https://doi.org/10.71248/9786583818089-9

PROTEINS IN NEUROLOGY AND NEUROSCIENCE: STRUCTURAL INSIGHTS, PATHOPHYSIOLOGICAL ROLES, AND THERAPEUTIC OPPORTUNITIES

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Abstract: Proteins are fundamental to neurological and neurobiological processes, serving as enzymes, receptors, ion channels, structural scaffolds, and molecular switches that regulate neuronal signaling. Dysregulation of protein folding, trafficking, or degradation leads to several neurological disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and prion diseases. This chapter explores the hierarchical structure of proteins, their functions in the nervous system, and their involvement in physiopathology. It also examines proteins as biomarkers and therapeutic targets, highlighting innovative strategies such as monoclonal antibodies, antisense oligonucleotide therapies, and biopharmaceuticals. Finally, we discuss challenges in translating protein research into clinical practice, particularly regarding selectivity, delivery across the blood–brain barrier, and long-term safety

Keywords: Proteins; Neurosciences; Neurology; Nervous System Diseases; Protein Structure; Neurodegenerative Diseases; Therapeutic Targets

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1. Introduction

Proteins are the molecular foundation of nervous system physiology. From ligand-gated ion channels that initiate synaptic transmission to chaperones that maintain proteostasis, proteins orchestrate complex cellular functions[1]. Neurological health depends on maintaining the integrity of these proteins; deviations in structure or activity lead to dysfunction and disease[2].

Advances in proteomics, cryo-electron microscopy (cryo-EM), and computational prediction tools such as AlphaFold have transformed protein research, enabling unprecedented resolution of structural and dynamic states[3]. In parallel, clinical neuroscience has increasingly focused on protein biomarkers and therapeutic proteins, underscoring their translational relevance[4].

This chapter reviews the structural principles of proteins, their role in neurological physiology and pathophysiology, and their potential as biomarkers and therapeutic targets.

2. Protein Structure and Function in the Nervous System

2.1 Structural hierarchy

Proteins exhibit hierarchical organization:

Primary structure: amino acid sequence encoding folding potential.

Secondary structure: alpha helices and beta sheets shaping motifs of ion channels and receptors.

Tertiary structure: folding into domains forming active sites or ligand-binding pockets.

Quaternary structure: assembly of subunits into receptor complexes and scaffolds[5].

2.2 Synaptic proteins

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Synaptic vesicle proteins (synaptophysin, synaptotagmin), SNARE complexes, and postsynaptic density proteins (PSD-95, SHANK family) coordinate neurotransmitter release and receptor clustering[6]. Their dysregulation underlies cognitive impairment and neurodevelopmental disorders.

2.3 Ion channels and receptors

Voltage-gated sodium and calcium channels, NMDA and AMPA receptors, and G-protein coupled receptors (GPCRs) are protein complexes that mediate excitability and plasticity[7]. Their structural elucidation has enabled rational design of neuromodulatory drugs.

3. Proteins in Neurological Disorders

3.1 Alzheimer's disease

Amyloid-β (Aβ) peptides and tau protein aggregates represent hallmarks of Alzheimer's pathology. Misfolding and aggregation produce neurotoxic oligomers, impairing synaptic function and inducing neuronal death[8].

3.2 Parkinson's disease

α-Synuclein misfolding leads to Lewy body formation, disrupting dopaminergic neurons[9]. Therapeutic strategies aim to inhibit aggregation or promote clearance via autophagy and proteasomal pathways.

3.3 Amyotrophic lateral sclerosis (ALS)

Mutations in superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP-43), and FUS proteins drive ALS pathogenesis, disrupting RNA metabolism and cytoskeletal integrity[10].

3.4 Prion diseases

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Misfolded prion proteins (PrP^{Sc}) induce conformational changes in normal prion protein (PrP^{C}), propagating neurodegeneration through a template-driven mechanism[11].

4. Proteins as Biomarkers in Neuroscience

Protein biomarkers are increasingly relevant for diagnosis and monitoring of neurological disease:

Cerebrospinal fluid (CSF): decreased Aβ42 and increased tau/phospho-tau levels for Alzheimer's disease[12].

Blood-based biomarkers: neurofilament light chain (NfL) for axonal injury, with applications in ALS and multiple sclerosis[13].

Proteomic panels: discovery of multiplexed protein signatures to improve sensitivity and specificity.

These markers facilitate early detection and patient stratification, but challenges include variability in sample handling and cross-disease overlap.

5. Proteins as Therapeutic Targets and Biopharmaceuticals

5.1 Small molecules targeting proteins

Tyrosine kinase inhibitors, allosteric modulators, and aggregation inhibitors exemplify rational approaches to protein targeting.

5.2 Monoclonal antibodies

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Antibodies against Aβ (aducanumab, lecanemab) illustrate attempts to clear toxic aggregates in Alzheimer's disease[14]. Although controversial, these therapies highlight the feasibility of targeting extracellular protein aggregates.

5.3 Protein replacement and antisense therapies

Enzyme replacement therapy is established for lysosomal storage disorders, and antisense oligonucleotides targeting SOD1 mutations have entered clinical practice for ALS[15].

5.4 Engineered proteins and peptides

Peptide mimetics and engineered scaffolds aim to disrupt protein–protein interactions once considered "undruggable." This area represents an expanding frontier in neurotherapeutics.

6. Innovations and Challenges in Protein-Based Neurotherapeutics

6.1 Innovations

AI-driven structure prediction (AlphaFold, RoseTTAFold) accelerating protein-based drug design[16].

High-throughput proteomics enabling personalized medicine.

Nanoparticle carriers improving delivery across the blood–brain barrier (BBB).

6.2 Challenges

Selectivity: ensuring drugs distinguish pathogenic from physiological conformations.

Delivery: crossing the BBB remains a formidable barrier.

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Safety: long-term modulation of essential proteins may cause off-target effects.

Clinical translation: discrepancies between preclinical models and human trials persist.

7. Final Considerations

Proteins are central to the physiology and pathology of the nervous system. Their study has illuminated disease mechanisms and informed innovative therapeutic strategies. While challenges remain in biomarker development, drug selectivity, and delivery across the BBB, ongoing advances in structural biology, proteomics, and bioinformatics promise to expand the role of protein research in neurology and neuroscience. Translating these insights into clinical practice represents both the innovation and the challenge that defines the current era of integrated neurological care.

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