Advances in Brain-Computer Interfaces for Real-Time Monitoring and Regulation of Deep Brain Neurotransmitters

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Abstract. This paper explores the application progress of brain-computer interfaces (BCIs) in real-time monitoring and regulation of deep brain neurotransmitters, with a focus on key neurotransmitters such as dopamine (DA), serotonin (5-HT), acetylcholine (ACh), and gamma-aminobutyric acid (GABA). Long-term changes in neurotransmitter levels are closely related to cognitive function, learning, and mental health. Monitoring these changes can provide valuable insights into neurodegenerative diseases and guide personalized treatment strategies. BCIs, which enable direct interaction between the central nervous system and external devices, offer a promising approach to neurotransmitter regulation through neuromodulation techniques. Some invasive BCIs utilize highly sensitive biosensors, such as metal-organic frameworks (MOFs) and solid-contact potentiometric sensors, to achieve real-time detection of neurotransmitter fluctuations. These advances facilitate more precise treatment strategies, particularly in combination with deep brain stimulation (DBS) systems. However, challenges remain in improving biocompatibility, long-term stability, and multi-target monitoring. This paper reviews existing invasive interfaces for neurotransmitter detection, analyzes their advantages and limitations, and highlights the need for further research on adaptive neuromodulation systems. Future advancements in this field could enhance the precision of neurodegenerative disease treatment, promote the integration of BCIs with DBS, and contribute to the sustainable development of neurotechnology in medicine.

Keywords: Brain-Computer Interface; deep brain the regulation of neurotransmitter.

1. Introduction

Long-term changes in chemical signals and neural transmission in the brain are considered the basis of cognition, learning and fluctuations in mental state [1]. Meanwhile, different neurotransmitters, such as dopamine (DA), serotonin (5-HT), norepinephrine, acetylcholine (Ach), and gamma-aminobutyric acid (GABA), maintain homeostasis in the brain to ensure the normal operation of the body's functions [2]. Changes in their levels are often closely related to specific disease states. Sustainable perception of neurotransmitter levels can provide healthcare providers with a clearer overall picture, enabling them to develop personalized treatment plans for patients and accurately assess the effectiveness of treatment. Therefore, methods for long-term and real time monitoring of neurotransmitter levels in the deep brain are particularly important. Brain-computer interfaces (BCIs), devices that establish a pathway between the brain and external devices with high biocompatibility to achieve information exchange and functional integration between the nervous system and external devices, have good prospects in practical applications. Some invasive interfaces make it possible to measure extremely subtle changes in neurotransmitter levels. For instance, a miniature implantable fluorescent probe integrated with a metal-organic framework (MOFs) is used for deep brain DA sensing. A fluorescence MOF that specifically binds DA was introduced to achieve a highly sensitive DA measurement, which was combined with a lightweight compact wireless circuit and subsequently applied to continuously monitor real-time DA levels during deep brain stimulation in rats [1]. A flexible solid-contact potentiometric sensor for in vitro and in vivo recording of ACh in the brain and tissue homogenate [3]. A fully implantable, wireless, and battery-free platform that enables optogenetic stimulation and electrochemical recording of catecholamine dynamics in real time,[4]. etc.

This article aims to introduce a series of neurotransmitters and the neurodegenerative diseases they cause, and to summarize the operating mechanisms and practical operation results of existing invasive

interfaces for real-time monitoring of deep brain neurotransmitter levels, and briefly analyze their advantages and areas that still need improvement, hoping to provide reference significance and search convenience for future research.

2. Neurotransmitters and the potential disease they may cause

2.1. DA and Parkinson's disease (PD)

2.1.1 Cause of PD

PD is a prevalent neurodegenerative disorder (NDD) characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, leading to a substantial reduction in DA levels within the striatum [5]. This pathological process results in a range of clinical manifestations, including tremor and bradykinesia. DA serves as a critical neurotransmitter with multiple physiological functions in modulating the central nervous system. It operates by being released from presynaptic neurons and transmitting signals to postsynaptic cells, facilitating neural impulse propagation. Dopaminergic neurons in the substantia nigra are projected to the striatum via long axons, forming the nigrostriatal pathway, which is essential for regulating striatal neuronal activity [5]. In PD patients, the ongoing loss of dopaminergic neurons disrupts the balance between DA and Ach transmission in the striatum. The resultant relative hyperactivity of Ach exacerbates motor dysfunction and coordination impairments [6].

2.1.2 Current treatment and its flaw

For the treatment of PD, drug substitution therapy is a widely employed approach. DA itself cannot directly cross the blood-brain barrier (BBB) due to its positively charged state in the bloodstream, which prevents it from traversing the lipophilic BBB that effectively restricts ionized substances [7]. By modifying the molecular structure to remove the proton-bound amino group responsible for the positive charge, the drug can successfully cross the BBB and subsequently be converted back to DA within the brain. Levodopa, a representative medication of this class, increases cerebral DA levels, thereby alleviating motor symptoms in patients. However, current conventional techniques lack the capability for real-time monitoring of DA levels, leading to issues such as hyperkinesia and fluctuating responses when patients receive prolonged levodopa administration at certain doses.

2.2. Ach and Alzheimer's disease (AD)

2.2.1 Cause of AD

AD is a NDD that gets progressively worse over time. The hippocampus and temporal lobes were the most affected. Long-term memory and the process of storing memories are greatly affected. Patients suffer from severe memory confusion, including both anterograde and retrograde memory loss [8]. ACh is an important neurotransmitter in the brain that plays a key role in a variety of cognitive and physiological functions. Its concentration in the hippocampus is strongly correlated with learning ability. It promotes memory formation and information storage by enhancing synaptic plasticity. In Alzheimer's patients, level of Ach experience a significant drop, and this abnormality directly leads to cell damage in key parts of the brain. Serotonin levels drop as a result, and at the same time, this exacerbates the development of neurofibrillary tangles (NFT), giving the condition a positive feedback that makes it more severe over time. In most cases, advanced patients showed significant brain shrinkage, most severe in the parietal and temporal lobes [9].

2.2.2 Current treatment and its flaw

Ach esterase (AChE) is considered to be key enzyme to inactivate ACh. For the treatment of Alzheimer’s disease, anticholinesterase can effectively block AChE, maintaining a comparatively higher level of Ach in the particular tissue, thereby relieving symptoms [10]. This treatment, which is based on basic mechanism of interaction between neurons by synapse, may has more potential than those directly focus on inhibit Tau hyperphosphorylation or clear neurofibrillary tangles. However,

ACh levels in the brain of patients are affected by disease stage, gene and metabolic efficiency, fixed dose is difficult to match the dynamic demand . In addition, excessive inhibition of AChE can lead to peripheral side effects such as nausea and bradycardia, limiting the room for dose adjustment. Finally, long-term use of anticholinesterase may lead to the increase of AChE compensatory, accelerate ACh decomposition and weaken the effect of the drugs [3].

2.3. GABA and Epilepsy

2.3.1 Cause of epilepsy

Epilepsy is a chronic brain disease, most likely caused by the abnormal firing of neurons. Symptoms of muscle rigidity or contraction may occur repeatedly in the short term. Due to the difference in the starting site and transmission mode of abnormal discharge, the clinical manifestations of epilepsy are complex and diverse, which can be manifested as paroxysmal motor, sensation, autonomic nervous system, consciousness and mental disorders. GABA is an inhibitory neurotransmitter that plays a role in regulating neuronal excitability in the nervous system. Enhancing GABA-mediated inhibition often helps reduce neuronal overexcitation, which can help prevent or reduce epilepsy. In epilepsy patients, level of GABA experiences a significant drop [11]. When Gamma-aminobutyric acid type A receptor (GABAAR) is activated by GABA, the receptor channel opens and chloride ions flow into the cell to hyperpolarize the neuron membrane, increase the threshold of action potential generation and reduce nerve excitability. When GABAAR dysfunction will lead to GABA transmission block, neuronal cell excitability increased, and eventually lead to epilepsy [12].

2.3.2 Current treatment and its flaw

At present, drug therapy is still the main method to control epilepsy, mainly by blocking ion channels, enhancing GABA-mediated nerve inhibition or regulating the function of related receptors to control epilepsy. Another promising treatment, AMinobutyric acid aminotransferase inhibitors , reduces neuronal overexcitation by inhibiting GABA degradation to increase its concentration. L-Homopropargylglycine (LHPG), a representative of this class of drugs, acts as an inhibitor of gamma-aminobutyric acid transaminase, resulting in reduced GABA degradation in the brain and therefore elevated overall levels [11]. However, long-term quantitative use of this method may lead to sharp fluctuations in GABA levels, and prone to drug resistance and local side effects. Intracranial dynamic monitoring can provide patients with a customized treatment plan that can optimize the dose of antiepileptic drugs and reduce side effects or treatment failure caused by excessive or insufficient doses [13]. Simultaneously, abnormal GABA levels often precede seizures, and real-time monitoring can lead to early intervention to reduce the frequency and severity of seizures.

3. Real-time Monitoring of Neurotransmitters in the Deep Brain

At present, the most popular method is to analyze the cerebrospinal fluid after it is taken, and even the interval between successive operations is too long. This method can't really treat the current state of the patient [3]. There is an urgent need for a tool that can monitor the level of deep brain neurotransmitters in real time and combine with the DBS system for neural adaptive operation. In this way, personalized treatment can be optimized, and real-time data on neurotransmitter levels can directly guide drug dose adjustment. For example, DA fluctuations in patients with Parkinson's disease can match the timing of levodopa administration, reducing the "end-of-dose phenomenon." With this new tool and adaptive adjustment system, patients can minimize drug side effects and visualize treatment progress.

4. New Methodology

4.1. Operation Mechanism of the Fluorescent Probe

In a 2024 research, Wei Ling and his colleagues develop a fluorescent probe integrated with Metal–Organic Frameworks (MOF) for monitor deep brain neurotransmitter levels in real time. This kind of device can be integrated with deep brain stimulation (DBS) systems for adaptive neuromodulation [1].

The probes include an ultraviolet LED for fluorescence excitation and a phototransistor for fluorescence intensity detection. Applied micro scale light-emitting diodes with small size and high luminous efficiency have been successfully applied for sensing and stimulating internal organs. The raw material of the MOF here is europium since it has a strong fluorescence emission ability, especially in the red light scope [1]. Meanwhile, based on the electrostatic interaction and energy transfer between MOFs and dopamine, europium-based fluorescent MOFs with large surface area and high affinity toward dopamine have been synthesized and modified on the probe, enabling real-time monitoring of deep brain dopamine concentrations without aspiration of cerebrospinal fluid.

4.2. Perceptive Ability

The researchers characterized the structural properties of the MOF and the sensing performance of the prepared fluorescent probe. Synthesized Eu-MOF particles exhibited inconsistent sizes ranging from submicron to several microns. The properties of the fluorescent Eu-MOF and the capability of the probe for dopamine sensing were shown. This suggests that the device can effectively detect tiny change of the dopamine level and visualize the chemical information [1]. The capability of Eu-MOF for dopamine sensing was then verified in PBS solutions by recording fluorescence spectra at different dopamine concentrations. A significant increase in fluorescence intensity at 617 nm was observed upon increasing dopamine concentration. Thus, the MOF also has excellent structural stability in liquid environment, and its fluorescence intensity varies linearly with dopamine concentration.

The researchers then implanted the fluorescent probe into living rats to further verify its ability to monitor dopamine in vivo .A probe was implanted into the nucleus accumbens (NAc), which is one of the primary regions that receives projections from dopaminergic neurons in the ventral tegmental area (VTA) [1]. Notably, a dynamic increase in dopamine concentration was observed upon application of electrical stimulation, implying the promising ability of the probe to monitor dopamine dynamics during deep brain stimulation. which may can be integrated with deep brain stimulation (DBS) systems for adaptive neuromodulation. The experiment proves the ability of the probe to monitor the dopamine concentration continuously. In addition, the probe also successfully captured the dopamine transient.

4.3. Biocompatibility

In order to prove favorable biocompatibility of the probe toward the nearby cells, PC12 cells from rat pheochromocytomas were cocultured with the probe, followed by florescence dye to characterize cytotoxicity. Fluorescent images show the distribution of live cells is over 99%, presenting negligible neurotoxicity. Thus, It is expected to be applied to the long-term monitoring of neurotransmitter dynamics [1].

4.4. Flexible Acetylcholine Sensing Thread

The dynamics of acetylcholine in the brain are crucial. The most common method for acetylcholine analysis is to sample the cerebrospinal fluid with a microdialysis probe and then analyze it using mass spectrometry combined with the liquid phase. Although this method can achieve low detection detail (LOD), the temporal resolution is not sufficient to understand concentration dynamics and requires sample collection and off-line analysis, so the method is not suitable for measurements in animals [3]. The work of Farbod Amirghasemi and colleagues has created a flexible solid-state contact potential

sensor for in vitro and in vivo recording of acetylcholine in brain and tissue homogenates. They used cotton yarn and an ACh sensing film containing calix arene ionophores to create the sensor. The exposed ion-electron transducer is sealed with a polyp-xylene coating to maintain the flexibility of the sensor. The resulting flexible ACh sensing thread (FAST) can measure ACh dynamics in sheep brain tissue and brain tissue homogenate after ACh peak. FAST is the first flexible electrochemical sensor for monitoring acetylcholine kinetics in the brain.

Improving the biocompatibility of neural probes has been the focus of research in recent decades. Many groups have worked to create flexible probes that enhance compatibility with surrounding tissue and minimize tissue damage and subsequent scar tissue formation and rejection. Electroneural probes have been able to reduce electrode sizes to tens of microns [3].

Unlike catecholamines, acetylcholine is not electroactive and cannot be reduced or oxidized within the potential window of water. Much of the past work has focused on the immobilization of acetylcholinesterase and choline oxidase, converting acetylcholinesterase into hydrogen peroxide, which can be detected by amperage or voltammetry. The main challenge with this type of biosensor is the limited lifetime of the enzyme. The team members presented a unique view of the electrochemical detection of ACh that does not rely on oxidation or reduction, but uses the permanent positive charge of ACh to generate a potential [3]. This type of sensor is called a potential electrode, where the sensing membrane and organic receptors provide selectivity. The potential sensor has a fast response time and is read in passive mode, which provides additional advantages for real-time in vivo recording.

5. Conclusion

This paper discusses the causes of neurotransmitters in neurodegenerative diseases. Due to the operational limitations and sequelae of existing treatment options, the effect of a tool that can monitor the level of deep brain neurotransmitters in real time and perform neural adaptive operation in combination with the DBS system has become promising in the field of treatment. With the use of this system, personalized treatment becomes possible and brings the best treatment results to the patient. This paper still lacks detailed experimental data guidance and in-depth feasibility analysis. Future research can further expand the stability in the biological brain and extend the research results to monitor the level of multiple deep brain substances and the operational construction of adaptive systems, so as to promote the sustainable development of the medical field.

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