Monoaminergic neurotransmitter systems underlie therapeutic and side effects of deep brain stimulation

IMPACT PARAGRAPH/VOLARIZATION

Relevance for the academic community and society

Deep brain stimulation is a well-established surgical procedure used to manage the symptoms of many neurological diseases, in particular Parkinson's disease. The procedure involves implanting a small device into the brain to deliver electrical impulses to specific areas that regulate movement. Moreover, deep brain stimulation has also helped us understand the brain and the mechanisms behind movement disorders. For instance, researchers have utilized it to map the neural connections responsible for movement and learn how alterations in these circuits might cause movement problems.

Among ten million people who are suffering from Parkinson's disease, roughly 208,000 patients have received deep brain stimulation treatment worldwide. Although this surgery is relatively safe, it still requires surgical intervention with costs and complications such as cerebral bleeding and infections. In fact, deep brain stimulation surgeries cost each Parkinson's disease patient roughly US$186,244 over five years of healthcare and follow-up surgeries that are required to optimize deep brain stimulation parameters or battery replacements. Consequently, patients are reluctant to undergo deep brain stimulation surgery, leading to the underutilization of this approach. This is why developing less invasive deep brain stimulation alternative approaches is necessary. Although deep brain stimulation has shown remarkable therapeutic outcomes for Parkinson's patients, it also indicates some side effects, including mood disorders like depression. Consequently, it is crucial to comprehend the neurochemical mechanisms behind deep brain stimulation, which could remarkably improve the current treatment and help optimize the pharmacological treatment combined with deep brain stimulation for Parkinson's patients and healthcare providers.

I reviewed the literature about the significant impacts of conventional deep brain stimulation on the most relevant monoaminergic neurotransmitter systems, namely the dopamine, noradrenaline and serotonin system and their counterpart-related neurotransmitter system, especially the cholinergic system. I have learned that deep brain stimulation has considerable local and remote effects on the neurotransmitter systems in several brain regions responsible for movement and mood regulation. The disbalance of these neurotransmitters contributes significantly to the development of neurological and psychological disorders. Consequently, the current thesis aims to investigate the underlying mechanism behind these neurochemical changes, which could improve this treatment and minimize the side effects of deep brain stimulation therapy. In addition, novel deep brain stimulation techniques using nano-scale materials were reviewed and tested the neurochemical effect in naive animals.

Target groups

The target groups of the research presented in this thesis are broad. I will start with the prioritized target groups, including patients with Parkinson's disease and their caregivers. Deep brain stimulation has been extensively studied and effectively improves motor symptoms in patients with Parkinson's disease. Furthermore, it has also been shown to enhance the quality of life, reduce dopamine medication use,

and decrease the number of hospitalizations for patients with Parkinson's disease. Individuals who underwent this surgery notice a considerable positive impact on their capacity to work, interact with others, and participate in daily activities. This can also reduce the stress on caregivers, who might need to help them with daily tasks and medication administration.

The general public is another target group. Parkinson's disease is the second most common neurogenerative progressive disorder. Ten million are suffering from this disease worldwide. It substantially affects the physical and mental health of patients. Pharmacological treatment has many drawbacks, such as the fluctuation of responses to the medication and medication resistance, especially in the advanced stage of Parkinson's disease. Deep brain stimulation has been successful in treating the motor symptoms of Parkinson's disease and improve the overall life quality for patients, which has an impact on the economy and society because patients can work, consume and invest longer. However, deep brain stimulation sometimes induces some mood side effects. Therefore, further research is required to understand the underlying mechanism of deep brain stimulation.

In line with this, another target group is the critical scientific mass. Previous research found that deep brain stimulation of the subthalamic nucleus reduces the neuronal serotonin activity in the dorsal raphe nucleus. This is particularly interesting because serotonin in the dorsal raphe nucleus is associated with mood disorders. The thesis found that brain stimulation of the subthalamic nucleus reduces neuronal activity in the dorsal raphe nucleus, which was accompanied by the loss of their cell phenotype. In addition, conventional deep brain stimulation requires an invasive procedure and leads to surgical complications such as brain bleeding and infections. Novel techniques using nano-scale materials may offer less invasive approaches with fewer complications.

Lastly, the academic community and companies developing neuromodulation techniques are also a target group as they can use these findings to improve their electrode designs with regard to inducing fewer side effects and more precise benefits and support future research.

Activity products

The primary product/outcome of the current thesis is divided into two parts. First, the outcome of deep brain stimulation on the main monoaminergic and related neurotransmitters. The second part tested a less invasive deep brain stimulation approach using nano-scale materials.

In Chapter 3, I started with investigating the neurochemical effect of deep brain stimulation of the subthalamic nucleus in the dorsal raphe nucleus serotonin neurotransmitter system. I found that it interferes with cellular serotonin balance, which could lead to side effects of brain stimulation surgery, such as depression. Understanding the exact mechanism of how brain stimulation surgery reduces serotonin will help improve the surgical treatment and may offer the optimal pharmacological intervention combined with brain stimulation surgery. In addition, I tested whether the globus pallidus externa is a relay of the subthalamic nucleus to the dorsal raphe nucleus anatomically, which inhibits the

serotonin release, as there is no direct connection between the subthalamic nucleus and dorsal raphe nucleus. It has been recently discovered that there is a connection between the globus pallidus externa and the dorsal raphe nucleus. In addition, there is a well-known connection between the globus pallidus externa and the subthalamic nucleus. Our findings did not verify that the globus pallidus externa is a relay station between the subthalamic and dorsal raphe nuclei. However, earlier studies suggest other relay pathways, such as lateral habenula and medial prefrontal cortex.

Furthermore, deep brain stimulation of the subthalamic nucleus treats the gait and balance symptoms of Parkinson's disease. The cholinergic system has a significant role in regulating gait and balance. I have assessed whether deep brain stimulation of the subthalamic nucleus affects the cholinergic system as a possible mechanism of improving the gait by this system. However, deep brain stimulation of the subthalamic nucleus did not affect the cholinergic system. This suggests that other pathways, such as the cortical and mesolimbic pathways, could explain the cause of improvement in gait and balance.

In the second part of my thesis, I reviewed novel approaches for less invasive deep brain stimulation. Then, in the final chapter of the current thesis, I assessed the effect of wireless deep brain stimulation using nanoparticles on the main monoaminergic (dopamine and serotonin) and cholinergic neurotransmitters and compared them to conventional deep brain stimulation. They have the same molecular effects in naïve animals compared to conventional deep brain stimulation. The findings of this thesis are a first step to understand this technology, and future research is necessary to develop this nanotechnology further.

Innovation

There are several innovative aspects of the current thesis. Deep brain stimulation of the subthalamic nucleus has reduced the effect of serotonin activity and caused the serotonin cell to lose its original phenotype. This indicates that deep brain stimulation may induce neuroplastic changes. However, the fate of the phenotype switch of the cells was not investigated. Future research is warranted to have a better understanding of this phenomenon.

In addition, in the thesis, I tested the globus pallidus externa as a potential relay route from the subthalamic nucleus to the dorsal raphe nucleus, as there is no direct connection between them. My findings suggest that the globus pallidus externa is not a relay station; however, more detailed, and specific cell-type studies are required to verify our results. Also, the cholinergic system is not involved in the treatment benefits of the deep brain stimulation of the subthalamic nucleus.

The thesis also innovatively introduces a novel technique to be developed into a less invasive approach. This technique uses nano-scale materials (nanoparticles) and can be wirelessly stimulated using a specific magnetic field. The findings of the thesis suggest that this nanoparticle induces locomotion and neuronal activities and has a neurochemical and cellular outcome similar to conventional (wired)

deep brain stimulation. However, this is the first step to understanding this technology. Scientists and researchers need to investigate this novel nanotechnology in future research on disease animal models.

Implementation

Overall deep brain stimulation surgery for Parkinson's disease has remarkable positive scientific and social impacts. However, it must be used cautiously, followed thoroughly, and evaluated independently for each patient, considering potential risks and benefits. Future research needs to unravel the exact mechanism further and thoroughly describe how to optimize this operation and minimize the harmful effects of these techniques. Lastly, improving less invasive approaches might help to make it more feasible and cost-effective for patients and healthcare.