Review
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Neuroprotective Effect of Fluoxetine via Targeting NLRP3 Inflammasome-Autophagy Crosstalk

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Abstract
Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) approved for major depressive disorder, exerts neuroprotective effects by modulating the NLRP3 inflammasome-autophagy crosstalk central to neuroinflammation in CNS disorders. This review synthesizes evidence demonstrating fluoxetine's dual mechanisms: direct inhibition of NLRP3 assembly and activation (reducing IL-1β/IL-18 release via NACHT domain binding and ROS mitigation through Nrf2/HO-1 pathways) alongside enhancement of autophagic flux (elevating LC3-II, Beclin-1, ATG5, and p62/SQSTM1), which promotes autophagic degradation of inflammasome components. This review highlights the need for deeper mechanistic insights into fluoxetine's regulation of autophagy-NLRP3 crosstalk, particularly through key regulatory proteins involved in this crosstalk. Enhanced understanding will unlock fluoxetine's full therapeutic potential for CNS disorder therapy.
Keywords: Fluoxetine, NLRP3, inflammasome, autophagy, neuroinflammation, CNS

Introduction

Fluoxetine binds to and inhibits the serotonin reuptake transporter (SERT) on presynaptic neurons, thereby enhancing the serotonin levels in the synaptic cleft.[1] While its well-established role involves increasing serotonin levels to alleviate depressive symptoms, recent studies have revealed additional therapeutic benefits related to its effects on the immune system and inflammatory processes.[2–6] Evidence shows that fluoxetine exhibits both direct and indirect immunomodulatory and anti-inflammatory effects. Indirect effects are primarily mediated through the serotonergic system.[7–9] Fluoxetine itself influences inflammatory pathways independently of serotonin. Such direct anti-inflammatory actions arise from interactions with factors and pathways, such as NF-κB, NLRP3 inflammasome, and Glycogen synthase kinase-3beta (GSK-3β) as well.[10–13]

Studies report that fluoxetine possesses considerable anti-inflammatory properties via modulating various inflammatory and pro-inflammatory mediators.[14] In patients with depression, fluoxetine administration normalized initially elevated plasma levels of the pro-inflammatory factors.[15,16] Fluoxetine significantly reduced IFN-γ levels while elevating IL-10 in depressed patients.[17] Almeida and colleagues performed a systematic review and meta-analysis, showing that fluoxetine directly modulates pro-inflammatory cytokines in depression.[18] Moreover, fluoxetine improves manifestations in other types of CNS disorders ranging from multiple sclerosis, traumatic brain injury, stroke, and epilepsy to Parkinson's, Huntington's, and Alzheimer's disease.[19] Fluoxetine improved neurological function in subarachnoid hemorrhage (SAH) via attenuating neuroinflammatory pathways.[20] Chronic fluoxetine treatment also ameliorated dysregulated inflammatory gene expression and PTSD-like symptoms.[21] Fluoxetine also inhibited degeneration of nigrostriatal dopamine neurons, enhanced striatal dopamine concentrations, and promoted partial motor recovery. This was accompanied by suppressing transient expression of pro-inflammatory elements along with microglial activation. These findings reveal that fluoxetine possesses anti-inflammatory properties and limits glial activation-mediated oxidative stress.[22]

The anti-inflammatory effects of fluoxetine appear to involve multiple mechanisms, including modulation of the NLRP3 inflammasome and autophagy.[23,24] The NLRP3 inflammasome is a key innate immune complex whose dysregulation contributes to various neuroinflammation-related CNS diseases,[25] while autophagy serves as a cellular degradation pathway that can limit excessive inflammasome activity.[26]

This review explores how fluoxetine modulates the NLRP3 inflammasome–autophagy crosstalk, providing insights into its neuroprotective potential. It highlights recent understanding of fluoxetine's molecular actions and proposes future research directions to elucidate its regulatory function. Investigating fluoxetine's impact on this crosstalk represents an exciting frontier in neuropharmacology, potentially expanding its applications across CNS disorders.

The NLRP3 Inflammasome

The NLRP3 inflammasome plays a vital function in the pathophysiology of numerous diseases, including central nervous system disorders.[25,27] This multiprotein complex consists of three main components: NLRP3, ASC, and pro-caspase-1.[28] Activation is initiated by different stimuli, which trigger intracellular mechanisms such as potassium efflux, lysosomal rupture, and mitochondrial dysfunction. The NLRP3 inflammasome activation proceeds through two phases: priming and activation. In the priming phase, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are detected by their receptors, which consequently promote the nuclear factor kappa B (NF-κB) signaling. Activation of NF-κB pathway initiates its translocation to the nucleus thereby increasing transcription of NLRP3, pro-IL-1β, and pro-IL-18. In the activation phase, NLRP3 undergoes oligomerization in an attempt to form a complex consisting of NLRP3, ASC, and pro-caspase-1. This leads to

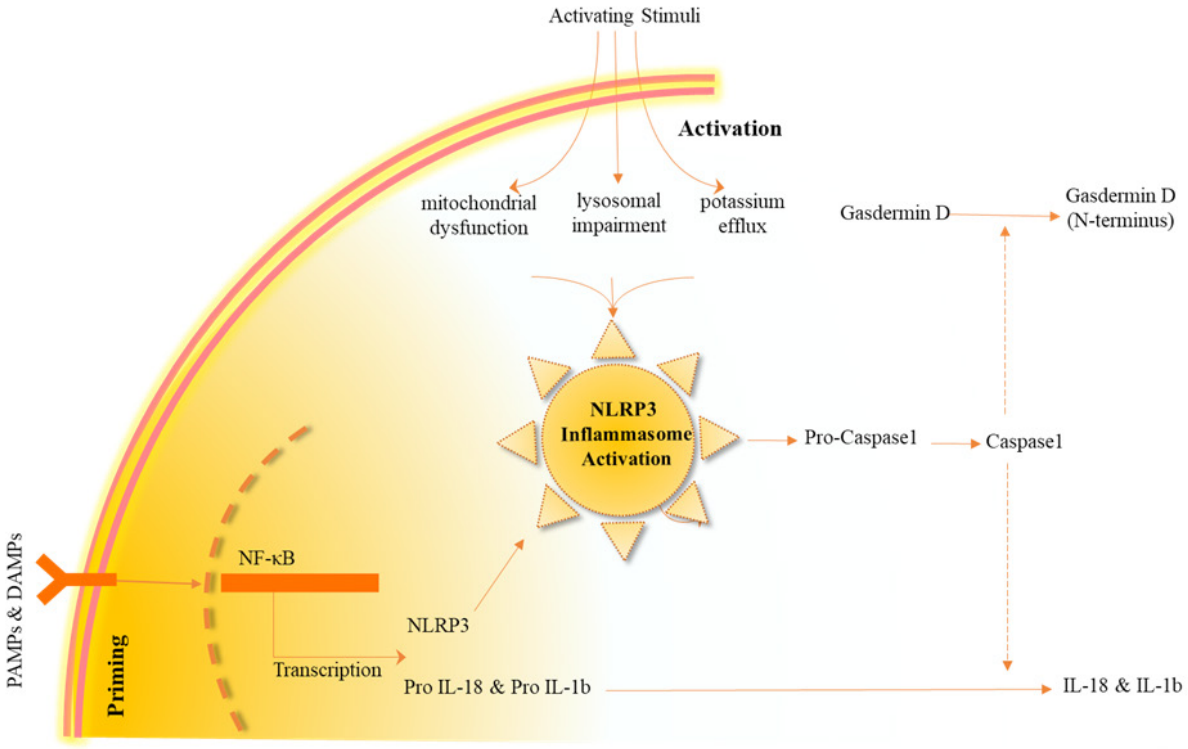

Fig. 1 **The NLRP3 inflammasome activity occurs through two main stages: priming and activation. During priming, after detection of PAMPs and DAMPs, the NF-κB pathway is initiated, which enhances the expression level of NLRP3 and the pro-forms of IL-1β and IL-18. The activation stage is triggered upon detecting activating stimuli, which leads to several upstream events such as potassium efflux, lysosomal damage, and mitochondrial dysfunction. NLRP3 protein then assembles with ASC and pro-caspase-1 to form the NLRP3 inflammasome complex that activates caspase-1. Activated caspase-1, in turn, processes pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18. Caspase-1 also cleaves gasdermin D to produce gadermin D (N-terminus), causing pyroptosis. PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; NF-κB, nuclear factor-κB; NLRP3, Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; IL-18, Interleukin-18; IL-1β, Interleukin-1β.**

the formation of active caspase-1, which then cleaves the precursors of IL-1β and IL-18 into their biologically active mature forms. Moreover, this active form of caspase-1, following activation of the NLRP3 inflammasome, can cleave gasdermin D (GSDMD), which ultimately induces an inflammatory form of programmed cell death known as pyroptosis Figure 1.[25]

The NLRP3 Inflammasome Activation and Neuroinflammation

Upon detection of PAMPs and DAMPs, the NLRP3 inflammasome acts beneficially in the early phases of neuroinflammation which results in enhancing the ability of host to remove pathogens and endogenous danger signals.[29,30] However, chronic inflammation mediated by abnormal, long-term over-activation of NLRP3 inflammasome causes sustained release of pro-inflammatory factors. This, in turn, leads to neuron damage and degeneration in CNS, indicating the crucial and complicated function of NLRP3 in neuroinflammation.[30] Furthermore, such over-activity in the inflammasome can initiate inflammatory reactions in glial cells, bringing about excessive secretion of many pro-inflammatory cytokines. This situation not only triggers the progression of neuroinflammation but also impairs neuronal survival and recovery process.[31]

Over-activation of this inflammasome complex has a close relation to the pathogenesis of numerous neurological diseases such as Alzheimer's disease, Parkinson's disease, stroke, and spinal cord injury.[32,33] Studies have also exhibited that targeting the NLRP3 inflammasome holds promise as a treatment strategy for central nervous system (CNS) disorders.[34–39] MCC950 (a highly selective and potent inhibitor of the NLRP3 inflammasome) has demonstrated significant neuroprotective effect via ameliorating neuroinflammation and related pathology in animal models.[30,40]

In Alzheimer's and Parkinson's disease, amyloid β and synuclein aggregates respectively initiates the activation of NLRP3 inflammasome and elevates secretion of inflammatory cytokines, IL-1β and IL-18. This promotes immune cell recruitment and sustains neuroinflammation that worsens neuronal injury and dysfunction.[41,42] It has also been demonstrated that stroke causes significant upregulation of NLRP3 expression. Activation of the NLRP3 inflammasome serves a pivotal function in driving the inflammatory responses to ischemic stroke.[29] Franke and colleagues observed that the expression of NLRP3 and related inflammasome genes increased 20–30 times in 24 hours following the stroke. They revealed after the onset of stroke, the NLRP3 inflammasome up-regulation happened in neurons, glia, and vascular endothelia, bringing about blood–brain barrier (BBB) dysfunction. They also reported that the

administration of NLRP3 inhibitor MCC950 decreased infarct volumes and protected BBB integrity in ischemic stroke.[43] Furthermore, previous studies exhibited that NLRP3 expression levels were markedly elevated in rodents with spinal cord injury (SCI).[34–39,44] Consistently Wu and colleagues showed that SCI can activate the NLRP3 inflammasome with a subsequent increment in the pyroptosis.[45] It was also clinically revealed that the level of NLRP3 and gasdermin D (marker of pyroptosis) expression in the peripheral blood samples of SCI patients markedly increased and was positively associated with the severity of the injury.[46] It is essential to realize the critical function of the NLRP3 inflammasome in neuroinflammation and neurological diseases in an attempt to develop novel therapeutic strategies. Hence, further investigation is required to delicately discover the association between CNS disorders and the over-activation of this inflammasome.

The Bidirectional Crosstalk of NLRP3 Inflammasome and Autophagy

Autophagy

Autophagy is a crucial self-regulating process that maintains cellular homeostasis. During this phenomenon, pathogens, misfolded proteins, and damaged organelles are enveloped by double-layered membranes, forming structures known as autophagosomes. These autophagosomes are subsequently delivered to lysosomes, where the enclosed materials undergo degradation.[47] Autophagy can be categorized into three main types: macroautophagy, microautophagy, and chaperone-mediated autophagy, based on the type of contents and the mechanism for carrying these contents to lysosomes. In macroautophagy, degradable components are encapsulated by a bilayer membrane, resulting in the formation of autophagosomes, which then fuse with lysosomes to form autolysosomes, where the cytoplasm is degraded.[48,49] Microautophagy involves the direct invagination of the lysosomal membrane, allowing it to engulf cellular contents.[50] In chaperone-mediated autophagy, specific intracellular proteins that are bound to molecular chaperones are directed to lysosomes for degradation by lysosomal enzymes. In this type of autophagy, chaperones such as Hsc70 detect the KFERQ peptide motif in target proteins. Then, the lysosomal-associated membrane protein 2 (LAMP2A) is recognized by Hsc70, leading to the unfolding and translocation of the target protein into the lysosomal lumen, where degradation then occurs, as shown in Figure 2.[51,52] Enhanced autophagy allows cells to initiate the removal of abnormal proteins, which helps cell survival during pathological conditions.[53] Certain conserved

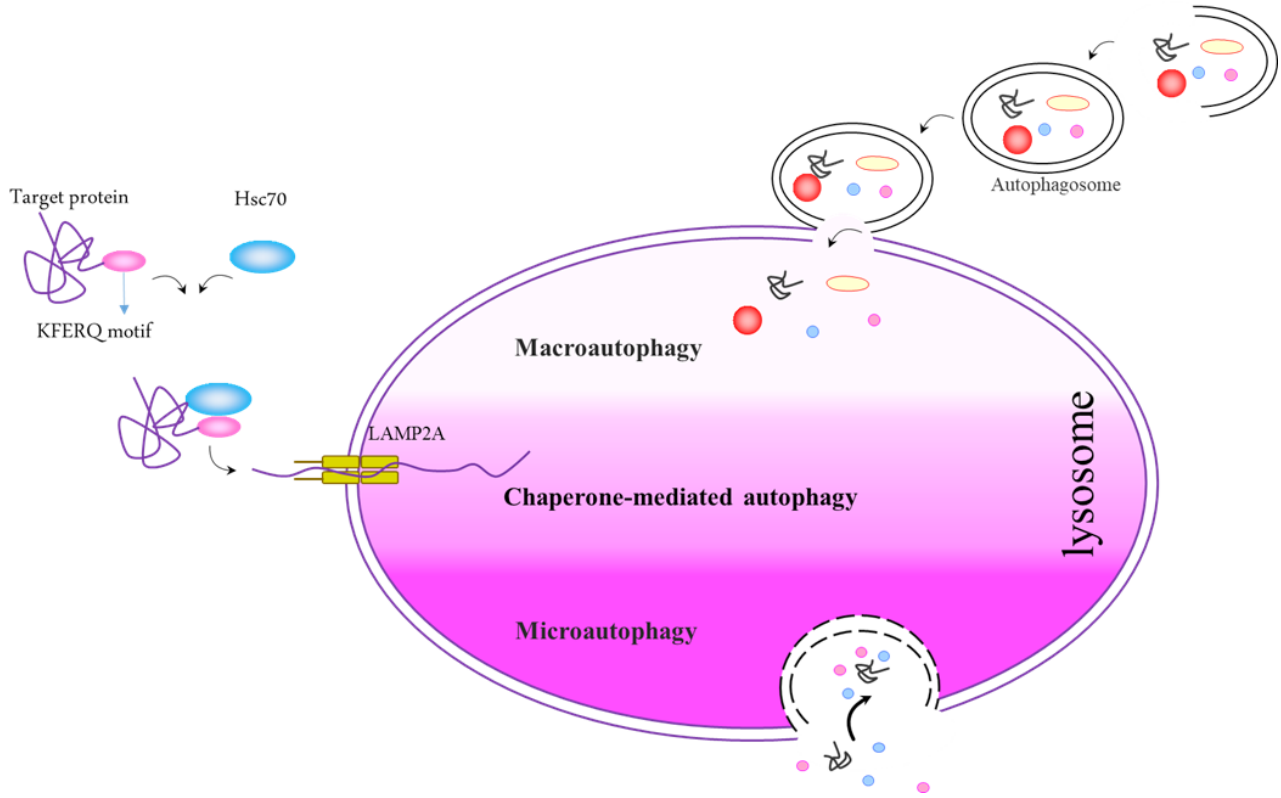

Fig. 2 **Autophagy represents an important cellular process wherein cells deliver degradable content to lysosomes for degradation. This is categorized into three main forms, including macroautophagy, microautophagy, and chaperone-mediated autophagy. In macroautophagy, the contents are engulfed by a double-membrane structure to form autophagosomes, which fuse with lysosomes, where the contents are subsequently degraded by lysosomal enzymes. Chaperone-mediated autophagy refers to a selective process in which intracellular proteins with the KFERQ motif bind to the chaperone protein, heat shock cognate 70 (HSC70). This complex then interacts with lysosomal-associated membrane protein 2 (LAMP2A) on the lysosomal membrane, resulting in unfolding and translocation of the target protein into the lysosome for degradation. Microautophagy involves the direct invagination of the lysosomal membrane to wrap the cytoplasmic contents.**

proteins, including LC3 and Beclin-1, are essential markers of autophagy and are known as autophagy-related proteins. Research demonstrates that autophagy has a pivotal function in preserving the balance between decomposition, synthesis, and reuse of cellular components. Disruptions in this delicate balance can contribute to the development and progression of various pathological states and diseases.[47]

Bidirectional Interaction between the NLRP3 Inflammasome and Autophagy

Evidence indicates a strong relationship between the cellular process of autophagy and inflammasome complexes, particularly the NLRP3 inflammasome. While the molecular signature underpinning the interaction between autophagy and the NLRP3 inflammasome remains poorly understood, their reciprocal regulation is critical for cellular homeostasis. However, in chronic inflammation, this vital crosstalk becomes uncontrolled.[54]

Autophagy negatively modulates the activation of the NLRP3 inflammasome, thereby attenuating the inflammatory response and mitigating tissue damage associated with various diseases.[55] Autophagy moderates the excessive activity of the NLRP3 inflammasome via three main regulatory mechanisms: degradation and reduction of ASC, the enhancement of NLRP3 phosphorylation, and the removal of ROS (Figure 3).[26,56,57] Inhibition of the NLRP3 inflammasome induced by autophagy may be linked to depletion or reduction of ASC within the cells.[55,58] Phosphorylation of NLRP3 facilitates its inactivation by enhancing autophagic degradation, consequently preventing the NLRP3 inflammasome activity.[59,60] Furthermore, autophagy has the capacity to inhibit the production of IL-1β and IL-18 triggered by the activation of the NLRP3 inflammasome, through the elimination of mitochondrial ROS.[61]

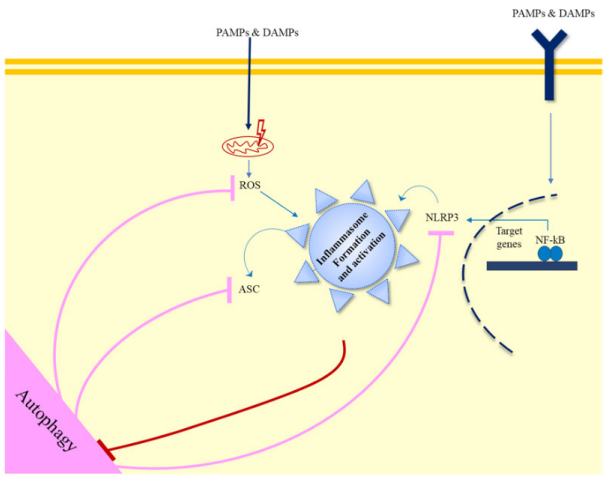

Fig. 3 **Autophagy limits hyper-activation of the NLRP3 inflammasome through three main ways: clearance of reactive oxygen species (ROS), degradation and reduction of ASC as well as increasing NLRP3 phosphorylation, thereby mediating the inactivation of NLRP3 by promoting its autophagic degradation. Conversely, activation of the NLRP3 inflammasome limits the autophagy process.**

By affecting NLRP3 inflammasome, autophagy is fundamental in the development and treatment of many disorders, including CNS diseases associated with neuroinflammation.[57] Andrographolide, a natural product with evident anti-inflammatory activities, alleviates depression in mice through preventing NLRP3 inflammasome-mediated inflammatory damage via the induction of autophagy.[62] In addition, autophagy within microglia contributes to degradation of extracellular amyloid fibers and is crucial for regulating β-amyloid fiber-mediated inflammatory reactions. Suppression of autophagy elevated the NLRP3 inflammasome activity, demonstrating that autophagy acts as a negative regulator of NLRP3 inflammasome induced by β-amyloid fibers.[63] Consistent with these results, Kaempferol (Ka), a flavonoid isolated from medicinal plants, improves neurodegeneration via inducing NLRP3 degradation through autophagic pathways. These results were further confirmed in vivo, as knockdown of Atg5 or administration of autophagy inhibitors markedly reversed the Ka-mediated NLRP3 inflammasome suppression as well as neurodegeneration attenuation in Parkinson's disease.[64]

Conversely, the NLRP3 inflammasome has the potential to limit the autophagy process. For example, activation of the NLRP3 inflammasome can suppress the signaling that induces autophagy, thereby exerting an inhibitory effect on autophagy[26,55,65] (Figure 3). Collectively, this complex interaction between NLRP3 inflammasome and autophagy is crucial for the equilibrium between the necessary inflammatory responses of host defense and the mitigation of deleterious excessive inflammation. Accordingly, in the context of neuroinflammation, the NLRP3-autophagy interplay can be a promising target for the therapy of many diseases such as CNS disorders.[57,66,67]

Neuroprotective Effect of Fluoxetine via Targeting the Complex Crosstalk of the NLRP3 Inflammasome and Autophagy

Fluoxetine Suppresses the NLRP3 Inflammasome Activity

Ambati and colleagues found that fluoxetine directly interacts with and inhibits the NLRP3 protein, thereby preventing the inflammasome assembling and subsequent IL-1β release in retinal pigmented epithelium and macrophage cells.[11] Pan et al. reported that a chronic stress procedure significantly activated the NLRP3 inflammasome and enhanced the levels of proinflammatory cytokines such as IL-1β in rat brain. They reported that these alterations were markedly reversed with chronic treatment of fluoxetine.[68] Moreover, Du et al. confirmed that fluoxetine effectively inhibits NLRP3 inflammasome activation both in vitro and in vivo. Fluoxetine reduces the expression of NLRP3 and pro-IL-1β, and suppresses caspase-1 activation, as well as IL-1β maturation, which indicates inhibition of both priming and activation signals of the NLRP3 inflammasome. They found that the molecular mechanism underlying fluoxetine's inhibition of NLRP3 inflammasome activation involves the reduction of ROS production, which is a known activator of the NLRP3 inflammasome.[24] Fluoxetine also suppresses neuroinflammation and neuronal apoptosis induced by sleep deprivation. This drug

reverses the stimulation of NLRP3 inflammasome expression and function by sleep deprivation via STAT3 activation.[69] Additionally, fluoxetine ameliorates Alzheimer's disease progression in depressed animals via activation of Nrf2/HO-1 and hindering TLR4/NLRP3 inflammasome signaling pathways[70] (see Figure 4).

Fluoxetine and Autophagy

Fluoxetine can significantly induce autophagy in the living cells.[71,72] It exhibits autophagy enhancement in lymphoma and triple-negative breast cancer cells which result in effective inhibition of tumor growth[73] The pro-autophagic effect of fluoxetine was also evaluated in human gastric adenocarcinoma cells.[74] In addition, Sun et al. showed that fluoxetine reduces the proliferation and differentiation of stem cells, likely through increasing the expression of the autophagy-related genes.[75] It also triggers autophagy in a rodent subarachnoid hemorrhage brain injury model.[76] Fluoxetine alleviates depressive symptoms and enhances the amount of BDNF and autophagy markers (ATG5, Beclin-1, and LC3II) in mice.[77] This drug enhances the autophagic pathways and clearance of damaged mitochondria in rodent model of depression and astrocyte cultures.[78] Additional in vitro studies showed fluoxetine initiates astrocytic autophagy in a mechanism depending on p53.[78] Microglia exposed to fluoxetine display a marked increment in LC3 puncta, suggesting that fluoxetine promotes autophagy and enhances autophagic flux.[23]

Fluoxetine Targets Crosstalk of the NLRP3 Inflammasome and Autophagy

Fluoxetine inhibits the NLRP3 inflammasome in cell culture, depressed animals, and patients, as evidenced by reduced serum levels of IL-1β, IL-18, and NLRP3 protein.[79] To find whether this inhibition depends on autophagy, autophagy-deficient cells were treated with ATP (to activate the inflammasome) and fluoxetine. In wild-type cells, fluoxetine inhibited ATP-induced NLRP3 activation, accompanied by increased LC3B-II and decreased active caspase-1, whereas in autophagy-deficient cells, fluoxetine failed to suppress NLRP3 activity. LC3B-II levels did not increase, active caspase-1 remained elevated, and IL-1 secretion continued. These results show that fluoxetine blocks the NLRP3 inflammasome via autophagy induction in depression.[79] It reduces NLRP3 expression, cleaved caspase-1, IL-1β, and IL-18 in subarachnoid hemorrhage (SAH), while decreasing cell death, brain edema, and neurological deficits. Consistent with prior autophagy dependence findings, using an autophagy inhibitor blocked these benefits, confirming that fluoxetine enhances neuroprotection by promoting autophagy to suppress NLRP3 activation.[76]

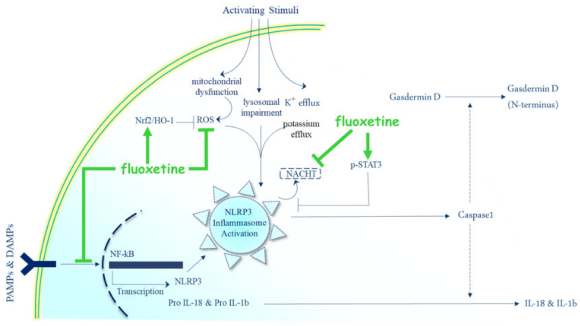

Fig. 4 **Fluoxetine limits the activity of the NLRP3 inflammasome through several ways. It directly binds to the NACHT domain of NLRP3 protein and suppresses formation and activation of the NLRP3 inflammasome. Furthermore, fluoxetine inhibits TLR4/NF-κB pathway which results in decrement in the gene expression of the NLRP3, pro-IL-1β and pro-IL-1β subsequently lowering assembly and activation of the NLRP3 inflammasome. Fluoxetine's inhibition of NLRP3 inflammasome also involves the reduction of ROS production. Fluoxetine decreases ROS production through activating Nrf2/HO-1 pathway. In addition, fluoxetine reverses the stimulation of NLRP3 inflammasome through elevating the activation of STAT3.**

Although these findings are encouraging, looking more closely at the available studies reveals key gaps and limitations that should be addressed. For example, preclinical investigations use relatively high fluoxetine doses in rodent models that do not match typical human doses. This potentially brings about additional drug effects that are independent of its primary SERT inhibition mechanism. Additionally, the connection between fluoxetine-triggered autophagy and NLRP3 inhibition is usually assumed from studies using pharmacologic inhibition, rather than more specific genetic methods. This leaves open questions about the exact signaling pathways, the particular cell types involved, and how different fluoxetine doses shape its regulatory effects on NLRP3–autophagy crosstalk.

The preceding investigations have provided further details regarding the modulatory impact of fluoxetine on the crosstalk of NLRP3 inflammasome and autophagy. Nevertheless, the precise function of fluoxetine in this complicated interplay remains poorly understood. Therefore, further investigations are required in order to assess the precise regulatory function of fluoxetine on this crosstalk.

Based on our literature review of existing studies, there are several key molecules linking autophagy to the NLRP3 inflammasome in the crosstalk between them, which highlight such molecules as promising targets for further investigations.[26,54,55,57,80,81] Hence, in the following paragraphs, we further discuss a number of these crucial molecules, alongside an explanation of how fluoxetine may govern the crosstalk between autophagy and the NLRP3 inflammasome through these invaluable targets.

The first molecule, SQSTM1/p62 protein, possesses a crucial function in the interaction among autophagy and the NLRP3 inflammasome. As previously noted, autophagy consistently removes damaged mitochondria that produce reactive oxygen species (ROS) to limit additional ROS generation, thus preventing the activation of the NLRP3 inflammasome. E3 ubiquitin ligase Parkin marks damaged mitochondria by ubiquitinating their outer membrane proteins, tagging them for autophagic removal.[82] It has been proposed that SQSTM1/p62 plays a crucial role in the autophagic removal of damaged mitochondria following NLRP3 activation. After NLRP3 activation, p62 is recruited to damaged mitochondria, a process that necessitates Parkin-mediated decoration of these mitochondria with poly-ubiquitin chains. Therefore, p62-mediated mitophagy (removal of damaged mitochondria through autophagy) might negatively modulate the NLRP3 inflammasome

activity via removing damaged mitochondria.[26,83-85] In addition, SQSTM1/p62 interacts with NLRP3 protein, the key part of the NLRP3 inflammasome, facilitating degradation of NLRP3 protein via autophagy. This interaction leads to the recognition and binding of ubiquitin-modified NLRP3 by p62, resulting in the engulfment and degradation of NLRP3 protein and subsequent regulation of the excessive inflammasome activation. Pharmacological prevention of autophagy and the depletion of p62 significantly increased NLRP3 inflammasome activity.[26,54,86,87] Emerging evidence shows that fluoxetine exerts its pro-autophagic property by increasing the levels of SQSTM1/p62 in different cells. Fluoxetine has been found to significantly increase the mRNA and protein levels of SQSTM1/p62 in human adipose-derived stem cells, indicating that it promotes autophagic flux in vitro.[75] Likely Shao et al. confirmed the interaction of fluoxetine with SQSTM1/p62 by a marked increment in the levels of SQSTM1/p62 in the fluoxetine-treated cancer cells in a dose- and time-dependent manner.[88] In conclusion, it is suggested that more investigations are required to delicately explore the potential of fluoxetine in reducing NLRP3 inflammasome activation through the enhancement of p62/SQSTM1-dependent selective autophagy. An essential step in pursuing such a meticulous inquiry involves examining whether fluoxetine could facilitate the co-localization of NLRP3 and p62. Additionally, it is important to assess the impact of p62 knockdown on the attenuating effects of fluoxetine on the NLRP3 inflammasome. Indeed, more investigations are required to elucidate whether fluoxetine affects this crosstalk particularly by autophagic degradation of the NLRP3 Inflammasome components and its endogenous stimulators such as mitochondrial ROS, due to the central role of p62/SQSTM1 in these processes.

In addition to p62/SQSTM1, TRIM20 is another key molecule for autophagic degradation of the inflammasome components via interacting with these components. This protein acting as an autophagy receptor can be an interesting regulatory molecule in the crosstalk of autophagy- NLRP3 inflammasome. TRIM20 has been demonstrated to interact with the inflammasome proteins, NLRP3, ASC, caspase-1, for delivery of them for autophagic degradation.[26,81,89,90] This selective autophagy mechanism involves TRIM20 directly binding to the NLRP3 inflammasome components and recruiting the autophagic machinery for degradation offering potential therapeutic benefits in managing these conditions.[89,91] Moreover, as shown in Figure 3, it has been proposed that phosphorylation of NLRP3 brings about its inactivation leading to its degradation in an autophagy-dependent manner. In fact, NLRP3 activity is inhibited by tyrosine phosphorylation, while protein tyrosine phosphatase non-receptor 22 (PTPN22) removes phosphate groups from NLRP3 following its activation.[58] It has been reported that only the phosphorylated version of NLRP3 can interact with p62 and be recruited into the phagophore. In contrast, NLRP3 that lacks the phosphorylation site does not engage with p62 and is not sequestered into the phagophore.[60] Hence, targeting TRIM20 and/or PTPN22 can be another potential therapeutic strategy in fluoxetine therapy by modulating the balance among autophagy and the NLRP3 inflammasome in an attempt to limit inflammatory responses.

Another target with an important function in the crosstalk of autophagy and the NLRP3 inflammasome may be CCDC50.[54,92] Lin and colleagues reported that coiled-coil domain-containing 50 (CCDC50), a novel autophagy cargo receptor, negatively regulates NLRP3 inflammasome assembly and activation and prevents the breakdown of pro-caspase-1 and IL-1β release by delivering NLRP3 protein for autophagic degradation. They also demonstrated that CCDC50 deficiency poses elevated proinflammatory cytokine response initiated by elevated NLRP3 inflammasome activity.[93] Importantly, the research concerning the involvement of the aforementioned molecular targets such as TRIM20, PTPN22 and CCDC50 in the context of fluoxetine therapy is currently absent. The substantial involvement of these targets in autophagy-NLRP3 inflammasome crosstalk implies a necessity for further investigation to determine if fluoxetine exerts its therapeutic impact on the autophagy-NLRP3 interplay through these molecular targets or not.

Taken together, the importance of the NLRP3 inflammasome and autophagy in the pathophysiology of various disorders renders these cellular systems highly appealing as therapeutic targets. As a result, a wide variety of NLRP3 inflammasome inhibitors or autophagy enhancers have been identified, with several already being utilized in clinical settings for diverse medical conditions.[94-96] Evidence from preclinical investigations strongly supports the therapeutic potential of more effective modulators that can regulate the autophagy–NLRP3 inflammasome interplay, than individually addressing each pathway.[54] In this regard, the repurposing of fluoxetine has demonstrated encouraging neuroprotective effects via affecting the crosstalk of the autophagy and the NLRP3 inflammasome. This suggests a potential breakthrough in understanding and treating related neurological conditions. Future studies aiming to explore the neuroprotective effect of fluoxetine through targeting the interplay of autophagy and NLRP3 should address several key questions and considerations. Firstly, investigations are recommended to concentrate on elucidating the precise molecular events by which fluoxetine modulates autophagy and NLRP3 activation. It should be answered the exact regulatory role of fluoxetine via autophagic clearance of endogenous NLRP3 inflammasome stimulators (e.g., ROS) and/or autophagic breakdown of the NLRP3 inflammasome components in association with other key molecules such as p62/SQSTM1, TRIM20, PTPN22 and CCDC50. Of interest, the potential synergistic effects of combining fluoxetine with other compounds targeting the crosstalk of the NLRP3 inflammasome and autophagy, such as HDAC6 inhibitors, should be more studied to enhance therapeutic outcomes in treatment of those CNS disorders such as depression.[54,80,97] HDAC6 appears to play a crucial function where NLRP3 assembly/activation and autophagy converge.[54,80] Previous studies demonstrate that HDAC6 inhibition can enhance the anti-depressive effect of fluoxetine.[97-99] Overall, future studies should aim to elucidate the exact underlying mechanisms and key players by which fluoxetine modulates autophagy and NLRP3 activation, and the potential synergistic effects of combining fluoxetine with other compounds targeting the crossrtalk of the NLRP3 inflammasome and autophagy.

Conclusion and Future Perspectives

Fluoxetine's multifaceted role in modulating the complicated interaction between autophagy and the NLRP3 inflammasome presents a promising therapeutic avenue for CNS

disorders. The neuroprotective effects of fluoxetine, driven by its dual capacity as a pro-autophagic agent and an NLRP3 inflammasome inhibitor, highlight its potential to restore cellular homeostasis and mitigate inflammatory pathways that underlie many CNS disorders.

Fluoxetine has been shown to inhibit NLRP3 inflammasome activation through various mechanisms, such as direct binding to NLRP3 protein, preventing mitochondrial ROS production, and promoting autophagic degradation of the inflammasome components. Additionally, fluoxetine significantly enhances autophagic pathways, as evidenced by increased levels of key autophagic markers like LC3 and Beclin-1.

The intricate crosstalk between autophagy and the NLRP3 inflammasome is critical in maintaining neuronal health and preventing excessive neuroinflammation, a key contributor to the pathogenesis CNS disorders. As we deepen our understanding of fluoxetine's interactions with key regulatory molecules involved in this vital crosstalk, we may open new research directions to fully elucidate its therapeutic mechanisms.

Future studies should focus on the precise molecular interactions through which fluoxetine regulates the autophagy-NLRP3 interplay. Furthermore, investigating the synergistic effects of combining fluoxetine with other modulators of the autophagy-NLRP3 crosstalk could enhance therapeutic outcomes, unlocking new avenues for treatment that could significantly improve outcomes for patients with depression and related conditions.

Conflict of Interest

The authors declare no conflict of interest.

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