population in the brain and play a vital role in maintaining normal brain function, by maintaining brain structure, neuronal metabolism, the extracellular environment, and neurotransmitter synthesis [104,122,123]. It is known that after cerebral ischemia, astrocytes manifest both harmful and beneficial roles. The neuroinflammatory reaction of astrocytes exacerbates damage after cerebral ischemia, while the neuroglial scar hinders axonal regeneration in the late-stage post-ischemia [124–126]. Astrocytes also provide benefits in angiogenesis, axonal remodeling, and synaptogenesis [127–129]. Autophagy in astrocytes is caused by brain ischemic injury, as shown by increased expression of autophagy- and autolysosome-connected proteins, such as microtubule-associated protein 1 light chain 3, lysosome-associated membrane protein 2, beclin 1, and lysosomal cathepsin B [90]. Moreover, inhibition of autophagy by 3-methyladenine reduced astrocyte death and increased the number of GFAP-positive cells in the cortex 12 h after permanent local cerebral ischemia [119]. Pharmacological or genetic inhibition of autophagy in ischemia-activated astrocytes blocked caspase-3 activation in astrocytes and subsequently reduced their mortality and infarct volume in rats [130]. Another study found that receptor-interacting protein 1 kinase contributes to the loss of neurons and astrocytes after focal brain ischemia by activating the autophagic-lysosomal pathway, while pharmacological or genetic inhibition of the kinase reduced astrocyte death and infarct volume and positively influenced neurological recovery [131]. Moreover, circular RNA HECTD1 was shown to promote the detrimental effects of astrocyte autophagy after local cerebral ischemia in mice. However, reducing the expression of this RNA impaired autophagy and astrocyte activity, which reduced the infarct area and reversed the neuronal deficits [132,133]. Notably, several other studies have reported the opposite, pointing to a protective role of astrocyte autophagy [134–136]. Activation of astrocytic G protein-coupled receptor 30 was shown to restore autophagy in glutamate-induced astrocytes, which resulted in inhibition of reactive astrogliosis and reduced pro-inflammatory cytokine release, ultimately limiting neurological deficits and infarct volume after local cerebral ischemia [137]. Interestingly, investigations have shown that the enhancement of astrocyte autophagy limited neuronal apoptosis in both an *in vivo* and in an *in vitro* ischemia study. Furthermore, induction of autophagy in astrocytes improved neurological recovery, indicating that astrocyte autophagy may contribute to endogenous neuroprotection and neurological recovery post-ischemia [78].

Acute neuroinflammation may promote healing of the central nervous system, while chronic neuroinflammation can lead to abnormal remodeling, loss of function, and neurological changes. Cytokines, along with chemokines, nitric oxide (NO) and reactive oxygen species (ROS), have been shown to be produced in large amounts during neuroinflammation [138]. Cytokines are released mostly by resident neuroglial cells such as microglia [139]. Continuous cytokine production and release leads to neurons injury through excitotoxicity, necrosis and apoptosis. In the presence of proinflammatory cytokines, the blood-brain barrier loses its integrity and the infiltration of immune cells into the brain tissue increases, leading to deterioration of its condition. Autophagy modulators, such as histone deacetylase inhibitors, induce autophagy-related genes, which may alleviate inflammation and improve neuronal survival during the neurodegenerative process, including those following cerebral ischemia [140].

Autophagy, Amyloid, and Tau Protein in the Post-Ischemic Brain

Although the exact mechanisms of interaction between autophagy, amyloid, and tau protein remain unclear, new research have revealed their interconnectedness [141]. In animals with Alzheimer's disease, a mutation in the gene responsible for the production of beclin-1 resulted in the stimulation of autophagy, a reduction in amyloid levels and improved cognitive function [142,143]. Another example shows that increasing the anti-aging hormone Klotho in the brains of APP/PS1 mice increased amyloid removal via autophagy and improved cognitive function [144]. These benefits are associated with the initiation of autophagy, which limits amyloid production and enhances its elimination [141]. It should be emphasized that the C-terminal of amyloid precursor protein (APP) is also associated with autophagy [141]; the adaptor protein 2 forms a complex with LC3, which facilitates the direct transport of the C-terminal of APP to autophagosomes, thereby reducing amyloid formation. Elimination of the C-terminal of APP by adaptor protein 2 binding is further facilitated by phosphatidylinositol binding clathrin assembly protein, which is involved in clathrin dependent endocytosis [145]. For example, phosphatidylinositol-binding clathrin assembly protein levels are reduced in the brains of patients with Alzheimer's disease, and this is associated with the production of amyloid and the accumulation of phosphorylated tau protein [145,146]. In contrast, beclin-1 knockout mice showed intracellular and extracellular amyloid accumulation compared to control mice [147].

The influence of autophagy on tau protein level was demonstrated by the buildup of phosphorylated tau protein and the development of brain neurodegeneration in mice deficient in autophagy-related gene 7 [148]. Both the ubiquitin-proteasome system and autophagy, which are biochemically linked, are involved in the removal of tau protein [149]. Genetic inactivation of p62 leads to alterations in the structure and solubility of tau protein, which results in impaired clearance [150]. In contrast, animals with

a genetic modification that permanently activated mTOR showed increased levels of tau protein and its phosphorylation [151]. Using mTOR antagonists that activated autophagy, a reduction in tau protein phosphorylation and its insoluble form was demonstrated in neurons derived from patient pluripotent stem cells expressing tau protein mutation [152]. Tea extract increased the expression of the autophagy receptor protein NDP52, which led to the clearance of phosphorylated tau protein from neuronal culture [153]. Autophagy dysfunction leads to the buildup of tau protein and amyloid in the brain, which impedes autophagy and initiates a harmful loop that ultimately leads to neurodegeneration.

In response to these conditions, there is an increase in the production or accumulation of proteins derived from neuronal cells. As these changes progress, protein aggregation becomes apparent because of protein misfolding. Genetic traits, neuropathological conditions, and aging are factors that can ease the development of protein aggregates outside or within neuronal cells. For example, amyloid, tau protein, and alpha-synuclein most often aggregate in the brain parenchyma [11,13,17,20,23,154]. The inherence of these proteins influences the metabolic state, intercellular contact, and paracrine action of host neuronal cells. As protein aggregates accumulate after cerebral ischemia, a neuroinflammatory response, oxidative stress, and consequently, neuronal cells damage or death occur [3,27,36]. To remove neurotoxins from the brain, endogenous processes are activated, such as the glymphatic system, the BBB, and autophagy. The BBB and the glymphatic system are the main mechanisms for removing protein aggregates from the extracellular matrix of neurons, interstitial fluid, and cerebrospinal fluid. Receptors such as p-glycoprotein and low-density lipoprotein receptor-related protein 1 play a significant role in the removal of protein aggregates [31].

Two main systems operate within neurons: ubiquitination-proteasome and autophagy, which help host cells remove protein aggregates. The ubiquitination-proteasome system targets specific proteins for degradation by ubiquitin molecules within proteasomes. In the process of autophagy, target molecules are sequestered by autophagosomes and degraded by the lysosome [155,156]. These processes are therefore vital for maintaining neuronal physiology and preventing or ameliorating neurodegenerative changes. Phagocytosis by microglia and astrocytes may help remove neurotoxins from the central nervous system [156,157].

When inflammation-stimulated microglia and astrocytes are unable to remove misfolded proteins, α-synuclein, tau protein, and amyloid accumulate. Recent data clearly indicate the key role of autophagy in brain pathologies [158]. It is important to note that both inhibitory and stimulatory properties of autophagy have been identified in inflammation. Nevertheless, incorrect autophagic action may still lead to the aggregation of some neuronal elements. Under these conditions, damage signals intensify, leading to an increased pro-inflammatory response. Autophagy is also effective in the generation and release of cytokines, where its inhibitory and stimulating abilities are tuned to different pathological states and their duration. Under circumstances where cytokine generation is simultaneously accompanied by the autophagic response, immune cells can effectively fight pathogens. Autophagy can influence immune cell responses and their excessive activity, which is crucial for preventing uncontrolled parenchyma damage, neuroinflammation and maintaining cellular homeostasis [159]. It has been shown that a tight interaction between NLRP3 inflammasomes and the autophagy machinery occurs at various levels. Overall, autophagy can sequester NLRP3 inflammasomes and direct lysosomal degradation to further suppress immune cell activation. In this context, the removal of damaged mitochondria by mitophagy, the major source of NLRP3 inflammasomes, may prevent subsequent immune cell responses [160,161]. Alternatively, autophagy modulates NLRP3 inflammasomes by regulating inflammasome-related cytokines such as IL-18 and IL-1β, and the degradation of pro-IL-18 and pro-IL-1β may tightly control their direct access to inflammasomes and their release from host cells. In contrast, active NLRP3 inflammasomes induce the autophagy mechanism, which leads to the removal of intracellular pathogens, aggregated proteins and injured organelles. The latter process, also known as inflammasome-mediated autophagy, helps host neuronal cells uphold homeostasis and neuroinflammation [160–162].

Autophagy as a Double-Edged Sword in the Post-Ischemic Brain

Our summary here indicates that autophagy is a double-edged sword for neurodegenerative changes in the brain after ischemia. As the evidence presented above shows, both lack of autophagy and excessive autophagy may have a negative impact on the outcome of brain ischemia. Nevertheless, there is currently no unified theory as to whether autophagy plays a clearly harmful or beneficial role after cerebral ischemia. Recent studies have revealed that the role of autophagy in cerebral ischemia is determined by its type, level, time of occurrence and duration.

It is generally accepted that the level of autophagy is crucial for cell fate; moderate level of autophagy may promote cell survival (pro-survival), while excessive level may cause cell death (pro-death) [163]. This is supported by an *in vitro* ischemia study, whose data revealed a dual role of 3-methyladenine at various times of reoxygenation. It was shown that inhibition of autophagy by 3-methyladenine 24 hours before reoxygenation resulted in a higher rate of neuronal death. However, 2 and 3 days after reoxygenation, 3-methyladenine significantly protected neuronal cells from death [164].

Evidence indicates that the timing of autophagy induction is another key variable determining the balance between protective and harmful autophagy. A study revealed that rapamycin or 3-methyladenine administered 20 minutes before hypoxia-ischemia, reduced neuronal cell loss and cerebral damage by inducing autophagy, whereas 3-methyladenine inhibited autophagy and promoted neuronal death [74,75]. This was confirmed by another study in which 3-methyladenine administration inhibited preconditioning-induced autophagy and attenuated the neuroprotection of preconditioning against brain ischemia [165]. In contrast, in local cerebral ischemia, intraventricular injections of 3-methyladenine has been shown to considerably decrease the infarct size by 46% [63]. Inhibition of autophagy has also been suggested to contribute to neuroprotection induced by ischemic post-conditioning in focal cerebral ischemia in rats [166]. Furthermore, it has been shown that the involvement of Bcl-2 phosphorylation in the cleavage of the Bcl-2/Beclin1 complex plays a key role in the induction of autophagy and is necessary for the neuroprotective effect of ischemia post-conditioning [167]. Leaning on these results, it can be concluded that the manipulation of autophagy at various time points following ischemia may determine its role. This suggests that in the early phase it may have a beneficial effect on neuronal survival, whereas chronic and excessive autophagy causes neuronal damage in the latter phase. The possibility of manipulating autophagy in a specific cell type by deleting cell type-specific autophagy-related genes should also be considered. However, this may not be effective as interfering with autophagy in a single cell type may not be the decisive factor in favorable or unfavorable effects on changes after cerebral ischemia [65,168]. Finally, the debatable consequences of autophagy may result from the inherent differences in the models of cerebral ischemia, survival times and brain structures studied after ischemia, different types of autophagy, different intervention methods, and even sex-specific differences in experimental animals (Table 1) [53,169,170].

Discussion

Some results suggest that the benefits associated with autophagy are connected to the duration of brain ischemia, and that prolonging the ischemia time causes neurotoxic effects. However, others propose that the bidirectional effects of autophagy may be explained by its association with ischemia and subsequent reperfusion time [8,48]. It can therefore be inferred that autophagy may have a neuroprotective effect during brain ischemia but a detrimental effect during recirculation. Some investigations have shown that autophagy protects cells from death by inhibiting apoptosis. In addition to preventing apoptosis and inhibiting cell death, autophagy also triggers cell death. Therefore, the conclusions in this study are preliminary and do not clearly determine whether autophagy is a friend or foe in brain ischemia. Due to these uncertainties, further studies are needed to understand what causes differences in neuronal autophagy in various cerebral regions and at different times after ischemia (Table 1) [15,38,48,54–56]. Given the available evidence, the scientific community must reach a consensus on the exact role of autophagy in post-ischemic brain injury.

As previously described, numerous evidence indicate that autophagy plays a key role in post-ischemic cerebral neurodegeneration and may represent a possible therapeutic target [8,48,59,60,90,170]. The information gathered over many years of research on autophagy allows only a partial understanding of this process and indicates its enormous complexity in cerebral ischemia. Despite this, there are still significant gaps in knowledge on this subject. The regulation of autophagy specific to different cells and organelles after cerebral ischemia remains only partially understood. Moreover, our knowledge of the relationships between autophagic activity and other pathways of glial and neuronal cell damage following cerebral ischemia remains minimal [108,119]. It should be emphasized that neurons require a specific and exceptionally high level of autophagic activity to maintain viability after ischemia, as they play a key role in restoring the structure and proper functioning of the neural network. This condition remains complex and its underlying mechanisms remain elusive. These mechanisms should be thoroughly and critically analyzed in future investigations aimed at exploring the utility of an autophagy-based post-ischemic brain therapy in clinical practice. Another issue that remains unclear is whether there are unusual pathways that initiate maladaptive autophagy detrimental to neurons survival post-ischemia. Autophagy after cerebral ischemia involves multiple pathways, but we currently do not know which mechanisms regulate the degree of autophagy, when, and to what extent. Currently, excessive autophagy is described as characterized by the buildup of autophagosomes, but the underlying molecular mechanisms remain unclear. A key issue is how to selectively manipulate autophagy specific to different cells without activating unwanted signaling pathways leading to their death. Given that brain ischemia-triggered autophagy has both beneficial and detrimental effects, it is necessary to determine the point at which it can be positively influenced. Importantly, the translation of autophagy-based therapeutic strategies from the laboratory to the clinic should be preceded by rigorous preclinical investigations in appropriate *in vitro* and *in vivo* models.

Furthermore, growing evidence indicates that cargo-laden autophagic structures formed in the neuronal network require transport from distant sites of formation to the soma for degradation. A study indicated that autophagy dysfunction in neurons have been demonstrated in post-ischemic brain neurodegeneration (Table 1) [171]. Understanding the details of autophagic flux changes in neurons

following cerebral ischemia remains crucial for developing autophagy-mediated therapeutic strategies. Changes in autophagic behavior also occur in non-neuronal cells following ischemia, which has a significant impact on the recovery of neurological functions [172,173]. The data indicate that autophagic activity in non-neuronal cells is crucial for brain regeneration after ischemia, indicating the need for further, in-depth research on this topic.

It should be noted that enhancing autophagy may not be an effective therapeutic strategy after ischemia. It is suggested that the treatment strategy should focus on correcting autophagic flux disturbances rather than solely on increasing autophagic activity in general. To evaluate this proposal, blood beclin 1 level could be used as a biomarker in the clinic. For example, inactivation of N-ethylmaleimide-sensitive factor ATPase may be a critical step in the entire autophagy pathway, resulting in impaired endolysosomal transport and the accumulation of toxic proteins and injured organelles in post-ischemic neurons [174–176]. Increasing phagocyte-specific autophagic flux may also be a double-edged sword as it eliminates damaged cellular structures and debris, maintaining cell/tissue homeostasis, while excessive increases may result in the removal of adjacent normal cells that could be preserved.

Generally, autophagy plays a key role in the removal of abnormal and neurotoxic proteins and in maintaining cellular homeostasis after cerebral ischemia. This complex phenomenon, by protecting cells, suppressing inflammation, reversing oxidative stress, and creating a desirable microenvironment, may improve cell survival, neural tissue repair, axonal regeneration, and cerebral function [177]. Although autophagy promotes neuroprotection and brain tissue repair, excessive or impaired autophagy can trigger neurons injury following ischemia [8,38].

Conclusions

The precise role of autophagy in the development and progression of post-ischemic neurodegeneration, as well as the temporal and mechanistic conditions under which autophagy exerts protective effects following ischemic brain injury, remains unclear. Despite expanding knowledge-base, further research is needed to elucidate the exact processes underlying the time-dependent and region-specific autophagic responses. Therefore, future research should focus on developing region-specific and time-dependent interventions that promote autophagy and mitophagy without excessive apoptosis. Identifying pharmacological agents or gene therapies for these conditions may prove beneficial. To optimize therapeutic strategies, further investigation is required to identify or develop biomarkers capable of monitoring autophagy dynamics in clinical settings.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, formal analysis, editing, writing the first draft, supervision: RP; methodology, investigation, visualization, writing: MUK. The authors contributed significantly to editorial changes of important content. The authors read and approved the final manuscript. The authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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