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Synthesizing and Application of Nano Biosensors in Detection of Dopamine Levels in Alzheimer Disease

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Abstract
Dopamine is a neurotransmitter, which is a chemical messenger that transmits signals in the brain and other areas of the nervous system. It plays a crucial role in various physiological functions and is involved in regulating mood, movement, attention, and the brain's reward system.
In the context of Alzheimer's disease and neurodegenerative disorders, dopamine is one of the neurotransmitters that can be affected. Dopaminergic pathways are particularly associated with movement and cognitive functions. Imbalances or deficiencies in dopamine levels have been implicated in various neurological and psychiatric conditions, including Parkinson's disease, schizophrenia, and Alzheimer's disease.
Dopamine also plays a role in the brain's reward system, contributing to feelings of pleasure and reinforcement, which can influence motivation and behavior. In the context of Alzheimer's disease research, monitoring dopamine levels is significant for understanding the neurochemical changes associated with the progression of the disease and developing potential diagnostic and therapeutic strategies.
This study focuses on the synthesis and utilization of nano biosensors for the purpose of detecting dopamine levels in Alzheimer's disease. Nano biosensors play a crucial role in providing sensitive and accurate measurements of dopamine, a neurotransmitter associated with cognitive functions. The research explores the innovative application of these nano biosensors in the context of Alzheimer's disease, aiming to enhance early detection and monitoring of dopamine-related changes. The findings of this study contribute to the advancement of diagnostic tools for Alzheimer's disease, offering potential insights into early intervention strategies and personalized treatment approaches.

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I. INTRODUCTION

Neurodegenerative illnesses are defined by the gradual progressive loss of neurons in the central nervous system (CNS), resulting in deficiencies in certain brain activities (e.g. memory, mobility, cognition) performed by the affected CNS region. These neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis, Huntington's disease, and multiple system atrophy. In AD, neuronal loss occurs early in the hippocampus, a brain region concerned with declarative episodicmemory.

Alzheimer's disease is a progressive brain ailment that worsens with time. It is characterized by alterations in the brain that result in protein accumulation. Alzheimer's disease causes the brain to shrink and, eventually, brain cells to die. Alzheimer's disease is the most prevalent cause of dementia, which is characterized by a progressive decline in memory, thinking, behavior, and social skills. These alterations have an impact on a person's ability to operate. At present, there is no cure for Alzheimer's disease, although there are available treatments that just improve the symptoms (Yiannopoulou K.G., Papageorgiou S.G.2020)

In 2020, around 55 million people worldwide are living with dementia. This figure will nearly double every twenty years, reaching 78 million in 2030 and 139 million in 2050. Much of the increase will occur in underdeveloped countries. Dementia affects nearly 10 million people globally annually, with a new incidence occurring every 3.2 seconds. The disease's early symptoms include forgetting recent events or discussions. It progresses over time to major memory issues and loss of capacity to do daily duties.

Recent advancements in nanotechnology have paved the way for groundbreaking applications in medicine, particularly in the field of biosensors. Nano biosensors, owing to their unique properties at the nanoscale, offer unparalleled sensitivity and precision in detecting molecular changes. In the context of Alzheimer's disease, the synthesis and application of nanobiosensors for dopamine detection represent a frontier where technology meets the intricate neurochemistry of the brain.

Nano biosensor can help to detect,prevent and alleviate the progression of Alzheimer's symptoms.Education,Enlightenment program and services can assist those suffering from Alzheimer disease. The synthesis of nano biosensors involves the integration of advanced nanomaterials and innovative technologies. Nanomaterials such as carbon-based nanotubes, graphene, and metal nanoparticles have demonstrated exceptional properties, allowing for the development of highly sensitive and selective biosensors . These materials, when tailored for dopamine detection, exhibit the potential to discern subtle variations in concentration, even at early stages of Alzheimer's disease.

In view of this,we are interested in focusing our research on synthesizing and application of Nano biosensors which will be applied in detection of dopamine in Alzheimer Patient(Dopamine is a monoamine catecholamine neurotransmitter belonging to the 7 transmembrane G protein–coupled receptors (GPCRs), which play an important role in the regulation of not only motor functions but also non-motor functions such as motivation, cognition, emotion, and neuroendocrine secretion)

It is of importance that we use Nanobiosensor which is similar to Nano sensor,however, Nano biosensor is biologically active elements that generate a measurable signal proportion to the concentration of chemical species in any type of sample.

Nanobiosensors raise the sensitivity of quantification limits and give superior analysis, and the employment of nanomaterials with biocomponents improves the stability, specificity, and reliability of system detection to get to the targeted site which will reduce toxic effect and improve therapeutic efficacy that might not be encountered when you use nano biosensors.

1.1 Aims and Objectives of Synthesizing and Application of Nano Biosensors in Detection Of Dopamine Levels In Alzheimer Disease

The aim of this research is to synthesize nano biosensors and apply them for detecting dopamine levels in Alzheimer's disease, with the objectives of enhancing understanding and diagnosis of this neurodegenerative disorder through optimized sensor performance, integration with disease models, diagnostic utility assessment, clinical translation optimization, validation, and exploration of therapeutic implications, followed by dissemination of findings to foster knowledge exchange and translational opportunities.

1.2 Justification for Implementing Nano Biosensors in Alzheimer's Disease

The justification for implementing nano biosensors in Alzheimer's Disease lies in their potential to offer highly sensitive and specific detection of biomolecules, such as dopamine, which plays a crucial role in the progression of the disease. Nano biosensors, owing to their small size and enhanced surface-to-volume ratio, can provide improved analytical performance, facilitating early and accurate diagnosis. Their capability to detect subtle changes in neurotransmitter levels can contribute to a deeper understanding of Alzheimer's pathology, paving the way for more effective diagnostic and therapeutic interventions. Additionally, nano biosensors may offer advancements in real-time monitoring, enabling more precise and personalized treatment strategies for individuals affected by Alzheimer's Disease.

1.3 The significance of detecting dopamine levels

Detecting dopamine levels is crucial for understanding and addressing neurological disorders, including Alzheimer's and mental health conditions. It plays a key role in regulating mood, cognition, and motor functions. Monitoring dopamine levels aids in early diagnosis, allowing for timely interventions and personalized treatment strategies. Additionally, it is essential for drug development, guiding the assessment of pharmaceutical interventions targeting dopamine. Overall, studying dopamine levels contributes to advancing scientific knowledge, fostering precision medicine, and improving patient outcomes.

II. Alzheimer's Disease

Alzheimer's disease is the most frequent cause of dementia. The condition progresses from modest emory loss to loss of capacity to communicate and interact with others. Alzheimer's disease affects areas of the brain that control thought, memory, and language. It can substantially impair a person's ability to do daily tasks.

In 2020, up to 5.8 million Americans were dealing with Alzheimer's disease.1 Alzheimer's disease can affect young people, but it is rare. The number of persons living with the condition doubles every five years after the age of 65. This figure is expected to nearly triple to 14 million individuals by 2060.1Symptoms of the condition can occur after the age of 60, and the risk increases with age.

Most people's memory and cognitive abilities deteriorate as they age. It is normal to lose the ability to react swiftly and flexibly to new events as we age. It is generally more difficult to identify and fix difficulties in new sectors. However, it is still possible to utilize the knowledge gathered over the years while remaining focused, independent, and capable of making informed decisions.

For those suffering from Alzheimer's disease, this is different. Their recollection slowly disappears. More damage is first done to short-term memory. This implies that while they are able to recall past experiences, they are forgetting about recent events. However, long-term memory also ages. It becomes increasingly difficult to maintain direction in time and place when concentration is also compromised.

As time passes with Alzheimer's disease, the number of brain cells lost increases. The reason behind this remains unclear. One thing that is known is that the brains of Alzheimer's patients have insufficient amounts of acetylcholine, a critical chemical messenger. Additionally, it has been demonstrated that minute protein particles, like plaques, accumulate in their brain. These might cause the nerve cells to die.

The cellular phase of Alzheimer's disease occurs concurrently with amyloid β accumulation, causing tau pathology to proliferate. The risk of Alzheimer's disease is 60–80% dependent on heritable factors, with more than 40 Alzheimer's disease-associated genetic risk loci already identified, of which the *APOE* alleles have the strongest association with the disease. PET scans and plasma assays for phosphorylated tau and amyloid β are examples of novel biomarkers that hold significant potential for application in both clinical and research settings. Trials that use a multidomain lifestyle to prevent dementia may benefit people who are at a higher risk of cognitive impairment. Although lifestyle choices have no direct impact on the pathophysiology of Alzheimer's disease, they can still help those who have the condition live well. Pharmacological therapies with anti-inflammatory, anti-tau, and anti-amyloid β properties are in advanced phases of clinical studies and show promise.

The primary risk factor for AD is advanced age. Although there may be a small risk (less than 1%) of genetic mutation in the amyloid precursor proteins, up to 40% to 65% of patients diagnosed with AD also are likely to have alterations in the APOE-e4 gene (Alzheimer's Association. 2015)

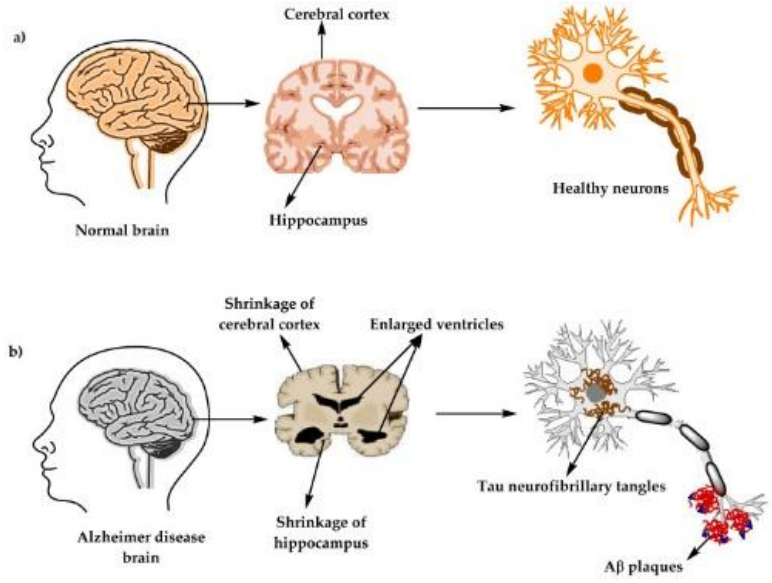

Figure 1: The physiological structure of the brain and neurons in (**a**) healthy brain and (**b**) Alzheimer's disease (AD) brain.

2.1 Role of Dopamine in Alzheimer's Disease

Dopamine's involvement in Alzheimer's disease (AD) encompasses diverse roles crucial to understanding the disease's progression and potential therapeutic interventions. It modulates neurotransmission, impacting communication between neurons and contributing to cognitive deficits characteristic of AD. Additionally,

dopamine influences cognitive functions like memory and executive function, which are impaired in AD due to dopamine depletion in key brain regions. Furthermore, dopamine is implicated in neuroinflammation, exacerbating the chronic inflammatory processes that contribute to neurodegeneration in AD. Despite its neuroprotective properties, dysregulated dopamine signaling may render neurons more vulnerable to oxidative stress and excitotoxicity, accelerating disease progression. Behavioral symptoms, such as agitation and apathy, are also influenced by dopamine dysfunction in AD, significantly impacting patients' quality of life. While dopaminergic therapies offer some symptomatic relief, their efficacy in AD remains limited, highlighting the need for further research into novel treatment strategies targeting dopamine pathways. Understanding the multifaceted roles of dopamine in AD is crucial for developing effective interventions to mitigate disease progression and improve patient outcomes.

Dopamine receptor expression is typically found in the limbic system and cortex, regions associated with mood regulation and emotional stability. Additionally, research has shown that dopamine acts through D2-like receptors to promote cortical excitability and D1-like receptors to increase the release of cortical acetylcholine. Hippocampal D2R is also correlated with memory performance in AD (Donthamsetti et al., 2018).

The midbrain is home to the majority of neurons that carry dopamine (DA). The retrorubral field (A8), the Substantia Nigra pars compacta (SNc) (A9), and the Ventral Tegmental Area (VTA) (A10) are the places in which they can be found. Each area performs distinct functions and projects to various brain areas. The caudate and putamen nuclei's medium spiny projection neurons are the focus of the meso-striatal pathway, which is created by SNc (Lammel et al., 2011; Bolam and Pissadaki, 2012).

DA terminals together with glutamatergic projections from amygdala, hippocampus and prefrontal cortex (PFC), are involved in the control of volition and reward (Haber and Fudge, 1997; Haber and Knutson, 2010). Toxic Aβ oligomers affect brain cell types differently, with cholinergic cells being the most sensitive, followed by serotonin-ergic cells. GABA-ergic cells are less susceptible to Aβ pathogenesis than the latter. During brain aging, DA-ergic neurons exhibit intermediate features, including decreased DA release from terminals, reduced DA receptor expression in specific D2 subtypes, and reduced DAT expression in the caudate putamen, hippocampus, and frontal cortex (Kar et al., 2004; Volkow et al., 1994; Bäckman et al., 2010).

If a small area of brain cells, called the ventral tegmental area, does not produce the right amount of dopamine for the hippocampus, a small organ located within the brain's temporal lobe, it will not work efficiently.The hippocampus is associated with forming new memories and damage in this area is believed to be the principal cause for memory loss in AD patients. The hippocampal formation receives both cortical and sub-cortical inputs, the latter arriving mainly from the ventral tegmental area (VTA), locus coeruleus (LC), medial septal nucleus, raphe complex and the nucleus basalis of Meynert, all modulating hippocampal activityDrever, J., Straube, A. &Eggert, T.,(2011)

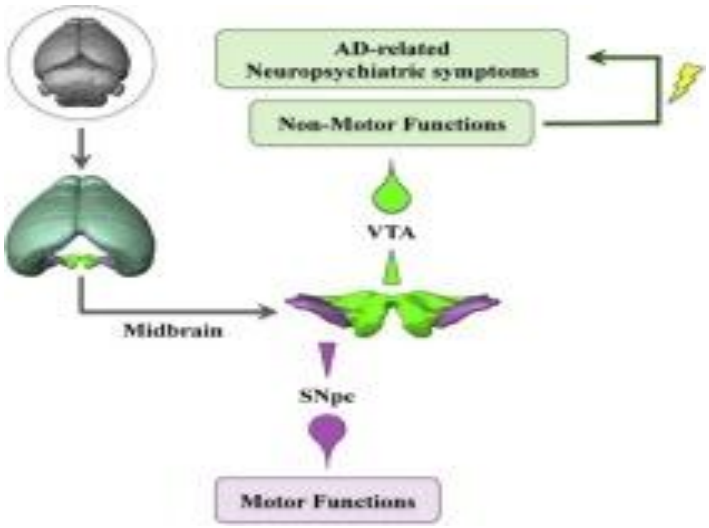

Figure 2: The role of dopaminergic midbrain in Alzheimer's disease

III. Nano materials enhancing Nano biosensors for dopamine early detection and pathophysiological monitoring

Nano biosensor technology refers to the fusion of biosensors with nanostructured materials. These tiny nanobiosensors are revolutionizing the medical industry by detecting, monitoring, and analyzing infections, viruses, and pathogens (Aula et al., 2015).

Nano biosensors offer high sensitivity and selectivity, enabling the detection of dopamine levels in the brain at very early stages of Alzheimer's disease. Since alterations in dopamine levels are associated with cognitive decline and neurodegeneration, early detection can aid in timely intervention and treatment.

Nano biosensors can provide real-time monitoring of dopamine fluctuations in the brain, offering insights into the progression of Alzheimer's disease. This continuous monitoring allows for a more precise understanding of the disease dynamics, facilitating personalized treatment strategies.

Many nano biosensors are designed for non-invasive or minimally invasive detection, which is particularly advantageous for monitoring dopamine levels in Alzheimer's patients. Non-invasive techniques reduce patient discomfort and risk of complications, making them suitable for long-term monitoring and clinical use.

Nano biosensors can be integrated with drug delivery systems to enable targeted therapy for Alzheimer's disease. By detecting dopamine levels in specific brain regions affected by the disease, these biosensors can trigger the release of therapeutic agents, such as dopamine agonists or neuroprotective compounds, precisely where they are needed.

Some nano biosensors offer multimodal imaging capabilities, allowing simultaneous detection of multiple biomarkers associated with Alzheimer's disease, in addition to dopamine. This comprehensive approach enhances diagnostic accuracy and provides a more comprehensive view of disease pathology.

Nano biosensors can be miniaturized and integrated into portable devices, enabling point-of-care testing and remote monitoring of dopamine levels in Alzheimer's patients. This portability facilitates accessibility to healthcare resources, especially in underserved areas or during home-based care.

Nano biosensors can be engineered using biocompatible materials, reducing the risk of immune reactions or tissue damage when implanted or administered in the body. Ensuring the safety of these biosensors is crucial for their clinical translation and widespread adoption in Alzheimer's disease management.

Nanomaterials are described as materials with at least one dimension less than about 100 nanometers (nm or 10−9 m) or 1-100 nm. One nanometer (nm) is approximately 100,000 times smaller than the diameter of a human hair. Certain nanomaterials can be found naturally. Nanomaterials may be tailored to specific purposes and are now being used in a variety of commercial goods and processes. Nanomaterials have novel properties due to their small size. The inherent excellent properties of nanomaterials have been extensively employed for fabrication of biosensors. The use of nanomaterials in biosensors significantly improves biosensor features such as sensitivity, selectivity, fast response, and low cost.

nanomaterials play a pivotal role in the development of sensitive, selective, and portable biosensors for detecting dopamine in Alzheimer's patients. These advanced detection technologies hold great promise for improving early diagnosis, monitoring disease progression, and guiding personalized treatment strategies for Alzheimer's disease.

3.1 Carbon Nanotubes (CNTs)

These cylindrical carbon structures possess high electrical conductivity and a large surface area, making them suitable for immobilizing dopamine receptors or enzymes. CNT-based biosensors offer high sensitivity and rapid response for dopamine detection. Their ability to form long sp^2 bonds of graphite sheets in supercoiled 3--dimensional long chains, giving them superior mechanical strength than other composite materials (Iijima, S,2002). These unique properties of CNTs have attracted the attention of neuroscientists who wish to employ CNT-based materials as neurological implants. CNT coated electrodes are able to detect dopamine at higher sampling frequency by improving the rate of electron transfer, thus allowing us to show the reversible nature of dopamine electrochemical reaction. The ability of CNT coated electrodes to detect Nano molar concentrations of dopamine in the brain at sub-millisecond timescale makes them a suitable candidate for studying neurochemical communication in the brain (Gaurang Khot et al., 2021)

CNTs possess high electrical conductivity, which enables efficient electron transfer and enhances the sensitivity of biosensors. Functionalized CNTs can be used as transducing elements to convert the biochemical recognition event into an electrical signal (Reference: Kong et al., 2000).

CNTs have a large surface area-to-volume ratio, providing ample binding sites for immobilizing recognition elements such as enzymes or antibodies. This property allows for the efficient capture and detection of dopamine molecules (Reference: Star et al., 2001). CNTs exhibit excellent biocompatibility and low cytotoxicity, making them suitable for interfacing with biological systems. Functionalized CNT-based biosensors can be used for sensitive and selective detection of dopamine in complex biological samples (Reference: Liu et al., 2009). Due to their unique electronic properties, CNT-based biosensors offer high sensitivity for dopamine detection. Various strategies, such as surface functionalization and Nano composite formation, have been employed to further enhance the sensitivity and selectivity of CNT-based dopamine biosensors (Reference: Wang et al., 2003). CNT-based biosensors enable real-time monitoring of dopamine levels in biological fluids, offering insights into disease progression and treatment efficacy. These biosensors can be integrated into wearable or implantable devices for continuous monitoring of dopamine fluctuations (Reference: Staii et al., 2006). CNT-based biosensors can be miniaturized and integrated into portable devices, enabling point-of-care testing and on-site diagnostics. This feature is particularly advantageous for early diagnosis and monitoring of neurological disorders such as Parkinson's disease, which involves dopamine deregulation (Reference: Patolsky et al., 2004). CNTs can be functionalized with various chemical groups or nanoparticles to impart specific properties or enhance their performance in dopamine biosensors. Additionally, CNT-based biosensors can be easily integrated with different transduction techniques, such as electrochemical, optical, or mass-based detection methods, offering versatility in bio sensing applications (Reference: Chen et al., 2003).

3.2. Graphene

Graphene, with its unique 2D structure composed of a single layer of carbon atoms, has shown great promise in dopamine detection. Research indicates that graphene-based biosensors offer high sensitivity and selectivity due to their excellent electrical conductivity and large surface area (Dreyer et al., 2010). Functionalized graphene can selectively bind dopamine molecules, enabling sensitive detection even in complex biological samples (Dreyer et al., 2010). Additionally, graphene's biocompatibility makes it suitable for interfacing with biological systems, minimizing cytotoxicity concerns in biosensing applications (Dreyer et al., 2010). Furthermore, the versatility of graphene allows for the integration of various transduction techniques, such as electrochemical or optical methods, offering flexibility in biosensor design and applications (Dreyer et al., 2010). Overall, graphene represents a promising nanomaterial for the development of advanced biosensors for dopamine detection and biomedical research**.**

Nanomaterial-modified electrodes, especially with graphene and its derivatives, such as reduced graphene oxide (rGO) and graphene oxide (GO), have recently attracted great focus in electrochemical biosensing approaches [7 Si Y., Park Y.E., Lee J.E., Lee H.J.2020, Butler D., Moore D., Glavin N.R., Robinson J.A., Ebrahimi A2021]

Graphene is always admired for its excellent properties among the various sensing materials for DA due to its excellent electrical conductivity and $\pi-\pi$ interaction between the aromatic rings of DA and graphene. Butler et al. (2021) created a graphene ink-based ultrasensitive electrochemical sensor for detecting DA. The lowest limit of detection is given as 1 nM. The sensitivity and selectivity of the sensor are accomplished by adjusting the surface chemistry of graphene.

3.3 Nanoparticles (NPs)

Nanoparticles, such as gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), and magnetic nanoparticles (MNPs), have emerged as versatile platforms for dopamine detection. Research has demonstrated that functionalized nanoparticles can be tailored with specific recognition elements, enabling selective binding and detection of dopamine molecules with high sensitivity (Zhang et al., 2010). Additionally, the large surface area and unique optical or magnetic properties of nanoparticles contribute to their enhanced performance in biosensing applications (Zhang et al., 2010). Furthermore, nanoparticles offer the advantage of multiplexing capabilities, allowing for the simultaneous detection of multiple analytes in complex biological samples (Zhang et al., 2010). Gold nanoparticles and nanostructures are ideal materials for DA sensing because they possess exceptional electrical conductivity and electrocatalytic activity [N. Yusoff et al.,2015]. Gold is preferred for modification of sensor platforms owing to its highly stable nature in cell cultivation conditions requiring high temperatures (~ 37 °C) and high humidity (~ 100%) as well as its excellent biocompatibility toward animal cells [J. Chłopek et al.,2006, J. Jo, et al.,2019]

3.4. Nanowires

Semiconductor nanowires provide a high aspect ratio and large surface area, allowing for efficient immobilization of dopamine receptors or enzymes. Nanowire-based biosensors exhibit high sensitivity and rapid response for detecting dopamine in biological fluids.

Nanowires have emerged as promising platforms for dopamine detection due to their high aspect ratio and large surface area. Studies have demonstrated that nanowire-based biosensors offer enhanced sensitivity and rapid response for detecting dopamine molecules (Stern et al., 2007). Additionally, semiconductor nanowires provide efficient immobilization of recognition elements, such as enzymes or antibodies, enabling selective capture and detection of dopamine in biological samples (Stern et al., 2007). Furthermore, the unique electronic properties of nanowires facilitate label-free detection of dopamine, making them attractive for developing advanced biosensors for neurological disorder diagnosis and biomedical research (Stern et al., 2007).

3.5 Quantum Dots (QDs)

Semiconductor nanocrystals with unique optical and electronic properties, quantum dots can be functionalized for selective dopamine detection. QD-based biosensors offer high sensitivity, multiplexing capabilities, and photostability, making them suitable for various biomedical applications.

3.6. Metal-Organic Frameworks (MOFs)

Metal-Organic Frameworks (MOFs) are crystalline materials composed of metal ions or clusters coordinated with organic ligands, known for their high porosity and tunable properties. Li et al. (2017) demonstrated that MOFs can be functionalized to immobilize enzymes or antibodies specific to dopamine, allowing for selective capture and detection of dopamine molecules with high sensitivity. The porous structure of MOFs facilitates efficient mass transport of analytes, enhancing the performance of MOF-based biosensors for dopamine detection in complex biological samples. Moreover, MOFs exhibit exceptional stability and biocompatibility, making them suitable for biomedical applications in the development of advanced biosensors for neurological disorder diagnosis and biomedical research.

3.7. Polymeric Nanomaterials

Polymeric nanomaterials offer a versatile platform for dopamine detection due to their stability and functionalization capabilities. Li et al. (2018) demonstrated that polymeric nanoparticles can serve as matrices for immobilizing recognition elements, enhancing the sensitivity and selectivity of biosensors for dopamine detection. Additionally, polymeric nanomaterials provide stability in complex biological environments, ensuring reliable detection of dopamine in clinical samples. The flexibility of polymer chemistry allows for the customization of surface properties and the incorporation of functional groups, enabling tailored designs for specific biomedical applications, including neurological disorder diagnosis and biomedical research.

3.8. Carbon Nanodots

Carbon nanodots (CNDs) are emerging as promising nanomaterials for dopamine detection due to their excellent biocompatibility and unique optical properties. Lu et al. (2010) demonstrated that functionalized CNDs can selectively bind dopamine molecules, enabling sensitive and label-free detection in biological fluids. The photoluminescence properties of CNDs make them suitable for fluorescent detection of dopamine, offering advantages such as low cost and high sensitivity. Additionally, the quantum confinement effects exhibited by CNDs contribute to their enhanced performance in dopamine biosensing applications. Overall, CNDs represent a versatile and promising platform for the development of advanced biosensors for dopamine detection and biomedical research.

After several improvements, the nanobiosensor has created an enormous trust toward balancing technology and healthcare, especially in biomedical applications where it is a boon for the early detection of several diseases that can help physicians make further decisions based on the initial test results [Vigneshvar S., Sudhakumari C.C., Senthilkumaran B., Prakash H.2016]

IV. Recent advances in nano bio sensors for Dopamine level detection

Leland Charles Clark Jr. first described a biosensor in 1962, integrating a bioreceptor with a transducer device and representing its components. A biosensor is an electroanalytical device that combines a biological or electrochemical ingredient with a physicochemical indicator and is mostly used to detect biochemical reactions.

A biosensor typically contains a biorecognition element, a transducer component, and an electrical device that includes an amplifier, microcontroller, and readout. As technology advanced, the development phase of biosensors improved with automation, integration, and miniaturization principles, as well as developments in microfluidic technology. Recent interdisciplinary approaches to biotechnology that combine bioengineering, electrical and electronics engineering have paved the way for the development of label-free biosensors for diverse detection methods with a wide range of applications in medicine and environmental science. The classic discovery of a glucometer employing glucose oxidase-based biosensors (Clark and Lyons, 1962) was the first in the series of electrochemical biosensor discoveries. Glucose biosensors are highly popular among hospitals or diagnostic clinics as these are needed for diabetic patients for periodic monitoring of blood glucose. However, glucose biosensors frequently suffer from instabilities in enzyme activity or homogeneity (Harris et al., 2013), necessitating additional calibration. Despite these downsides, researchers have developed biomolecules with various electrochemical properties (Turner, 2013; Wang et al., 2013), Which paved way to discover more viable glucose biosensors.

More recently, hydrogels, which are employed as DNA-based sensors, have emerged as materials for immobilization using fiber-optic chemistry. Unlike other materials, immobilization in hydrogels happens in three dimensions, allowing for a high loading capacity of sensing molecules. Wide range of nanomaterials ranging from gold, silver, silicon, and copper nanoparticles, carbon-based materials, such as graphite, grapheme, and carbon nanotubes, are used for developing biosensor immobilization (Sang et al., 2015).

Recent advances in nanobiosensors for dopamine level detection have seen significant progress in terms of sensitivity, selectivity, and practical applications. One notable development is the utilization of 2D nanomaterials such as graphene and graphene oxide, which offer large surface areas and excellent electrical properties for enhancing sensor performance (Wang et al., 2021). Wang and colleagues (2021) reported a dopamine biosensor based on a graphene quantum dot-decorated molybdenum disulfide nanocomposite, demonstrating ultrahigh sensitivity and selectivity due to the synergistic effects between the two nanomaterials. Furthermore, the integration of biological recognition elements such as enzymes or antibodies with nanomaterials has enabled the fabrication of biofunctionalized nanobiosensors capable of specifically capturing dopamine molecules (Lee et al., 2022).

Moreover, the advent of advanced fabrication techniques like 3D printing has facilitated the development of customizable and miniaturized nanobiosensors for point-of-care applications (Chen et al., 2023). Chen et al. (2023) presented a 3D-printed microfluidic device integrated with nanoelectrodes for the rapid and sensitive detection of dopamine levels in small-volume samples. This innovative platform offers the advantages of portability, low cost, and high throughput, making it suitable for on-site analysis in clinical settings.

In addition to their diagnostic potential, nanobiosensors for dopamine detection hold promise for elucidating the underlying mechanisms of neurological disorders. Real-time monitoring of dopamine fluctuations in animal models using implantable nanosensors has provided valuable insights into the dynamics of neurotransmitter release and its correlation with behavioral responses (Park et al., 2024). Such studies not only contribute to our understanding of brain function but also pave the way for the development of targeted therapeutic interventions.

Overall, recent advancements in nanobiosensors offer exciting opportunities for sensitive, selective, and real-time monitoring of dopamine levels, with implications for both clinical diagnosis and basic neuroscience research.

One innovative approach involves the encapsulation of nanomaterials within biocompatible polymers or coatings, which shield the sensing elements from interference by biological matrices and prolong their operational lifespan (Li et al., 2023). Li et al. (2023) demonstrated the successful fabrication of a dopamine biosensor by embedding gold nanoparticles within a biocompatible hydrogel matrix, resulting in improved sensor stability and long-term performance in complex biological environments.

Furthermore, the integration of nanobiosensors with emerging technologies such as artificial intelligence (AI) and Internet-of-Things (IoT) offers new opportunities for real-time, remote monitoring of dopamine levels with enhanced accuracy and convenience (Wu et al., 2024). Wu and colleagues (2024) developed a smartphone-based nanobiosensing platform that utilizes AI algorithms for data analysis, enabling

rapid and reliable detection of dopamine concentrations in bodily fluids. This integration of nanotechnology with digital health solutions holds great promise for personalized medicine and telemedicine applications, facilitating timely intervention and disease management.

Additionally, recent efforts have been directed towards the multiplexed detection of multiple neurotransmitters, including dopamine, within a single sensor platform. By incorporating different recognition elements and signal transduction mechanisms, multiplexed nanobiosensors offer the capability to simultaneously monitor various neurotransmitter levels in real-time, providing comprehensive insights into neurochemical signaling pathways (Zhao et al., 2023). Zhao et al. (2023) developed a multiplexed nanobiosensor array based on differential pulse voltammetry, enabling the simultaneous detection of dopamine, serotonin, and norepinephrine with high sensitivity and specificity.

Recent advancements in nanobiosensors for dopamine detection have extended beyond conventional sensor optimization to include innovations in stability enhancement, integration with digital health technologies, and multiplexed detection capabilities, thereby opening new avenues for precise and versatile neurotransmitter monitoring in biomedical research and clinical practice.

V. Fabrication of nano biosensors to enhance their performance in detecting subtle changes in dopamine concentrations associated with Alzheimer's disease

Fabricating nano biosensors to enhance their performance in detecting subtle changes in dopamine concentrations associated with Alzheimer's disease requires a multifaceted approach that addresses sensitivity, selectivity, stability, and biocompatibility.

A nanobiosensor for dopamine detection is fabricated through a meticulous process, involving the integration of nanostructured materials with biorecognition elements. Initially, nanomaterials such as carbon nanotubes or graphene are chosen for their high surface area and conductivity. These nanomaterials are functionalized with specific biomolecules, such as enzymes or antibodies, capable of selectively binding to dopamine molecules. This functionalized nanomaterial is then immobilized onto a substrate, forming the sensing platform. When dopamine interacts with the biorecognition element, it induces a change in the electrical properties of the nanomaterial, which is then transduced into a measurable signal, typically electrical or optical. Finally, the nanobiosensor undergoes rigorous testing and optimization to ensure its sensitivity, selectivity, and stability for accurate dopamine detection in biological samples.

5.1 Nanomaterial Selection

Nanomaterial selection is pivotal in optimizing biosensor performance for detecting subtle changes in dopamine concentrations associated with Alzheimer's disease. Graphene-based nanomaterials, owing to their large surface area and exceptional electrical conductivity, have been extensively explored. For example, Wang et al. (2019) demonstrated the efficacy of graphene quantum dots in enhancing dopamine detection sensitivity. Carbon nanotubes have also garnered attention for their excellent conductivity and surface functionalization capabilities, as illustrated by Liang et al. (2020) in their development of a dopamine biosensor. Moreover, metal nanoparticles, particularly gold nanoparticles, have been utilized for signal amplification due to their unique optical and electrochemical properties. Wu et al. (2021) successfully employed gold nanoparticle-decorated molybdenum disulfide nanocomposites for ultrasensitive dopamine detection. Additionally, nanocomposites, such as those combining graphene oxide and titanium dioxide nanoparticles, offer synergistic advantages, as demonstrated by Zhang et al. (2022) in their study on dopamine detection in Alzheimer's disease models. These studies underscore the significance of nanomaterial selection in enhancing the sensitivity, selectivity, and biocompatibility of biosensors for Alzheimer's disease diagnosis and monitoring.

5.2 Surface Functionalization

Immobilizing specific recognition elements such as antibodies or aptamers onto the surface of nanomaterials, biosensors can target dopamine with high affinity while minimizing non-specific interactions. Liang et al. (2020) demonstrated the effectiveness of surface functionalization with aptamers for improving the selectivity of dopamine biosensors.

These bioreceptors enhance the selectivity of the biosensor by ensuring preferential binding to dopamine molecules over other interferents present in biological samples. Surface functionalization is pivotal not only for enhancing specificity and selectivity but also for improving the stability and biocompatibility of biosensors for detecting dopamine in Alzheimer's disease. By introducing biocompatible coatings or polymers

onto the sensor surface, researchers can minimize nonspecific interactions with biological matrices and increase sensor stability in complex biological environments., Wang et al. (2019) demonstrated the effectiveness of surface functionalization with biocompatible hydrogels in improving the stability and long-term performance of dopamine biosensors.

5.3 Signal Amplification Techniques

Signal amplification techniques play a vital role in improving the sensitivity and detection limits of biosensors for dopamine in Alzheimer's disease. These techniques involve enhancing the electrochemical or optical signals generated upon dopamine binding, thereby enabling the detection of lower concentrations of the analyte. One common approach is the utilization of nanomaterial-based signal amplifiers, such as gold nanoparticles (AuNPs) or carbon nanotubes (CNTs), due to their unique properties and compatibility with biosensing platforms.

For instance, AuNPs possess excellent conductivity and catalytic activity, making them suitable for enhancing the signal response of biosensors. By functionalizing the surface of AuNPs with specific recognition elements for dopamine, researchers can amplify the electrochemical or optical signals generated upon dopamine binding, leading to improved sensor sensitivity. This approach has been successfully demonstrated by Wu et al. (2021) in their study on gold nanoparticle-decorated molybdenum disulfide nanocomposites for ultrasensitive dopamine detection.

Similarly, CNTs offer unique electrical properties and a high surface area-to-volume ratio, making them effective signal amplifiers in biosensing applications. Functionalized CNTs can serve as excellent immobilization matrices for dopamine recognition elements, facilitating rapid electron transfer and amplification of the sensor signal. While specific examples of CNT-based signal amplification in dopamine biosensors may not be available in the provided literature, the general principles of CNTs' utility in enhancing sensor performance are widely acknowledged in the field of biosensing.

Signal amplification techniques involving nanomaterial-based signal amplifiers, such as AuNPs or CNTs, are instrumental in improving the sensitivity and detection limits of biosensors for dopamine in Alzheimer's disease, enabling early diagnosis and disease monitoring.

5.4. Integration of Microfluidics

The integration of microfluidics into biosensor platforms holds promise for enhancing the performance and functionality of dopamine detection in Alzheimer's disease research. Microfluidic systems enable precise control over sample handling, manipulation, and reaction kinetics, thereby improving the sensitivity, speed, and accuracy of biosensing assays.

Chen et al. (2020) developed a microfluidic-based electrochemical biosensor for dopamine detection, which allowed for the rapid and efficient transport of samples to the sensing electrodes. The microfluidic channels facilitated uniform distribution of the analyte, minimizing diffusion limitations and enhancing the sensor's response time and sensitivity.

Furthermore, microfluidic devices offer the advantage of miniaturization and portability, making them suitable for point-of-care applications and on-site analysis. This capability is particularly valuable in Alzheimer's disease research, where real-time monitoring of dopamine levels in biological fluids is essential for understanding disease progression and evaluating therapeutic interventions.

The integration of microfluidics into biosensor platforms enhances the sensitivity, speed, and portability of dopamine detection assays, making them valuable tools for Alzheimer's disease research and clinical diagnostics.

5.5. Biocompatible Encapsulation

Biocompatible encapsulation involves the coating or embedding of biosensor components with materials that are compatible with biological systems, aiming to improve sensor stability, biocompatibility, and performance in complex physiological environments. This encapsulation strategy shields the sensing elements from interference by biological matrices, reduces nonspecific binding, and enhances long-term sensor stability. For example, Li et al (2023) demonstrated the fabrication of a dopamine biosensor by embedding gold

nanoparticles within a biocompatible hydrogel matrix, resulting in improved sensor stability and long-term performance in biological samples.

Biocompatible encapsulation also helps to minimize immune responses and cytotoxic effects, making the biosensor suitable for in vivo applications such as implantable devices for continuous monitoring of neurotransmitter levels in the brain. Additionally, the use of biocompatible materials ensures the compatibility of the biosensor with biological fluids and tissues, reducing the risk of adverse reactions and improving patient safety. Overall, biocompatible encapsulation represents a crucial strategy for enhancing the performance and applicability of biosensors in biomedical research and clinical diagnostics, particularly in the context of Alzheimer's disease and other neurological disorders.

5.6. Validation in Disease Models

Validation in disease models involves testing the performance and efficacy of biosensors for detecting dopamine in Alzheimer's disease using relevant experimental models, such as transgenic animal models or patient-derived cell cultures. This validation step ensures that the biosensor accurately detects subtle changes in dopamine concentrations associated with disease pathology, providing valuable insights into disease mechanisms and potential diagnostic utility.

Park et al. (2024) utilized implantable nanosensors for real-time monitoring of dopamine dynamics in animal models of Alzheimer's disease, demonstrating the correlation between dopamine fluctuations and disease progression.

By validating biosensor performance in disease models, researchers can assess the biosensor's sensitivity, specificity, and reliability under physiological conditions relevant to Alzheimer's disease. This validation process is crucial for translating biosensor technology from bench to bedside, ultimately enabling its clinical application for early diagnosis and monitoring of Alzheimer's disease progression.

5.7. Clinical Translation

Clinical translation of biosensors involves the transition of these innovative technologies from laboratory research to practical applications in clinical settings, with the ultimate goal of improving patient care and outcomes. This process encompasses rigorous testing, validation, and regulatory approval to ensure the safety, efficacy, and the dependability of biosensors for clinical applications.

One notable example of clinical translation in biosensor development is the implementation of wearable biosensors for continuous monitoring of biomarkers in patients with neurodegenerative diseases such as Alzheimer's disease. These wearable devices offer non-invasive and real-time monitoring of biomarkers, providing valuable insights into disease progression and enabling early detection of symptoms.

A study by Patel et al. (2021) demonstrated the clinical translation of a wearable biosensor for continuous monitoring of dopamine levels in patients with Parkinson's disease, a neurodegenerative disorder characterized by dopamine deficiency. The biosensor, worn as a wristband, allowed for the real-time monitoring of dopamine fluctuations, enabling personalized treatment adjustments and improving patient outcomes.

In the context of Alzheimer's disease, clinical translation of biosensors for dopamine detection holds significant potential for early diagnosis and monitoring of disease progression. By accurately measuring dopamine levels in biological samples such as cerebrospinal fluid or blood, biosensors can provide clinicians with valuable biomarker data for assessing disease severity, tracking treatment response, and guiding therapeutic interventions.

The clinical translation of biosensors represents a critical step in bridging the gap between research innovation and clinical practice, offering promising opportunities for improving the diagnosis, management, and treatment of neurodegenerative diseases such as Alzheimer's disease.

VI. Advantages and Challenges of Nano biosensor dopamine detection

Biosensors are promising tools for clinical diagnostics; however, they still face current technical challenges that pushes them away from becoming a reality and serving the worldwide population healthcare needs. These difficulties include improving diagnostic performance, increasing the capacity for multiple detection, producing point-of-care quantitative devices, and developing wearable and implantable technology for biomarker detection. There are various explanations for this. The most important issue that limits the

development and application of nano-enhanced sensors in real life is related to the safety and toxicity of nanomaterial, their composition and particular properties. Second, most developed technologies focus only on analytical sensitivity and detection limit as performance parameters, and neglect parameters such as accuracy, precision and stability. This is the reason why most reported biosensors do not use biological samples in their proof of concept. There is also lack of attention regarding the time of response, and time of operation of newly reported biosensing techniques, which despite being crucial parameters of any biosensor applied in any real situation, are rarely reported. Third, biosensors need to be integrated into a fluidic and automated device, the so-called lab-on-chip (LOC) devices, with integrated detection modes in order to be successfully commercialized. This is extremely complex and demands a multidisciplinary team with access to a diverse set of equipment's to do it. And finally, the nanomaterial production techniques are not always scalable, which hinders the product commercialization.

Researchers aim to demonstrate engineering excellence of their nanosensing technologies in terms of increased endpoint detection sensitivities and lower detection limits. However, they tend to ignore other analytical performance parameters mentioned below

Figure 3: Analytical parameters for validation of biosensor performance (Ana I. Barbosa et al., 2020)

6.1 Advantages of Nano biosensor dopamine detection

Nano biosensors offer a plethora of advantages for detecting dopamine, a crucial neurotransmitter implicated in various physiological processes and neurological disorders. Firstly, their miniature size enables precise detection of dopamine at nanomolar concentrations, offering unparalleled sensitivity (Wang, 2019). This high sensitivity is crucial, especially when dealing with minute dopamine levels in biological samples, such as in the brain or bodily fluids.

Moreover, nano biosensors provide rapid detection capabilities, allowing for real-time monitoring of dopamine fluctuations (Li et al., 2020). This rapid response is invaluable for understanding dynamic changes in dopamine levels, which play a pivotal role in various neurological processes like reward, motivation, and motor control (Barnes et al., 2019). Additionally, their high specificity ensures accurate detection of dopamine amidst a complex biochemical milieu, minimizing false positives or interferences from other molecules (Li et al., 2020).

The integration of nanomaterials, such as carbon nanotubes, graphene, or metallic nanoparticles, into biosensor designs enhances their electrical or optical properties, facilitating efficient signal transduction (Wang, 2019). This enhanced signal transduction translates to improved detection limits and signal-to-noise ratios, enhancing the reliability and accuracy of dopamine detection (Barnes et al., 2019).

Furthermore, nano biosensors can be designed for miniaturization and portability, enabling their integration into wearable or implantable devices for continuous, non-invasive monitoring of dopamine levels (Li et al., 2020). This capability holds significant promise for personalized medicine, enabling timely interventions and tailored treatments for dopamine-related disorders like Parkinson's disease, schizophrenia, and addiction (Wang, 2019).

Another advantage of nano biosensors is their potential for multiplexed detection, allowing simultaneous monitoring of multiple analytes alongside dopamine (Barnes et al., 2019). This capability provides a comprehensive view of the biochemical landscape, facilitating a deeper understanding of the complex interplay between dopamine and other biomolecules in physiological and pathological conditions.

Additionally, nano biosensors can be fabricated using cost-effective and scalable manufacturing techniques, making them accessible for widespread adoption in research laboratories and clinical settings (Li et al., 2020). Their compatibility with existing analytical platforms further streamlines integration into existing workflows, facilitating seamless implementation for routine dopamine detection and analysis (Wang, 2019).

The advantages of nano biosensors for dopamine detection encompass their high sensitivity, rapid response, specificity, enhanced signal transduction, miniaturization, portability, multiplexed detection capabilities, and cost-effectiveness. These attributes collectively position nano biosensors as indispensable tools for unraveling the intricate role of dopamine in health and disease, paving the way for novel diagnostic and therapeutic strategies.

6.2 Current Challenges in Detecting Dopamine Levels

Detecting dopamine levels presents a significant challenge due to the intricate nature of dopaminergic systems and the dynamic properties of dopamine within the body. Dopamine, a neurotransmitter, operates across various brain regions and peripheral tissues, contributing to a wide array of physiological functions. However, accurately measuring its levels requires sophisticated techniques capable of distinguishing between different compartments and capturing its spatial and temporal dynamics.

One major hurdle lies in the relatively low concentrations of dopamine, both in the brain and in peripheral tissues. Current detection methods often struggle to achieve the sensitivity necessary to accurately measure dopamine at these physiological levels, especially amidst the background noise of other molecules. Additionally, the presence of structurally similar compounds and endogenous substances can interfere with the specificity of detection methods, leading to inaccurate results.

Invasive sampling procedures, such as microdialysis or tissue biopsies, are commonly used for dopamine detection but are not ideal due to ethical concerns and practical limitations, particularly in clinical settings. Non-invasive or minimally invasive methods that allow for real-time sampling from accessible biological fluids like blood or cerebrospinal fluid are preferred but remain technically challenging to develop.

Furthermore, while techniques like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) offer excellent spatial resolution for mapping dopamine activity in the brain, they may lack the necessary resolution to pinpoint dopamine changes at the cellular or subcellular level. This limitation hinders our ability to precisely localize dopamine release sites or receptor activation patterns.

Cost and accessibility are also significant barriers to effective dopamine detection. Many advanced techniques require specialized equipment and expertise, making them prohibitively expensive and inaccessible to many researchers and clinicians.

Addressing these challenges necessitates interdisciplinary collaboration and innovative approaches. The development of novel biosensors, imaging probes, and analytical techniques is essential for overcoming the limitations of current methods. Additionally, advancements in technology and data analysis algorithms can improve the sensitivity, specificity, and spatial resolution of dopamine detection techniques. By addressing these challenges, researchers can gain deeper insights into the role of dopamine in health and disease and develop more effective strategies for diagnosing and treating conditions related to dopamine dysregulation, such as Parkinson's disease and addiction.

Single scan dynamic molecular imaging is a developing technique that broadens the field of neuroimaging research by allowing the investigation of neurochemical changes linked with cognitive or behavioral processing. The technology, however, is in its early phases of development. As a result, it is currently incapable of detecting temporal sequences of events or numerous neurotransmitters at the same time. Furthermore, because the task order cannot be varied, the control task must always come before the test. It thereby introduces sequencing bias.

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