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Autophagy dysfunction in neuropathic pain

Xiaojuan Liu[a], Manhui Zhu[b], Yuanyuan Ju[c], Aihong Li[d,*,1], Xiaolei Sun[a,*,1]

[a] Department of Pathogen Biology, Medical College, Nantong University, Nantong 226001, Jiangsu, China
[b] Department of Ophthalmology, Affiliated Lixiang Eye Hospital of Soochow University, Suzhou 210005, Jiangsu, China
[c] Medical College, Nantong University, Nantong 2266001, Jiangsu, China
[d] Department of Neurology, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu, China

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ABSTRACT

Autophagy is a lysosomal degradation pathway that maintains tissue homeostasis by recycling damaged and aged cellular components, which plays important roles in development of the nervous system, as well as in neuronal function and survival. In addition, autophagy dysfunction underlies neuropathic pain. Thus, the modulation of autophagy can alleviate neuropathic pain. Here, we describe the definition, mechanisms of autophagy and neuropathic pain. On this basis, we further discuss the role of autophagy dysfunction in neuropathic pain. This review updates our knowledge on autophagy mechanisms which propose potential therapeutic targets for the treatment of neuropathic pain.

1. Introduction

Autophagy is a cellular process in which long-lived, dysfunctional, or excess proteins are degraded to preserve normal tissue homeostasis (Martinet and De Meyer, 2008; Shiomi et al., 2014). Essentially, the cell "eats" itself to maintain energy and provide cellular housekeeping (Glick et al., 2010).

In central nervous system (CNS), autophagy is critical for neuronal homeostasis and survival (Ariosa and Klionsky, 2016; Kulkarni and Maday, 2018). Neural-specific depletion of genes required for autophagy is sufficient to cause axon degeneration and neuron death in mice (Komatsu et al., 2007; Nishiyama et al., 2007). Autophagy is also important for synaptic maintenance and plasticity in CNS (Luningschror and Sendtner, 2018; Nikoletopoulou et al., 2017; Shen et al., 2015) which we don't discuss in this manuscript. In peripheral nervous system (PNS), autophagy is essential for synaptic integrity and receptor turnover (Luningschror et al., 2017; Rudolf et al., 2016). Moreover, a specific role for autophagy in Schwann cell (SC) function during myelination and re-myelination has been identified (Brosius Lutz et al., 2017; Gomez-Sanchez et al., 2015).

Neuropathic pain is a kind of chronic pain, termed by the International Association for the Study of Pain (IASP) as a pain arising after a lesion or disease affecting the somatosensory system (Jensen et al., 2011), characterized by symptoms including spontaneous pain, hyperalgesia (increased pain in response to a stimulus that normally provokes pain) and allodynia (pain in response to a stimulus that does not normally provoke pain). For its high incidence, complex pathogenesis and lack of efficient treatments, neuropathic pain is still the focus of related studies.

In fact, imbalances between excitatory and inhibitory somatosensory signaling (Leite et al., 2017; Watson, 2016), changes in ion channels (Busserolles et al., 2016; Tsantoulas et al., 2017) and glia cell activation (Bravo et al., 2015; Meacham et al., 2017) all contribute to neuropathic pain. Recently, accumulating studies reveal that autophagy dysfunction underlies neuropathic pain (Zhang et al., 2013) and corresponding modulation of autophagy can alleviate pain behavior (Ma et al., 2016b; Rangaraju et al., 2010).

2. Autophagy

2.1. Associated molecules of autophagy

A breakthrough of the molecular mechanism for autophagy is obtained by determining unique sets of molecules involved in membrane dynamics during autophagy in yeast, which are named as autophagy-related genes (ATG) (Thumm et al., 1994; Tsukada and Ohsumi, 1993). These core Atg proteins are divided into four subgroups, including the Atg1/unc-51-like kinase (ULK) complex regulating the autophagy initiation; two ubiquitin-like proteins Atg12 and Atg8/microtubule-associated protein light chain 3 (LC3) conjugation systems helping the

* Corresponding authors.
E-mail addresses: liaihongbox@ntu.edu.cn (A. Li), sxl@ntu.edu.cn (X. Sun).
[1] Aihong Li and Xiaolei Sun contributed equally to this work.

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autophagic membrane elongation; the class III phosphatidylinositol 3-kinase (PI3K)/Vps34 complex I involving at the early stage of the autophagosome membrane formation; two transmembrane proteins Atg9/mAtg9 (and associated proteins involved in its movement such as Atg18/WIPI-1) and VMP1 contributing to the delivery of membrane to the forming autophagosome (Xie and Klionsky, 2007). The process of autophagy involves two major steps including induction of autophagosome and fusion of autophagosome with lysosome.

2.2. Classification and process of autophagy

Autophagy is classified into five types including chaperone-mediated autophagy, endosomal microautophagy, macroautophagy, microautophagy, and selective macroautophagy (Scrivo et al., 2018). Chaperone-mediated autophagy comprises selective delivery of single protein (substrate) to lysosomes by recognition and binding of a specific KFERQ-like pentapeptide motif to cytosolic chaperone heat shock cognate 70 kDa protein (Hsc70). The chaperone-substrate complex binds to the cytosolic tail of lysosome-associated membrane protein type 2A (LAMP-2A), initiating its assembly into a multimeric complex that mediates substrate translocation. Following complete unfolding, and with the aid of luminal chaperones, the substrate reaches the lysosomal matrix for degradation (Xilouri and Stefanis, 2015). Endosomal microautophagy involves trapping of cytosolic proteins and organelles into small vesicles that form on the surface of late endosomes by invagination of their membrane, mediated by the endosomal sorting complexes required for transport. Vesicles fall off from the membrane into the lumen of the endosome, where they are degraded after lysis of the microvesicle membrane. Some proteins that bear a KFERQ-like motif, such as tau, can be selectively targeted for endosomal microautophagy by Hsc70s that recognize the same KFERQ-like pentapeptide motif as in the chaperone-mediated autophagy (Tekirdag and Cuervo, 2018). Macroautophagy contains sequestration of cytosolic components by a membrane that elongates through a coordinated assembly of lipids and autophagy-related proteins, and then seals to form a double membrane vesicle which is named autophagosome. The sequestered cargo inside the autophagosome is transported towards the lysosomes and, upon fusion of these two vesicles, is degraded by the resident lysosome hydrolases (van Beek et al., 2018). Microautophagy means cytosolic cargo, proteins, and organelles are internalized inside lysosomes by invaginations that form at the lysosomal membrane (McPherson, 2015). Selective macroautophagy utilizes the same machinery of macroautophagy but selectively target specific cytosolic components for degradation. Categories of selective macroautophagy are consisted of mitophagy (elimination of mitochondria), lipophagy (elimination of lipids), and aggrephagy (elimination of aggregate proteins) (Wu et al., 2018b).

3. Neuropathic pain

3.1. Causes

Central neuropathic pain is due to a lesion or disease of the spinal cord and/or brain (Jones 3rd et al., 2016). Cerebrovascular disease affecting the central somatosensory pathways (post-stroke pain) and neurodegenerative diseases (especially Parkinson's disease) are brain disorders that often cause central neuropathic pain (Borsook, 2012). Spinal cord lesions or diseases that cause neuropathic pain include spinal cord injury, syringomyelia and demyelinating diseases, such as multiple sclerosis, transverse myelitis and neuromyelitis optica (Watson and Sandroni, 2016).

Peripheral neuropathic pain will probably become more common due to the ageing global population, increased incidence of diabetes mellitus and the increasing rates of cancer and the consequence of chemotherapy (Baron et al., 2017). Peripheral neuropathic pain disorders can be subdivided into those that have a generalized (usually symmetrical) distribution and those that have a focal distribution. The most clinically important painful generalized peripheral neuropathies include those associated with diabetes mellitus (Singh et al., 2014), prediabetes (Duksal et al., 2016; Stino and Smith, 2017) and other metabolic dysfunctions (Jha et al., 2016), infectious diseases (mainly HIV infection (Stavros and Simpson, 2014) and leprosy (Thakur et al., 2015)), chemotherapy (Carozzi et al., 2015), immune [for example, Guillain-Barre syndrome (Merkies and Kieseier, 2016)] and inflammatory disorders (Dalakas, 2015; Dimitroulas et al., 2014), inherited neuropathies and channelopathies [such as inherited erythromelalgia (Crunkhorn, 2016), a disorder in which blood vessels are episodically blocked then become hyperaemic and inflamed] (Imbrici et al., 2016; Li, 2015).

3.2. Regulation of autophagy in neuropathic pain

Autophagy is regulated by various signaling pathways. Healthy mammalian cells undergo a low basal level of autophagy (Funderburk et al., 2010), which plays a fundamental role in the intracellular homeostatic turnover of proteins and organelles (Funderburk et al., 2010). Autophagy is regulated by diverse stresses including nutrient starvation, hypoxia, reactive oxygen species (ROS), mitotoxicity, inflammation, and endoplasmic reticulum (ER) stress (Ma et al., 2014; Melendez and Neufeld, 2008; Moloudizargari et al., 2017).

3.2.1. Reactive oxygen species (ROS)

Mitochondrial ROS levels are elevated in spinal neurons, microglia, and astrocytes in neuropathic pain models (Kim et al., 2010). Furthermore, blocking the mitochondrial electron transport chain (mETC) attenuates hyperalgesia associated with a range of inflammatory and neuropathic pain models (Chu et al., 2011; Ferrari and Levine, 2010). ROS contribute to peripheral and central sensitization after nerve-system injury, which leads to neuropathic pain. It is well established that ROS are important endogenous agonists of transient receptor potential ankyrin 1 (TRPA1) (Andersson et al., 2008), a calcium-permeable non-selective cation channel expressed in the nervous system on a subpopulation of primary afferent nociceptors (Story et al., 2003), and astrocytes (Shigetomi et al., 2011). ROS have been shown to both positively and negatively regulate autophagy, depending on the levels and context (Filomeni et al., 2015). The positive effects of ROS on autophagy flux can be exerted directly via redox-sensitive mediators such as ATG4, or indirectly via upstream regulatory pathways such as the adenosine 5¢-monophosphate-activated protein kinase (AMPK) (Zmijewski et al., 2010). On the other hand, excessive ROS as well as reactive nitrogen species (RNS) can inhibit autophagy, for example, by means of S-nitrosylation of the components of JNK and mTOR pathways (Sarkar et al., 2011). Although basal activation of autophagy in response to ROS generation occurs in neuropathic pain (Yin et al., 2018), enormous amount of ROS mediated oxidative stress and also helps to recycle the damaged components with new healthy components.

3.2.2. Mitotoxicity

Mitotoxicity refers to toxic effect on mitochondria. Mitochondrial dysfunction has been found to be a major mechanism underlying the neuronal dysfunction associated with peripheral neuropathies. Neurons meet high metabolic demands for growth and neurotransmission from oxidative phosphorylation (Kann and Kovacs, 2007). Hence, mitochondrial dysfunction in neurons may lead to neuropathological consequences such as impaired growth, metabolism and disturbed neurotransmission. Defective autophagy/mitophagy signaling is known to occur in neuropathic pain (Berliocchi et al., 2011; Guo et al., 2015). Hence, identification of drugs which sustain the mitochondrial function and health could aid the search of finding a better therapeutic strategy, which might open new prospect in the treatment of neuropathic pain.

Table 1
Autophagy dysfunction in animal neuropathic pain models.

Model	Animal	Major results	Methods	Reference
SNL	Male C57BL/6 mice	LC3 and Beclin 1 in L4-L5 portion of the ipsilateral spinal cord increase	WB	(Berliocchi et al., 2011)
SNL	male SD rats	LC3 and Beclin 1 in GABAergic interneurons of spinal dorsal horn increase	IF	(Zhang et al., 2013)
SNL	male ICR mice	LC3-II in DRG neurons increases	WB, IF	(Guo et al., 2015)
SNL, SNI, CCI	male C57Bl/6 mice	Spinal LC3-II, p62 increase in SNL; LC3-II increases in SNI; Beclin 1 increases in CCI	WB, IF	(Berliocchi et al., 2015)
Diabetes induced neuropathic pain	male SD rats	LC3 and Beclin increase in sciatic nerve samples	WB	(Inceoglu et al., 2015)

Abbreviates: CCI, chronic constriction injury; DRG, dorsal root ganglion; GABAergic, γ-aminobutyric acid-ergic; IF, Immunofluorescence; LC3, microtubule-associated proteins 1A/1B light chains 3; SD, Sprague-Dawley; SNI, spared nerve injury; SNL, spinal nerve ligation; WB, Western blot.

3.2.3. Endoplasmic reticulum (ER) stress

Following perturbations in the ER microenvironment, cells will be leading to further accumulation of unfolded proteins leading to unfolded protein response (UPR) generally referred as ER stress (Hetz and Papa, 2018). ER stress in the peripheral nervous system is a significant driver of neuropathic pain in rat diabetic polyneuropathy model (Inceoglu et al., 2015). ER stress is induced in the injured DRG and contributes to the development of pain hypersensitivity after nerve injury in rat SNL model (Yamaguchi et al., 2018). Furthermore, ER stress in the spinal dorsal horn might be involved in the induction and maintenance of neuropathic pain in rat SNL model (Zhang et al., 2015). However, some studies recover autophagy own-regulation in neuropathic pain with the vague mechanisms (Kosacka et al., 2013; Wang et al., 2018).

3.3. The important molecules in autophagy of neuropathic pain

3.3.1. Heat shock protein B8 (HSPB8)

HSPB8, belonging to a superfamily of small HSPs, acts as a chaperone binding Bcl-2 associated athanogene 3 (BAG3) during autophagy (Mymrikov et al., 2011). The BAG family of proteins acts as co-chaperones by helping molecular chaperones to recruit target proteins (Gurusamy et al., 2009). The BAG3 protein is a number of the BAG family, which interacts with the ATPase domain of HSPB8 to facilitate autophagy (Ma et al., 2016a). Additionally, HSPB8 promotes the fusion of autophagosome and lysosome during autophagy in high-glucose-exposed RGC5 (retinal ganglion cell-5) cells (human neuroblastoma cell line) (Li et al., 2017). K141E and K141T Mutations in *HSPB8* gene are associated with distal hereditary motor neuropathy (dHMN) (Kwok et al., 2011) and with the axonal form of Charcot-Marie-Tooth disease type 2 (CMT2) (Nakhro et al., 2013), respectively. Using a new transgenic mouse model leading to the expression of the mutant protein (knock-in lines) or the loss-of-function (functional knock-out lines) of HSP, the research reveals toxic gain-of-function of mutant Hspb8 aggregates is a major contributor to the peripheral neuropathy and the myopathy (Bouhy et al., 2018).

3.3.2. Autophagy-related 7 (ATG7)

Autophagy is a lysosome-mediated degradation pathway vigorously participating in drug addiction (Hayashi et al., 2014), as well as regulates the axonal and dendritic degeneration of neurons (Yang et al., 2013). ATG7 is indispensable for the maintenance of axonal homeostasis (Komatsu et al., 2007). Atg7-deficient mice die within 1 day after birth (Komatsu et al., 2005), whereas CNS (central nervous system) specific Atg7 knockout mice are featured by growth retardation, motor and behavioral deficits, extensive neuronal loss and die between 3 and 28 weeks after birth (Komatsu et al., 2006). Compared to wild-type mice, mice deficient in Atg7 specifically in the dopaminergic neurons are less sensitive to developing a morphine reward response, behavioral sensitization, analgesic tolerance and physical dependence (Su et al., 2017). Transient receptor potential vanilloid type 1 (TRPV1), which functions as regulating body temperature and sensations such as scalding heat, pain and pungency, is degraded is reduced by genetic silencing of Atg7 (ATG7 siRNA transfection) in HeLa cells (Ahn et al., 2014).

3.3.3. Mammalian target of rapamycin (mTOR)

mTOR induces the phosphorylation of its effector proteins, which subsequently inhibits ULK1/2 complex, a complex needed in the early steps of autophagy (Jung et al., 2010). Thus several drug therapeutic studies target mTOR pathway. *Lycium barbarum* polysaccharide protects diabetic peripheral neuropathy by enhancing autophagy via mTOR / ribosomal protein S6 kinase I (p70S6K) inhibition in streptozotocin-induced diabetic rats (Liu et al., 2018). High glucose up-regulates Semaphorin 3A expression via the mTOR signaling pathway in HaCaT cells (a human keratinocyte cell line), which supplies a potential mechanism and therapeutic target for diabetic small fiber neuropathy (Wu et al., 2018a). AKT/TSC2/mTOR pathway is activated in rat SNL-induced neuropathic pain, while hyperbaric oxygen (HBO) treatment attenuates neuropathic pain via neutralizing protein kinase B (AKT)/tuberous sclerosis 2 protein (TSC2)/mTOR pathway activation (Liu et al., 2019). Suberoylanilide hydroxamic acid (SAHA), one of histone deacetylase inhibitors (HDACIs), attenuates rat SNL-induced neuropathic pain and contributes to autophagy flux in spinal dorsal horn astrocytes and neuronal cells via the mTOR signaling pathway (Feng et al., 2019). Electroacupuncture (EA) intervention attenuated the up-regulation of mTOR signaling and alleviated mechanical and thermal pain responses in SCI rats.

4. Autophagy dysfunction in neuropathic pain animal models

Recent studies show that the dysfunction of autophagy in neuropathic pain (Table 1). Levels of microtubule-associated protein 1 light chain 3 (LC3)-II, the autophagosome-associated LC3 form, are markedly higher in the mouse ipsilateral spinal cord after spinal nerve ligation (SNL). However, LC3-I and Beclin 1 expression only slightly increases. On the contrary, SNL promotes the accumulation of the ubiquitin- and LC3-binding protein p62, which inversely correlates with autophagic activity, indicating a block of autophagosome turnover. These data showed that autophagy is disrupted in the mouse spinal cord that undergo SNL and suggest that accumulation of autophagy markers is likely to result from a block in completion of basal autophagy rather than up-regulation of the pathway (Berliocchi et al., 2011). LC3 and Beclin 1 expression is upregulated in GABAergic interneurons of rat spinal dorsal horn after SNL, suggesting autophagic disruption following SNL might be involved in the induction and maintenance of neuropathic pain (Zhang et al., 2013). The level of LC3-II increases in mouse L5 dorsal root ganglion (DRG) after SNL, showing that the autophagy in L5 DRG neurons is a defensive reaction to L5 spinal nerve injury (Guo et al., 2015). Rat spinal LC3-II, p62 expression increases in SNL, LC3-II expression increases in spared nerve injury (SNI), while Beclin 1 increases in chronic constriction injury (CCI) model, showing that autophagy is differentially affected in the spinal dorsal horn depending on the type of peripheral injury (Berliocchi et al., 2015). LC3 and Beclin significantly increased in sciatic nerve samples in rat diabetes induced neuropathic pain model, demonstrating a continuous and organized

effort to replenish subcellular structures (Inceoglu et al., 2015).

In summary, almost all of the previous studies above show that the expression of autophagy-related molecules such as LC3-II and Beclin 1 increases following peripheral nerve injury or neuropathy. However, authors conclude in different ways via autophagy decrease (Berliocchi et al., 2011; Zhang et al., 2013) or autophagy enhance (Berliocchi et al., 2015; Guo et al., 2015; Inceoglu et al., 2015), which might due to the understanding for the up-regulating expression of autophagy-associated molecules and the limitation of experimental strategies (Western blot, immunofluorescence). Further investigations are needed to identify the status of autophagy in different neuropathic pain models, such as the detection of phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT)/mTOR signaling axis, a well-recognized negative regulator of autophagy (Gottlieb et al., 2015; Heras-Sandoval et al., 2014).

Until now it is unclear what mechanisms cause the dysfunction of autophagy following neuropathic pain. But we can suppose the possible mechanisms from the previous studies. For example, ROS which contributes to neuropathic pain in mouse SNL model (Yowtak et al., 2011), also increasing in rat sciatic nerve transection (SNT) model (Guedes et al., 2008), might induce autophagy following peripheral nerve injury. Another possible mechanism is inflammation, which is a cause of neuropathic pain (Ji et al., 2016; Silva et al., 2015), can also induce the up-regulation of autophagy.

5. Modulations of autophagy in animals alleviate neuropathic pain behaviors

Since the dysfunction of autophagy participate the pathological process of neuropthic pain, researchers use drugs, inhibitors which modulate autophagy in animals to alleviate neuropathic pain behavior (Table 2). Here we discuss the major agents used to alleviate neuropathic pain via controlling autophagy.

5.1. Rapamycin

mTOR, a serine/threonine kinase, has been identified as a master regulator of macroautophagy, exists in two protein complexes including mTORC1 or mTORC2. mTORC1 which is inhibited by paramycin negatively regulates macroautophagy, while mTORC2 majorly participates in regulation of cellular survival and cytoskeletal organization (Laplante and Sabatini, 2012). Rapamycin is a strong inducer of autophagy that may eventually find utility in the treatment of neuropathic pain. Rapamycin anterior cingulate cortex (ACC) (Um et al., 2018) or insular cortex (IC) (Kwon et al., 2017) injection reduces mechanical allodynia in rat SNI model. Treatment with intrathecal rapamycin significantly attenuates mechanical allodynia and thermal hyperalgesia in rat SNL model (Feng et al., 2014). Intrathecal infusion of rapamycin attenuates bortezomib (anti-tumor drug)-induced mechanical pain and cold hypersensitivity (Duan et al., 2018), while microinjection of rapamycin into mouse L5 DRG before or after SNL dose-dependently attenuates mechanical allodynia (Guo et al., 2015). In mouse CCI model, intraplantarly injection of rapamycin into the hind paw ipsilateral to the injury, 3 days after CCI immediately after behavioral measurement, can induce long-lasting analgesic and anti-inflammatory effects, facilitate nerve regeneration, and prevent pain chronification (Marinelli et al., 2014). Additionally, in mouse experimental autoimmune encephalomyelitis (EAE) model, intraperitoneal injection of rapamycin reduces mechanical allodynia (Lisi et al., 2012). Generally speaking, rapamycin used in peripheral nerve lesion and EAE can reduce neuropathic pain via enhancing autophagic activity. However, central nerve injury-induced neuropathic pain has not been explored for rapamycin treatment, which is a potential future research direction.

5.2. RNA agents

Some researchers also apply RNA agents including micro RNA and siRNA in neuropathic pain animal models. MicroRNAs (miRNAs) are 21–22-nucleotide RNAs that mediate post-transcriptional gene silencing to regulate gene expression and promote microglia activation (Hausser and Zavolan, 2014; Parisi et al., 2016). Following peripheral nerve lesion, spinal microglia activation and produce of pro-inflammatory cytokines contribute to the development and maintenance of neuropathic pain (Echeverry et al., 2017). MiR-145 injection at lumbar 5 DRG mollifies mechanical allodynia and thermal hyperalgesia in rat CCI model (Shi et al., 2018). Another study reveals miR-183 can suppress neuropathic pain and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors by inhibiting mTOR / vascular endothelial growth factor (VEGF) pathway in rat CCI model (Xie et al., 2017). Previous study finds that miR-195 level increases in rats subjected to SNL, locating in spinal microglia. Up-regulated miR-195 results in increased mechanical and cold hypersensitivity after SNL, whereas miR-195 inhibition has the opposite effect via increased autophagy activation. More important, autophagy inhibition impairs miR-195 inhibitor-induced down-regulation of neuropathic pain, indicating that miR-195 aggravates neuropathic pain by inhibiting autophagy following SNL (Shi et al., 2013).

Activating transcription factor 6 (ATF6) is membrane-bound that activates genes in the endoplasmic reticulum (ER) stress (Yu et al., 2017), while ER stress triggers autophagy (Yorimitsu et al., 2006). Intrathecal injection of ATF6 siRNA alleviates mechanical hypersensitivity and autophagy in rats following SNL (Zhang et al., 2015). Toll-like receptor 3 (TLR3) facilitates the development and maintenance of neuropathic pain (Obata et al., 2008). Furthermore, intrathecal administration of siRNA mixtures against TLR3 inhibits SNL-induced microglial autophagy and alleviates mechanical hyperalgesia in rats (Chen and Lu, 2017).

5.3. Other major agents

Melatonin, a potent antioxidant (Tan et al., 2015), decreases neuronal excitability in a sub-population of DRG neurons (Oliveira-Abreu et al., 2018). Melatonin intraperitoneal injection significantly alleviates oxaliplatin-induced pain behavior and neuropathic deficits in rats through increasing autophagy pathway in peripheral nerves and DRG (Areti et al., 2017). For melatonin already has the clinical application (Bruni et al., 2015; Miroddi et al., 2015), whether it can be taken for neuropathic pain therapy is feasible.

Progranulin is expressed in neurons and microglia in the nervous system, functioning trophic factor support for neurons to suppression of microglia activation (Tanaka et al., 2013; Van Damme et al., 2008). Researchers generate mice with specific overexpression of progranulin in nociceptive neurons of the DRG and construct the SNI model showing that progranulin overexpression can improve autophagy in the injured nerve and pain behavior (Altmann et al., 2016).

Cloroquine (CQ) is an autophagy blocker by inhibiting lysosomal proteases and autophagosome-lysosomal fusion events (Geng et al., 2010). Intrathecal injection of CQ in naïve mice induces spinal accumulation of microtubule-associated protein 1 light chain 3 (LC3) and p62 paralleled by significant mechanical hypersensitivity, implying the block in autophagosome clearance and showing the participation of the autophagic process in spinal mechanisms of pain processing (Berliocchi et al., 2015).

6. Conclusions and prospects

Though autophagy in neuropathic pain has been investigated for several years, gaining the credible data for the role of autophagy dysfunction and modulation of autophagy in neuropathic pain, there are still problems in this field to be solved in the future: (1) the cellular and molecular mechanisms which induce the dysfunction of autophagy are unclear; (2) the contribution of autophagy to neuropathic pain is contradictory; (3) the relationship between autophagy dysfunction and glia

Table 2
The autophagy-affect interventions used in animal neuropathic pain models.

Modulation	Method	Animal model	Findings	Ref.
The modulations enhance the autophagy				
Rapamycin	ACC injection	SNI in male SD rats	Reduces mechanical allodynia	(Um et al., 2018)
	Intrathecal injection	Bortezomib ip in male SD rats	Alleviates peripheral neuropathic pain	(Duan et al., 2018)
	IC injection	SNI in male SD rats	Reduces mechanical allodynia	(Kwon et al., 2017)
	L5 DRG microinjection	SNL in ICR male mice	Attenuates neuropathic pain.	(Guo et al., 2015)
	Ip injection	EAE in female C57BL/6 mice	reduces demyelization, increases the threshold of neuropathic pain	(Lisi et al., 2012)
	Ipl injection	SNL in male SD rats	Enhances autophagy, reduces IL-1β, attenuates the mechanical allodynia and thermal hyperalgesia	(Feng et al., 2014)
	Ipl injection	CCI in male CD1 mice	Enhancement of autophagy leads to long-lasting analgesic and anti-inflammatory effects.	(Marinelli et al., 2014)
MiR-145	L5 DRG injection	CCI in male SD rats	Mollifies mechanical allodynia and thermal hyperalgesia	(Shi et al., 2018)
MiR-183	Rapamycin left sciatic nerve injection	CCI in male SD rats	relieves neuropathic pain	(Xie et al., 2017)
Exercise intervention	four to five weeks of exercise	STZ ip in SD rats	Inhibits neuropathic pain	(Ma et al., 2018)
DMBC	Ip injection	Acetic acid-writhing model in male and female mice	Enhances peripheral autophagy, alleviates pain	(Gu et al., 2013)
Melatonin	Ip injection	oxaliplatin-induced peripheral neuropathy male SD rats	Alleviates pain by increasing autophagy in peripheral nerves and DRG	(Areti et al., 2017)
HBO	HBO chamber	CCI in male SD rats	Palliates neuropathic pain	(Han et al., 2017)
	Put rats in cylindrical HBO treatment chamber.	SNL in male SD rats	Attenuates neuropathic pain by increasing spinal autophagic flux	(Liu et al., 2017)
Progranulin	Transgenesis in nociceptive neurons of DRG	SNI in male C57BL/6 mice	Autophagy and pain are improved	(Altmann et al., 2016)
CatB	Gene knockout	morphine i.p. injection in male mice	excessive autophagy is partly responsible for morphine antinociceptive tolerance	(Hayashi et al., 2014)
The modulations weaken the autophagy				
MCP (a gal3 inhibitor)	Intrathecal injection	SNL in male SD rats	suppresses SNL-induced autophagy activation and decreased mechanical and cold hypersensitivity following SNL	(Ma et al., 2016)
Chloroquine (autophagy blocker)	Ipl injection	Naïve male C57Bl/6 mice	spinal accumulation of LC3 and p62, mechanical hypersensitivity	(Berliocchi et al., 2015)
MiR-195	Intrathecal injection	SNL in male Wistar rats	Aggravates neuropathic pain by inhibiting autophagy	(Shi et al., 2013)
ATF6 siRNA	Intrathecal injection	SNL in male SD rats	Alleviate mechanical hypersensitivity and autophagy	(Zhang et al., 2015)
TLR3 siRNA	Ipl injection	SNL in male SD rats	Inhibits SNL-induced microglial autophagy, alleviates pain	(Chen and Lu, 2017)

Abbreviates: ACC, anterior cingulate cortex; ATF6, activating transcription factor 6; CatB, cathepsin B; CCI, chronic constriction injury; DMBC, 2-(3′, 5′-Dimethoxybenzylidene) cyclopentanone; DRG, dorsal root ganglion; EAE, experimental autoimmune encephalomyelitis; gal3, galectin-3; HBO, Hyperbaric oxygen; IC, insular cortex; ip, intraperitoneal; ipl, intraplantarly; L5, lumbar 5; LC3, microtubule-associated proteins 1A/1B light chains 3; MCP, modified citrus pectin; SD, Sprague-Dawley; SNI, spared nerve injury; SNL, spinal nerve ligation; TLR3, Toll-like receptor 3; STZ, streptozotocin.

cell activation is unknown; (4) the modulations of autophagy is just applied on animals especially rodents and when the methods can be used in human.

Conflict of interest

The authors declare that they have no conflicts of interest.

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