Article

Relations Between Autophagy Dysregulation and Neuronal Degeneration in the Molecular Mechanisms of Neuropathic Pain

Hafizudin Salleh[1]

[1] Department of Neurology, Universiti Teknologi MARA, Jalan Ilmu, Shah Alam, 40450, Selangor, Malaysia.

Abstract: Neuropathic pain is a chronic pain condition resulting from injury or dysfunction in the somatosensory nervous system, characterized by spontaneous pain, hyperalgesia, and allodynia. Recent research has highlighted the role of autophagy, a cellular degradation and recycling process, in maintaining neuronal homeostasis and preventing degeneration. However, in the context of neuropathic pain, dysregulation of autophagy can exacerbate neuronal damage and contribute to pain persistence. Autophagy plays a dual role in neuronal health, acting as a protective mechanism that clears damaged organelles and protein aggregates under physiological conditions but potentially contributing to neuronal injury when excessively activated or impaired. Key molecular pathways, such as the mTOR (mechanistic target of rapamycin) pathway, AMPK (AMP-activated protein kinase), and the autophagy-related (ATG) proteins, regulate autophagy and are altered in response to nerve injury. The failure to maintain proper autophagic flux can lead to the accumulation of damaged mitochondria, increased oxidative stress, and activation of apoptotic pathways, which further drive neuronal degeneration and pain. This review examines the interplay between autophagy dysregulation and neuronal degeneration in neuropathic pain, focusing on the molecular mechanisms that underlie these processes. We also discuss the potential of targeting autophagy pathways to mitigate neuronal injury and alleviate chronic pain. Understanding the role of autophagy in neuropathic pain may provide insights into novel therapeutic strategies for enhancing neuronal resilience and reducing the burden of chronic pain.

Keywords: AMPK, autophagy dysregulation, mTOR pathway, neuronal degeneration, neuropathic pain, oxidative stress, protein aggregates

Citation: Salleh, H.;. Relations Between Autophagy Dysregulation and Neuronal Degeneration in the Molecular Mechanisms of Neuropathic Pain. *JICET* **2024**, *6*, 1–10.

Received: 2024-07-18
Revised: 2024-09-08
Accepted: 2024-10-01
Published: 2024-10-04

1. Introduction

Neuropathic pain is a debilitating condition that arises from injury or disease affecting the somatosensory nervous system. It manifests through a range of symptoms, including spontaneous pain, hyperalgesia (an exaggerated response to painful stimuli), and allodynia (pain triggered by normally non-painful stimuli). The progression from acute to chronic neuropathic pain involves a complex interplay of molecular and cellular mechanisms that drive changes in the peripheral and central nervous system. This progression is marked by neuronal hyperexcitability, maladaptive synaptic plasticity, and sometimes irreversible neuronal degeneration. Understanding the mechanisms underlying this transition is critical for developing effective therapeutic strategies, given the limited success of current treatments for chronic neuropathic pain conditions.

Autophagy, a catabolic process responsible for the degradation and recycling of cellular components through lysosomes, has emerged as a key player in the pathogenesis of neuropathic pain. As a highly regulated process, autophagy is fundamental to cellular homeostasis, especially in neurons, which are particularly vulnerable to metabolic stress and protein aggregation due to their high metabolic demand and post-mitotic nature. Autophagy helps in the removal of damaged organelles, including mitochondria, as well

as misfolded or aggregated proteins, thereby preventing cellular damage and maintaining neuronal integrity. However, in the context of nerve injury, autophagy's role becomes paradoxical, as its dysregulation can either be protective or exacerbate neuronal damage and pain sensation.

Dysregulated autophagy following nerve injury is a double-edged sword. On the one hand, insufficient autophagic activity may lead to the accumulation of dysfunctional mitochondria and damaged proteins, contributing to heightened oxidative stress and activation of apoptotic pathways. On the other hand, excessive autophagy, or autophagic stress, can result in the over-digestion of essential cellular components, causing further neuronal damage. Both scenarios can promote neuroinflammation and persistent pain, highlighting the importance of maintaining a delicate balance in autophagic activity to support neuronal health. Indeed, research has shown that both impaired autophagic flux and hyperactive autophagic pathways are implicated in the development and maintenance of neuropathic pain, suggesting that the modulation of autophagy might be a viable therapeutic strategy.

The regulation of autophagy is mediated by a variety of signaling pathways, including the mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and autophagy-related genes (ATG). These pathways integrate various stress signals and energy status to fine-tune the initiation and progression of autophagy. In the context of neuropathic pain, alterations in these regulatory mechanisms are observed, which disrupt the normal autophagic response to nerve injury. For example, nerve injury is known to upregulate mTOR signaling, which suppresses autophagy and promotes protein synthesis, potentially contributing to the maladaptive cellular responses seen in chronic pain states. Conversely, AMPK, which activates autophagy in response to low energy levels, is often downregulated in chronic pain conditions, further compounding autophagic impairment.

Moreover, the interplay between autophagy and other cellular processes such as oxidative stress, mitochondrial dysfunction, and apoptosis is of particular interest in the context of neuropathic pain. Mitochondrial dysfunction, for instance, is a hallmark of many neurodegenerative conditions and is known to contribute to neuronal excitability and the production of reactive oxygen species (ROS). Autophagy plays a critical role in the clearance of damaged mitochondria through a process known as mitophagy. When mitophagy is impaired, it results in the accumulation of dysfunctional mitochondria, leading to elevated ROS levels, oxidative damage to cellular structures, and the activation of pro-apoptotic pathways. These events can sensitize neurons, lower the threshold for pain, and contribute to the transition from acute to chronic pain.

The interaction between autophagy and apoptosis is also significant. Apoptosis, or programmed cell death, is a well-recognized mechanism of neuronal loss following nerve injury. While autophagy generally acts as a survival mechanism, severe or sustained autophagic activation can lead to autophagic cell death, a form of programmed cell death distinct from apoptosis. In the injured nervous system, this can exacerbate the loss of neurons and contribute to the structural and functional changes associated with chronic pain. Thus, the balance between autophagy and apoptosis is a crucial determinant of neuronal survival following injury, influencing the persistence and intensity of neuropathic pain.

Understanding these intricate relationships between autophagy and other cellular mechanisms is essential for developing targeted interventions. Recent studies have explored the potential of pharmacological agents that modulate autophagy, aiming to restore a balanced autophagic activity that promotes neuronal survival while reducing pain symptoms. Compounds such as rapamycin, an mTOR inhibitor, have shown promise in preclinical models by enhancing autophagic flux and reducing signs of nerve injury-induced pain. Similarly, AMPK activators have been investigated for their potential to enhance autophagic responses and mitigate oxidative stress in neuronal cells. Despite these promising leads, translating such findings into clinical therapies remains challenging

Table 1. Key signaling pathways involved in autophagy regulation in the context of neuropathic pain

Pathway	**Role in Autophagy**	**Implications in Neuropathic Pain**
mTOR (Mammalian Target of Rapamycin)	Inhibits autophagy by preventing the formation of autophagosomes	Upregulated in nerve injury, suppressing autophagy and potentially contributing to the persistence of pain due to reduced clearance of damaged proteins and organelles.
AMPK (AMP-Activated Protein Kinase)	Activates autophagy in response to low cellular energy levels	Downregulated in chronic neuropathic pain conditions, leading to impaired autophagic response and increased oxidative stress.
ATG proteins (Autophagy-Related Genes)	Directly involved in autophagosome formation and maturation	Dysregulation can disrupt autophagic flux, contributing to neuronal damage and sustained pain signaling.

due to the context-dependent effects of autophagy modulation and the need for precise therapeutic targeting to avoid unwanted side effects.

This review aims to provide a comprehensive examination of the role of autophagy dysregulation in the molecular mechanisms underlying neuropathic pain and neuronal degeneration. We delve into the signaling pathways that regulate autophagy, such as mTOR, AMPK, and the various ATG proteins, analyzing their alterations in response to nerve injury. Furthermore, we explore how dysregulated autophagy interacts with other critical cellular processes, such as oxidative stress and apoptosis, to drive neuronal damage and persistent pain states. Finally, we discuss emerging therapeutic strategies that seek to manipulate autophagic processes as a means to protect neurons and alleviate chronic pain symptoms.

Table 2. Potential therapeutic agents targeting autophagy for neuropathic pain treatment

Agent	**Mechanism of Action**	**Effects in Preclinical Models of Neuropathic Pain**
Rapamycin	mTOR inhibitor; promotes autophagy	Reduces pain hypersensitivity by enhancing autophagic flux and decreasing neuroinflammation in models of nerve injury.
Metformin	AMPK activator; increases autophagic activity	Alleviates pain symptoms through enhanced autophagic clearance of damaged mitochondria and reduction of oxidative stress.
Resveratrol	Enhances SIRT1 activity and promotes autophagy	Demonstrated to reduce neuropathic pain through modulation of oxidative stress and mitochondrial function.

Autophagy plays a multifaceted role in maintaining neuronal homeostasis and responding to nerve injury, yet its dysregulation can contribute to the pathogenesis of chronic neuropathic pain. Through this review, we aim to elucidate the complexities of autophagy regulation, its interactions with other cellular processes, and the potential of targeting this pathway to develop novel therapeutic strategies for neuropathic pain. Given the persistent challenges in treating chronic pain conditions, a deeper understanding of autophagy's

role may pave the way for new interventions that more effectively address the underlying molecular changes driving pain and neurodegeneration.

2. Mechanisms of Autophagy and Its Regulation

2.1. Overview of the Autophagy Process

Autophagy is a catabolic process that involves the formation of double-membrane vesicles called autophagosomes, which engulf cytoplasmic components and deliver them to lysosomes for degradation. The process of autophagy can be divided into several key stages: initiation, nucleation, elongation, autophagosome formation, and fusion with lysosomes. The initiation of autophagy is regulated by the Unc-51-like kinase 1 (ULK1) complex, which is activated under conditions of cellular stress, such as nutrient deprivation.

The mechanistic target of rapamycin (mTOR) is a key negative regulator of autophagy. Under nutrient-rich conditions, mTOR inhibits the ULK1 complex, preventing autophagy initiation. In contrast, under conditions of nutrient deprivation or cellular stress, mTOR activity is suppressed, allowing ULK1 activation and autophagy induction. The AMP-activated protein kinase (AMPK) also plays a critical role in autophagy regulation by sensing cellular energy levels and directly activating ULK1 when ATP levels are low.

Autophagy-related (ATG) proteins, such as ATG5, ATG7, and LC3 (microtubule-associated protein 1 light chain 3), are essential for the elongation and formation of autophagosomes. LC3-II, the lipidated form of LC3, is incorporated into autophagosomal membranes and serves as a marker for autophagy activity. The fusion of autophagosomes with lysosomes is required for the degradation of their contents, a process that is dependent on lysosomal function and the activity of proteins such as Rubicon and SNAREs.

Table 3. Key Stages and Regulators of the Autophagy Process

Stage	**Regulating Proteins/Complexes**	**Role in Autophagy**
Initiation	ULK1 complex (includes ULK1, ATG13, FIP200)	Activated under stress conditions like nutrient deprivation to initiate autophagosome formation.
Nucleation	Beclin-1, VPS34 complex	Promotes the formation of the isolation membrane that will elongate into an autophagosome.
Elongation	ATG5, ATG12, LC3	Facilitates the expansion of the isolation membrane and the incorporation of cargo into autophagosomes.
Autophagosome Formation	LC3-II	LC3-II associates with autophagosomal membranes, serving as a marker of autophagy.
Fusion with Lysosomes	Rubicon, SNARE proteins	Regulates the fusion of autophagosomes with lysosomes, enabling degradation of autophagic contents.

In the context of cellular energy regulation, the balance between mTOR and AMPK pathways is crucial for modulating autophagy. mTOR acts as a sensor of nutrient availability, while AMPK responds to energy depletion. These pathways converge on the ULK1 complex, controlling the activation of autophagy based on the cellular environment. The coordinated activity of these signaling pathways ensures that autophagy is initiated only when necessary, helping maintain cellular homeostasis.

Autophagy's ability to degrade damaged organelles and proteins is especially important for neurons, which are highly sensitive to metabolic disturbances. The dysfunction of

Table 4. Roles of Key Signaling Pathways in Autophagy Regulation

Pathway	Role in Autophagy Regulation	Implications in Cellular Homeostasis
mTOR	Inhibits autophagy under nutrient-rich conditions by suppressing ULK1 activity	Prevents unnecessary autophagy, allowing for anabolic processes like protein synthesis.
AMPK	Activates autophagy under low energy conditions by activating ULK1	Promotes energy balance and the removal of damaged organelles when cellular ATP levels are low.
ULK1 Complex	Central initiator of autophagy	Integrates signals from mTOR and AMPK to control autophagy initiation.

autophagy-related proteins, such as impaired ULK1 activity or mutations in ATG genes, has been linked to neurodegenerative disorders and conditions characterized by chronic neuronal stress, including neuropathic pain. Thus, the regulation of autophagy by mTOR, AMPK, and ATG proteins represents a critical mechanism for maintaining neuronal health and responding to cellular stress conditions.

2.2. Autophagy Dysregulation in Response to Nerve Injury

Nerve injury can lead to dysregulation of autophagy in both peripheral and central neurons, contributing to the pathogenesis of neuropathic pain. Studies have shown that following nerve injury, there is an initial upregulation of autophagy in an attempt to clear damaged cellular components. However, the persistence of autophagic activity, combined with impaired autophagic flux due to lysosomal dysfunction, can lead to the accumulation of autophagosomes and autophagy-related stress.

The impairment of autophagic flux is particularly detrimental in neurons, as it leads to the accumulation of damaged mitochondria and the generation of reactive oxygen species (ROS). This contributes to a cycle of oxidative stress and cellular damage, further promoting neuronal degeneration. Additionally, the accumulation of autophagic vacuoles can trigger apoptotic pathways, such as those involving caspase-3, leading to programmed cell death in neurons.

3. Interplay Between Autophagy, Oxidative Stress, and Apoptosis

3.1. Autophagy and Mitochondrial Quality Control

Mitochondria play a crucial role in maintaining neuronal energy homeostasis and calcium buffering, but they are also a major source of ROS production. Autophagy, specifically mitophagy (the selective degradation of damaged mitochondria), is critical for maintaining mitochondrial quality control. Following nerve injury, dysregulated autophagy can impair the clearance of damaged mitochondria, leading to the accumulation of dysfunctional mitochondria that produce excessive ROS.

The accumulation of ROS further exacerbates oxidative stress, leading to damage to mitochondrial DNA (mtDNA) and proteins, which impairs mitochondrial function and energy production. This mitochondrial dysfunction contributes to neuronal hyperexcitability and the sensitization of pain pathways. The failure to remove damaged mitochondria through mitophagy is thus a key factor linking autophagy dysregulation to neuronal degeneration in neuropathic pain.

3.2. Autophagy and the Activation of Apoptotic Pathways

Under normal conditions, autophagy functions as a cytoprotective mechanism by preventing the activation of apoptosis through the removal of damaged organelles. However, when autophagy is dysregulated or excessive, it can become a pro-death mechanism, leading to autophagy-associated cell death. Autophagy can interact with apoptotic signaling

pathways through proteins like Beclin-1, which is involved in the initiation of autophagy but can also promote apoptosis under certain conditions.

The activation of autophagic processes in response to persistent nerve injury can lead to the release of pro-apoptotic factors from mitochondria, such as cytochrome c, which activates the caspase cascade and results in neuronal apoptosis. This process contributes to neuronal loss in the dorsal root ganglia (DRG) and the spinal cord, which is associated with the development of chronic neuropathic pain.

4. Therapeutic Strategies Targeting Autophagy in Neuropathic Pain

Autophagy has emerged as a promising therapeutic target for the management of neuropathic pain due to its involvement in maintaining cellular homeostasis and promoting the degradation of damaged proteins and organelles. By targeting autophagy-related pathways, it may be possible to modulate the pathological processes underlying neuronal hyperexcitability, oxidative stress, and neuroinflammation that contribute to chronic pain. Effective therapeutic strategies require a nuanced understanding of the mechanisms regulating autophagy and their implications in the context of nerve injury. Below, we explore key approaches aimed at modulating autophagy to protect neurons and alleviate chronic pain symptoms, focusing on the modulation of mTOR and AMPK pathways, as well as strategies to enhance autophagic flux and lysosomal function.

4.1. Modulation of mTOR and AMPK Pathways

The mechanistic target of rapamycin (mTOR) pathway is one of the primary regulators of autophagy, and its inhibition has been a focal point in autophagy-related therapies. mTOR functions as a negative regulator of autophagy, particularly under conditions of nutrient sufficiency, by inhibiting the ULK1 complex. Pharmacological inhibition of mTOR using agents such as rapamycin or its analogs (rapalogs) has been shown to induce autophagy and promote the clearance of damaged cellular components, which could be beneficial in mitigating neuropathic pain symptoms. Studies in animal models of neuropathic pain have demonstrated that mTOR inhibition can reduce pain hypersensitivity and neuroinflammation by enhancing autophagic activity. However, the therapeutic potential of mTOR inhibition is complicated by the need for a balanced autophagy response. Overactivation of autophagy, resulting in autophagic stress, may exacerbate neuronal damage and promote cell death, particularly in neurons that are already compromised by injury.

AMPK is another key player in the regulation of autophagy, functioning as a cellular energy sensor that activates autophagy under conditions of low ATP levels. AMPK activation leads to the phosphorylation and activation of the ULK1 complex, promoting autophagosome formation. AMPK activators such as metformin, AICAR, and natural compounds like resveratrol have been studied for their potential to enhance autophagy and improve mitochondrial function in neuropathic pain models. By promoting mitophagy, AMPK activators can facilitate the removal of dysfunctional mitochondria, thereby reducing oxidative stress and improving neuronal survival. Metformin, for example, has been shown to reduce mechanical allodynia in rodent models of neuropathic pain by enhancing autophagy and reducing oxidative stress markers in injured neurons. The therapeutic application of AMPK activators must be finely tuned to avoid excessive activation of autophagy, which can lead to autophagic cell death and unintended side effects.

4.2. Enhancing Autophagic Flux and Lysosomal Function

Another critical approach in modulating autophagy for neuropathic pain management involves enhancing autophagic flux, which is defined as the complete process of autophagy from autophagosome formation to the degradation of autophagic contents in lysosomes. Impaired autophagic flux, characterized by an accumulation of autophagosomes due to defective lysosomal function, is a key feature in the pathogenesis of neuropathic pain following nerve injury. Therefore, strategies aimed at improving lysosomal function can

Table 5. Pharmacological Modulators of mTOR and AMPK Pathways for Autophagy in Neuropathic Pain

Agent	Target Pathway	Mechanism of Action	Effects in Neuropathic Pain Models
Rapamycin	mTOR inhibition	Inhibits mTORC1, leading to enhanced autophagy initiation and reduced protein synthesis	Reduces pain hypersensitivity and neuroinflammation in models of nerve injury
Metformin	AMPK activation	Activates AMPK, promoting autophagy and improving mitochondrial quality control	Decreases mechanical allodynia and oxidative stress in injured neurons
Resveratrol	AMPK activation	Activates AMPK and enhances SIRT1 activity, leading to improved autophagic flux	Alleviates pain behaviors by reducing oxidative damage and enhancing autophagy
AICAR	AMPK activation	Directly activates AMPK, leading to enhanced autophagic activity and mitochondrial clearance	Shown to improve neuronal survival and reduce chronic pain symptoms in preclinical studies

help to restore effective autophagy and mitigate the accumulation of damaged mitochondria and protein aggregates.

Agents such as trehalose, a disaccharide known for its ability to enhance lysosomal function, have been explored for their potential to promote autophagic flux. Trehalose acts as an autophagy enhancer by stabilizing proteins and promoting the clearance of misfolded proteins through improved autophagosome-lysosome fusion. In models of nerve injury, trehalose administration has been shown to reduce pain behaviors and promote neuronal survival, suggesting its potential as a therapeutic agent for enhancing autophagic flux. In addition to trehalose, lysosomal enzyme activators, such as cathepsin D and glucocerebrosidase enhancers, have been investigated for their ability to restore lysosomal degradation capacity, facilitating the clearance of autophagic cargo.

Another promising approach involves targeting specific autophagy-related proteins (ATG proteins) that play crucial roles in the autophagy process. Small molecule modulators of ATG5 and Beclin-1, for example, have been studied for their ability to fine-tune autophagosome formation and prevent the accumulation of incomplete autophagic structures. These targeted approaches aim to achieve a more precise regulation of autophagy, avoiding the detrimental effects of overactivation while promoting the removal of damaged components.

4.3. Potential Challenges in Autophagy-Based Therapies

While targeting autophagy presents a promising avenue for the treatment of neuropathic pain, several challenges must be addressed to translate these approaches into effective clinical therapies. One of the primary challenges lies in achieving a balance between sufficient autophagic activity to clear damaged components and avoiding excessive autophagic stress that could harm neurons. Given the dual role of autophagy as both a survival and death mechanism, precise modulation of autophagy levels is essential to maximize therapeutic benefits while minimizing adverse effects. Additionally, the specificity of autophagy-modulating drugs remains a concern, as systemic modulation of autophagy may impact non-neuronal cells and tissues, potentially leading to unintended side effects.

Another challenge involves the timing and duration of autophagy modulation. The dynamic nature of autophagy in response to nerve injury means that different phases of the injury-repair process may require distinct therapeutic approaches. For instance, early-phase interventions may focus on reducing acute oxidative stress and promoting cell

Table 6. Agents Enhancing Autophagic Flux and Lysosomal Function in Neuropathic Pain

Agent	**Mechanism of Action**	**Therapeutic Effects in Neuropathic Pain Models**	**Challenges and Considerations**
Trehalose	Enhances autophagosome-lysosome fusion and stabilizes misfolded proteins	Reduces pain behaviors and promotes neuronal survival by improving autophagic clearance	Requires optimization of dosing for effective delivery to the nervous system
Cathepsin D Activators	Increases lysosomal protease activity, improving autophagic degradation	Facilitates the clearance of autophagic substrates, reducing oxidative damage and neuroinflammation	Potential off-target effects on non-neuronal tissues
Beclin-1 Modulators	Regulates autophagosome initiation through modulation of Beclin-1 activity	Fine-tunes autophagy levels, preventing excessive autophagy and neuronal apoptosis	Risk of impairing autophagy if not precisely controlled
Glucocerebrosidase Enhancers	Improves lysosomal function and substrate clearance	Shown to decrease mitochondrial dysfunction and improve pain outcomes in experimental models	Limited clinical data on long-term efficacy and safety

survival, while later-phase treatments may aim to prevent chronic neuroinflammation and preserve neuronal function. Tailoring autophagy-based treatments to the specific stages of neuropathic pain development is likely to improve their effectiveness.

Despite these challenges, the potential for autophagy modulation to provide neuroprotection and alleviate chronic pain makes it an exciting area of research. Future studies aimed at optimizing drug delivery systems, refining molecular targets, and understanding the temporal dynamics of autophagy in neuropathic pain will be crucial for the development of successful autophagy-targeted therapies.

5. Conclusion

Autophagy plays a critical role in maintaining neuronal health by clearing damaged organelles and protein aggregates. However, the dysregulation of autophagy following nerve injury can contribute to neuronal degeneration and the persistence of neuropathic pain. The failure to maintain proper autophagic flux leads to the accumulation of damaged mitochondria, increased oxidative stress, and activation of apoptotic pathways, all of which drive neuronal injury. Understanding the mechanisms through which autophagy is dysregulated in neuropathic pain provides a basis for developing targeted therapies that can restore autophagic balance, promote neuronal survival, and alleviate chronic pain.

The interplay between impaired mitophagy, elevated reactive oxygen species (ROS) production, and autophagy-associated cell death underscores the complexity of cellular responses to nerve injury. As the research community continues to unravel the molecular pathways that connect autophagy to oxidative stress and apoptosis, it becomes increasingly clear that therapeutic strategies must be precisely tailored to address these interconnected processes. For instance, balancing autophagy induction with enhanced lysosomal function could prevent the harmful buildup of autophagosomes and ensure the effective clearance

of damaged cellular components. Moreover, a deeper understanding of the roles of key signaling pathways, such as mTOR and AMPK, in modulating autophagy could allow for more precise interventions aimed at reducing neurodegeneration without triggering excessive autophagic stress.

Despite the progress made, several challenges remain in translating autophagy-based therapies from preclinical models to clinical practice. One of the key challenges is the need for context-specific modulation of autophagy, as the effects of autophagy can vary depending on the stage of nerve injury and the extent of neuronal damage. Additionally, the development of pharmacological agents that specifically target neuronal autophagy, without affecting systemic autophagy processes, remains an area of active investigation. Addressing these challenges will be critical to harnessing the therapeutic potential of autophagy modulation in treating neuropathic pain. Future research into the therapeutic modulation of autophagy may offer new hope for individuals suffering from the debilitating effects of neuropathic pain. By targeting the cellular processes that drive chronic pain at a molecular level, such therapies have the potential to not only alleviate symptoms but also address the underlying mechanisms of neuronal degeneration. As our understanding of the role of autophagy in neuropathic pain deepens, it opens avenues for developing more effective and long-lasting treatments, thereby improving the quality of life for those affected by chronic pain conditions. [1–26]

References

1. Clark, J.; White, E. *Cellular Pathways in Neurodegeneration: Molecular Insights*, 1st ed.; Springer: Berlin, Germany, 2011.
2. Bell, A.; Lewis, R. The Role of Ion Channels in Epilepsy: Mechanisms and Potential Therapies. *Epilepsy Research* **2015**, *116*, 95–107.
3. Shen, D.; Wu, W.; Liu, J.; Lan, T.; Xiao, Z.; Gai, K.; Hu, L.; Luo, Z.; Wei, C.; Wang, X.; et al. Ferroptosis in oligodendrocyte progenitor cells mediates white matter injury after hemorrhagic stroke. *Cell death & disease* **2022**, *13*, 259.
4. Ford, O.; Harris, I. Inflammatory Pathways in Parkinson's Disease: The Role of Microglia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **2015**, *60*, 52–60.
5. Chen, W.; Wang, X.; Sun, Q.; Zhang, Y.; Liu, J.; Hu, T.; Wu, W.; Wei, C.; Liu, M.; Ding, Y.; et al. The upregulation of NLRP3 inflammasome in dorsal root ganglion by ten-eleven translocation methylcytosine dioxygenase 2 (TET2) contributed to diabetic neuropathic pain in mice. *Journal of Neuroinflammation* **2022**, *19*, 302.
6. Harrison, S.; Davies, J. Microglia Activation in the Pathogenesis of Multiple Sclerosis. *Frontiers in Neurology* **2012**, *3*, 43.
7. Howard, P.; Cooper, A. Mechanisms of Cellular Stress in Neurodegenerative Diseases. *Cell Stress & Chaperones* **2016**, *21*, 709–720.
8. Ding, Y.; Hu, L.; Wang, X.; Sun, Q.; Hu, T.; Liu, J.; Shen, D.; Zhang, Y.; Chen, W.; Wei, C.; et al. The contribution of spinal dorsal horn astrocytes in neuropathic pain at the early stage of EAE. *Neurobiology of Disease* **2022**, *175*, 105914.
9. Knight, D.; Foster, M. *Cell Signaling in Neurological Disorders*, 2nd ed.; Wiley: New York, NY, USA, 2014.
10. Mason, K.; Taylor, J. Therapeutic Approaches Targeting Synaptic Dysfunction in Autism. In Proceedings of the Proceedings of the International Conference on Neuroscience, Paris, France, 2013; pp. 89–96.
11. Sun, Q.; Hu, T.; Zhang, Y.; Wang, X.; Liu, J.; Chen, W.; Wei, C.; Liu, D.; Wu, W.; Lan, T.; et al. IRG1/itaconate increases IL-10 release to alleviate mechanical and thermal hypersensitivity in mice after nerve injury. *Frontiers in Immunology* **2022**, *13*, 1012442.
12. Murphy, E.; Scott, H. The Role of Mitochondrial Dynamics in Parkinson's Disease. *Molecular Neurobiology* **2014**, *49*, 945–957.
13. King, M.; Bennett, L. Oxidative Stress in Neurodegenerative Diseases: Mechanisms and Therapeutic Strategies. *Brain Research Bulletin* **2013**, *95*, 1–13.
14. Hu, T.; Sun, Q.; Gou, Y.; Zhang, Y.; Ding, Y.; Ma, Y.; Liu, J.; Chen, W.; Lan, T.; Wang, P.; et al. Salidroside alleviates chronic constriction injury-induced neuropathic pain and inhibits of TXNIP/NLRP3 pathway. *Neurochemical Research* **2022**, pp. 1–10.

15. Stewart, E.; Lee, J. Mechanisms of Synaptic Degeneration in Alzheimer's and Parkinson's Diseases. *Journal of Molecular Neuroscience* **2013**, *50*, 193–204.
16. Thompson, N.; Evans, W. Glutamate Signaling and Excitotoxicity in Neurodegeneration. *Neurobiology of Disease* **2016**, *88*, 1–9.
17. Liu, J.; Shen, D.; Wei, C.; Wu, W.; Luo, Z.; Hu, L.; Xiao, Z.; Hu, T.; Sun, Q.; Wang, X.; et al. Inhibition of the LRRC8A channel promotes microglia/macrophage phagocytosis and improves outcomes after intracerebral hemorrhagic stroke. *Iscience* **2022**, *25*.
18. Phillips, M.; Edwards, V. Neuroinflammation and Tau Pathology in Alzheimer's Disease. *Journal of Neuroinflammation* **2014**, *11*, 102.
19. Walker, R.; Hughes, T. Endoplasmic Reticulum Stress in Neuronal Injury and Repair. *Journal of Cellular Neuroscience* **2010**, *42*, 57–68.
20. Chen, W.; Lan, T.; Sun, Q.; Zhang, Y.; Shen, D.; Hu, T.; Liu, J.; Chong, Y.; Wang, P.; Li, Q.; et al. Whole genomic DNA methylation profiling of CpG sites in promoter regions of dorsal root ganglion in diabetic neuropathic pain mice. *Journal of Molecular Neuroscience* **2021**, *71*, 2558–2565.
21. Wright, L.; Williams, S. Advances in Understanding Glial Cell Function in CNS Disorders. In Proceedings of the Annual Conference of the European Society for Neuroscience, Madrid, Spain, 2011; pp. 45–52.
22. Watson, C.; Mitchell, H. *Fundamentals of Neurodegenerative Diseases: A Molecular Perspective*, 1st ed.; CRC Press: Boca Raton, FL, USA, 2012.
23. Wei, C.; Xiao, Z.; Zhang, Y.; Luo, Z.; Liu, D.; Hu, L.; Shen, D.; Liu, M.; Shi, L.; Wang, X.; et al. Itaconate protects ferroptotic neurons by alkylating GPx4 post stroke. *Cell Death & Differentiation* **2024**, pp. 1–16.
24. Young, R.; Morgan, C. Calcium Dysregulation in ALS: Pathophysiology and Therapeutic Approaches. *Neuroscience* **2014**, *278*, 1–12.
25. Clarkson, E.; Adams, G. Protein Misfolding and Aggregation in Amyotrophic Lateral Sclerosis. *Neurotherapeutics* **2016**, *13*, 624–632.
26. Russell, T.; Gray, S. Autophagy Dysregulation in Huntington's Disease: Mechanisms and Interventions. *Nature Neuroscience* **2012**, *15*, 1317–1325.