Abstract

The present thesis elaborates the evolution of bioinspired hybrid nanostructures, their therapeutic potential and underlying neuroprotective mechanisms for the two most common and prevalent neurodegenerative diseases worldwide namely Alzheimer's disease (AD) and Parkinson's disease (PD). Predominantly, the role of two neurohormones, dopamine and melatonin, has been investigated in the regulation of these neurodegenerative diseases; however, the evolution of nanosized hybrid structures from these precursors under physiologically stressed environment was the new development emphasized in the thesis. The present nanostructures showed brain tissue accumulation, sustainable release of neuroprotective melatonin, and prevents PD progression. The synergistic neuroprotection re- establishes the mitochondrial membrane potential, suppresses cellular reactive oxygen species (ROS) generation, inhibits activation of both caspase-dependent and independent apoptotic pathways and confer a strong anti-inflammatory effect. It suppresses α-synuclein phosphorylation at Serine 129 pα-SYN (S129) with reduced pathological processing, and cellular accumulations investigated in ex-vivo organotypic brain slice culture and in-vivo experimental PD models. The epigenetic polycomb repressor complex 1 (PRC1) subunit BMI- 1, which plays a crucial role in the repression of key regulatory genes in neurogenic tissues linked as a critical negative regulator of pα-SYN (S129) and underlying regulatory mechanism of pathogenic processing in different PD models. The nanostructures exposure upregulates BMI-1 expression and associated polycomb E3 ligase activity, whereas significantly downregulates the pα-SYN (S129) level in the substantia nigra and hippocampal region of the brain. Further, the regulatory interaction between BMI-1 and pα-SYN (S129), promotes ubiquitin-mediated proteasomal degradation of pα-SYN (S129) and alleviates neuronal functions. The fine-tuning of present nanostructures provided multimodal characteristics as near-infrared responsive combined photothermal/chemo-inhibitory role on exogenous and in- situ Amyloid beta (Aβ) aggregation, disintegrate preformed Aβ aggregates and disrupt Aβ self- seeding capacity. With a profound resilience effect on axonal degeneration, it lowers the cellular Aβ processing and accumulations in the hippocampal region studied using ex-vivo midbrain slice culture (MBSC) experimental AD model. Besides, state of the art, bottom-up approach, solvothermal route has been used to achieve the highly biocompatible quantum sized dots for the multi-wavelength fluorescence imaging and differential screening of neuronal cell viability. The nanoparticle-protein corona-based fluorescence biosensor has been developed for selective detection of the Aβ protein, which can also delineate pathological Aβ states. Conclusively, the thesis explores the evolution of nature-inspired nanostructure, conferring multimodal biosensing and collective neuroprotective sequels of anti-oxidative, anti- inflammatory, anti-apoptotic pathways activation, and underlying brain region-specific crucial epigenetic regulatory interactions as a potential therapeutic target in neurodegeneration.