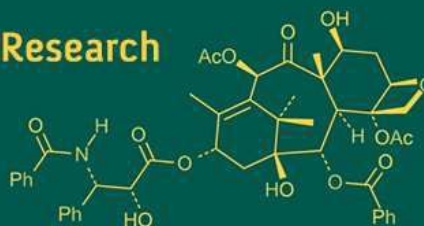


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
NAAS Rating (2026): 5.29
IJABR 2026; 10(1): 1138-1140
www.biochemjournal.com
Received: 23-11-2025
Accepted: 26-12-2025

Priyanka M
ICAR-Indian Veterinary
Research Institute (IVRI),
Izatnagar, Bareilly, Uttar
Pradesh, India

Kanchan S
ICAR-Indian Veterinary
Research Institute (IVRI),
Izatnagar, Bareilly, Uttar
Pradesh, India

Pashupathi M
College of Veterinary and
Animal Sciences (CoVAS),
Rani Lakshmi Bai Central
Agricultural University
(RLBCAU), Jhansi, Uttar
Pradesh, India

Molecular interaction of α -synuclein with P2X7 receptor

Priyanka M, Kanchan S and Pashupathi M

DOI: <https://www.doi.org/10.33545/26174693.2026.v10.i1n.7227>

Abstract

Alpha-synuclein (α -Syn) is a neuronal protein predominantly located at presynaptic terminals, where it interacts with synaptic vesicle membranes and facilitates neurotransmitter release under normal physiological conditions [18]. Its abnormal aggregation is a hallmark of synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy [23]. The purinergic receptor P2RX7, in contrast, is an ATP-gated transmembrane ion channel that becomes active during acute and chronic inflammatory states [12]. Activation of P2RX7 by ATP triggers pore formation, influx of multiple cations, and downstream effects ranging from cell proliferation to cytotoxicity. Prolonged activation can lead to receptor desensitization, excessive pore dilation, cell death, and amplified inflammation [6]. Recent studies suggest a functional interplay between α -Syn and P2RX7, which promotes mitochondrial impairment, elevated reactive oxygen species (ROS), oxidative stress, and neuroinflammation [26]. Computational analyses, including molecular docking and dynamics simulations, have identified the N-terminal region of α -Syn as a key mediator of its binding to P2RX7 [21]. Understanding this interaction sheds light on the mechanisms underlying synucleinopathies and highlights P2RX7 as a potential target for therapeutic interventions [14].

Keywords: Alpha-synuclein, P2RX7, neuroinflammation, synucleinopathies, oxidative stress

Introduction

Alpha-synuclein

Researchers have identified and sequenced two proteins in the human brain, consisting of 140 and 134 amino acids, respectively. These proteins, alpha-synuclein (140 amino acids) and beta-synuclein (134 amino acids), share 61% sequence identity. Both are predominantly expressed in the brain and are concentrated in presynaptic nerve terminals. The name "alpha-synuclein" originates from its discovery on synaptic vesicles and nuclear envelopes isolated from the Torpedo electric organ [5].

The α -synuclein protein, encoded by the SNCA gene on the long arm of chromosome 4 (4q22.1), has a molecular weight of approximately 15 kDa [2]. Under normal physiological conditions, α -synuclein associates with synaptic vesicle membranes, facilitating neurotransmitter release via the SNARE complex. When α -synuclein becomes abnormal or forms toxic aggregates, this process is disrupted, leading to impaired vesicle clustering and inefficient SNARE complex assembly. Such disruptions can compromise neuronal communication and contribute to long-term neuronal damage and cell death [10].

The misfolding and aggregation of α -synuclein into amyloid fibrils are key features of several neurodegenerative disorders, collectively termed synucleinopathies [8, 20]. Its aggregation propensity is further enhanced by post-translational modifications, including phosphorylation, ubiquitination, nitration, and truncation [3]. α -Synuclein is distributed across multiple cellular compartments, including the nucleus, mitochondria, endoplasmic reticulum, Golgi apparatus, lysosomes, and synaptic vesicles [22].

Structure of α -Syn

Alpha-synuclein (α -Syn) is composed of three distinct domains. The N-terminal domain (residues 1-60) is α -helical in structure and exhibits membrane-binding properties. The non-amyloid- β component (NAC) domain (residues 61-95) is highly prone to aggregation, forming amyloid fibrils and protofibrils. The C-terminal domain (residues 96-140) is rich in anionic residues [9]. Structurally, α -Syn can exist as an intrinsically disordered protein, adopt

Corresponding Author:
Priyanka M
ICAR-Indian Veterinary
Research Institute (IVRI),
Izatnagar, Bareilly, Uttar
Pradesh, India

helical conformations, or display a combination of both [16]. The N-terminal region contains several amphipathic 11-residue repeats, including the KTKEGV consensus sequence, which is a hotspot for familial mutations [4]. Alterations in α -Syn structure and function lead to its extracellular accumulation and fibril formation, ultimately causing damage to surrounding cells [11].

P2RX7

De Salis *et al.* (2022), report that P2X receptors are classified into seven subtypes, P2X1 through P2X7, each encoded by distinct genes. Among these, the P2X7 receptor (P2X7R), encoded by the P2RX7 gene, is notable for its unique structure and functional properties [6]. Structurally, P2X7R is a trimeric receptor that functions as a non-selective cation channel activated by elevated extracellular ATP levels. Prolonged stimulation of P2X7R can lead to the formation of a large membrane pore, promoting cell death and increased ATP release into the extracellular environment [1]. This receptor allows the passage of small cations such as Ca^{2+} , Na^{+} , and K^{+} , and in certain cell types, it can also transport larger positively charged molecules up to 900 Da in size [7].

P2X7R is widely expressed throughout the central nervous system and is implicated in the pathophysiology of several neurodegenerative and psychiatric disorders [7]. The human P2RX7 gene is located on chromosome 12q24.31, while in mice it is found on chromosome 5; it comprises 13 exons and encodes a 595-amino acid subunit. Before 2019, structural models of P2X7R were primarily based on X-ray crystallography, which, however, had limitations in accurately resolving the receptor's intracellular domains [13].

Structure

In 2019, McCarthy and colleagues used cryogenic electron microscopy to elucidate the full structure of the rat P2RX7 receptor for the first time. Each P2RX7 subunit possesses intracellular N-terminal and C-terminal regions, two hydrophobic transmembrane domains, and a large extracellular loop that contains the ATP-binding site [6, 28]. Structurally, the P2X7 receptor subunit has a dolphin-like appearance, with the extracellular domain forming the head and fins and the two transmembrane helices (TM1 and TM2) forming the tail [15].

Robinson *et al.* (2014), observed that P2X7 receptors situated in cholesterol-rich lipid rafts are regulated in their pore-forming capacity by the membrane's cholesterol content. Lipid rafts, characterized by high levels of cholesterol and sphingolipids, provide a supportive environment for receptor function. Elevating cellular cholesterol inhibits pore formation, whereas acute cholesterol depletion using methyl- β -cyclodextrin (MCD) enhances pore formation in response to agonists [19]. Cholesterol may exert its inhibitory effect either by directly binding to the P2X7 receptor or by altering membrane properties, though the precise mechanism remains unclear [17].

Alpha-Synuclein and P2RX7 interaction

Multiple studies have highlighted the pivotal role of the purinergic receptor P2RX7 in α -synuclein induced mitochondrial dysfunction and neuroinflammation. Wilkaniec *et al.* (2020), reported that α -synuclein interaction with P2RX7 impairs mitochondrial function, elevates

oxidative stress, and activates cytokines and immune cells, thereby initiating inflammatory responses. Additionally, increased extracellular ATP has been shown to activate P2RX7 in tumor microenvironments, enhancing antitumor immunity and underscoring the receptor's broader immunomodulatory functions [26, 12].

Singh *et al.* (2024), provided further mechanistic insight using integrated computational methods, including data curation, molecular docking, molecular dynamics (MD) simulations, and structural analyses. Their results demonstrated that the N-terminal domain of α -synuclein preferentially binds to the proximal region of P2RX7's transmembrane domain. Microsecond-scale MD simulations within a lipid bilayer revealed that this binding induces significant structural fluctuations in P2RX7, particularly in regions involved in pore dilation, receptor desensitization, and calcium transport. Additional analyses of structural networks, residue contacts, and solvent accessibility identified key amino acids mediating this interaction [21, 14]. Supporting these findings, Wei *et al.* (2025), showed that α -synuclein binding to the P2X7R transmembrane domain triggers reduced complex I activity of mitochondria. Furthermore, P2X7R activation recruits pannexin-1, forming large membrane pores that amplify oxidative stress and cellular damage. Together, these studies establish P2X7R as a central mediator of α -synuclein driven mitochondrial dysfunction, oxidative stress, neuroinflammation, and neurodegeneration [25].

Discussion

α -Synuclein (α -Syn) is an intrinsically disordered protein predominantly expressed in neural tissues, where it plays a vital role in synaptic vesicle remodeling and neurotransmission [18, 24]. Alterations in its structure or function are closely associated with neurological disorders, including Parkinson's disease (PD) and Alzheimer's disease [8, 20]. P2RX7, an ATP-gated transmembrane ion channel, is activated during both acute and chronic inflammatory states [12]. Prolonged activation of P2RX7 can lead to receptor desensitization, pore overstretching, cell death, and exacerbated inflammation [6]. Recent evidence indicates that α -Syn directly interacts with P2RX7, activating the receptor and promoting pore dilation, which contributes to mitochondrial dysfunction [27, 26]. Computational studies, including data curation, molecular docking, molecular dynamics (MD) simulations, and structural analyses, suggest that the N-terminal domain of α -Syn preferentially binds near the transmembrane region of P2RX7 [21, 14]. Furthermore, Wei *et al.*, (2025) demonstrated that this interaction induces excessive Ca^{2+} influx, mitochondrial depolarization, complex I impairment, and reactive oxygen species (ROS) generation. P2RX7 also recruits pannexin-1 to form large membrane pores, amplifying oxidative stress and cellular damage, highlighting its central role in α -Syn-mediated mitochondrial dysfunction, neuroinflammation, and neurodegeneration. Understanding the interaction between P2RX7 and α -synuclein could be helpful in developing therapeutic strategies for diseases like involving these proteins [14].

References

1. Andrejew R, Oliveira-Giacomelli Á, Ribeiro DE, Glaser T, Arnaud-Sampaio VF, Lameu C, *et al.* The

- P2X7 receptor: central hub of brain diseases. *Front Mol Neurosci.* 2020;13:124.
2. Bernal-Conde LD, Ramos-Acevedo R, Reyes-Hernández MA, Balbuena-Olvera AJ, Morales-Moreno ID, Argüero-Sánchez R, *et al.* Alpha-synuclein physiology and pathology: a perspective on cellular structures and organelles. *Front Neurosci.* 2020;13:1399.
 3. Beyer K, Ariza A. Alpha-synuclein posttranslational modification and alternative splicing as a trigger for neurodegeneration. *Mol Neurobiol.* 2013;47(2):509-524.
 4. Bisi N, Feni L, Pegini K, Pérez-Peña H, Onger S, Pieraccini S, *et al.* α -Synuclein: an all-inclusive trip around its structure, influencing factors and applied techniques. *Front Chem.* 2021;9:666585.
 5. Burré J. The synaptic function of α -synuclein. *J Parkinsons Dis.* 2015;5(4):699-713.
 6. De Salis SK, Li L, Chen Z, Lam KW, Skarratt KK, Balle T, *et al.* Alternatively spliced isoforms of the P2X7 receptor: structure, function and disease associations. *Int J Mol Sci.* 2022;23(15):8174.
 7. Di Virgilio F, Jiang LH, Roger S, Falzoni S, Sarti AC, Vultaggio-Poma V, *et al.* Structure, function and techniques of investigation of the P2X7 receptor (P2X7R) in mammalian cells. *Methods Enzymol.* 2019;629:115-150.
 8. Emamzadeh FN. Alpha-synuclein structure, functions, and interactions. *J Res Med Sci.* 2016;21:29.
 9. Fan TS, Liu SCH, Wu RM. Alpha-synuclein and cognitive decline in Parkinson disease. *Life (Basel).* 2021;11(11):1239.
 10. Gao V, Briano JA, Komer LE, Burré J. Functional and pathological effects of α -synuclein on synaptic SNARE complexes. *J Mol Biol.* 2023;435(1):167714.
 11. Ito N, Tsuji M, Adachi N, Nakamura S, Sarkar AK, Ikenaka K, *et al.* Extracellular high molecular weight α -synuclein oligomers induce cell death by disrupting the plasma membrane. *NPJ Parkinsons Dis.* 2023;9(1):139.
 12. Janho Dit Hreich S, Benzaquen J, Hofman P, Vouret-Craviari V. To inhibit or to boost the ATP/P2RX7 pathway to fight cancer that is the question. *Purinergic Signal.* 2021;17(4):619-631.
 13. Karasawa A, Kawate T. Structural basis for subtype-specific inhibition of the P2X7 receptor. *Elife.* 2016;5:e22153.
 14. Kumar M, Singh K, Joshi J, Sharma S, Kumar A, Irungbam K, *et al.* Mechanistic insights into alpha-synuclein binding to P2RX7: a molecular dynamic and docking study. *PLoS One.* 2025;20(5):e0319098.
 15. Martínez-Cuesta MÁ, Blanch-Ruiz MA, Ortega-Luna R, Sánchez-López A, Álvarez Á. Structural and functional basis for understanding the biological significance of P2X7 receptor. *Int J Mol Sci.* 2020;21(22):8454.
 16. Meade RM, Fairlie DP, Mason JM. Alpha-synuclein structure and Parkinson's disease lessons and emerging principles. *Mol Neurodegener.* 2019;14(1):29.
 17. Murrell-Lagnado RD, Kawate T. Methods for studying cholesterol-dependent regulation of P2X7 receptors. In: *The P2X7 receptor: methods and protocols.* New York: Springer; 2022. p.253-264.
 18. Nordengen K, Morland C. From synaptic physiology to synaptic pathology: the enigma of α -synuclein. *Int J Mol Sci.* 2024;25(2):986.
 19. Robinson LE, Shridar M, Smith P, Murrell-Lagnado RD. Plasma membrane cholesterol as a regulator of human and rodent P2X7 receptor activation and sensitization. *J Biol Chem.* 2014;289(46):31983-31994.
 20. Shim KH, Kang MJ, Youn YC, An SSA, Kim S. Alpha-synuclein: a pathological factor with A β and tau and biomarker in Alzheimer's disease. *Alzheimers Res Ther.* 2022;14(1):201.
 21. Singh K, Joshi J, Sharma S, Kumar A, Devi K, Saini M, *et al.* Insights from molecular docking and dynamics simulations of P2RX7- α Syn complex. *bioRxiv.* 2024.
 22. Somayaji M, Lanseur Z, Choi SJ, Sulzer D, Mosharov EV. Roles for α -synuclein in gene expression. *Genes (Basel).* 2021;12(8):1166.
 23. Srinivasan E, Chandrasekhar G, Chandrasekar P, Anbarasu K, Vickram AS, Karunakaran R, *et al.* Alpha-synuclein aggregation in Parkinson's disease. *Front Med.* 2021;8:736978.
 24. Stefanis L. α -Synuclein in Parkinson's disease. *Cold Spring Harb Perspect Med.* 2012;2(2):a009399.
 25. Wei S, Song X, Mou Y, Yang T, Wang Y, Wang H, *et al.* New insights into pathogenesis and therapies of P2X7R in Parkinson's disease. *NPJ Parkinsons Dis.* 2025;11(1):108.
 26. Wilkaniec A, Cieřlik M, Murawska E, Babiec L, Gąssowska-Dobrowolska M, Pałasz E, *et al.* P2X7 receptor is involved in mitochondrial dysfunction induced by extracellular alpha-synuclein in neuroblastoma SH-SY5Y cells. *Int J Mol Sci.* 2020;21(11):3959.
 27. Wilkaniec A, Gąssowska M, Czapski GA, Cieřlik M, Sulkowski G, Adamczyk A. P2X7 receptor-pannexin 1 interaction mediates extracellular alpha-synuclein-induced ATP release in neuroblastoma SH-SY5Y cells. *Purinergic Signal.* 2017;13(3):347-361.
 28. Young CN, Górecki DC. P2RX7 purinoceptor as a therapeutic target the second coming? *Front Chem.* 2018;6:248.