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

SUMMARY

Parkinson's disease (PD) is a neurogenerative disease affecting over ten million people worldwide. PD was first described in 1817 by a British physician named James Parkinson. Its key motor symptoms include tremors, rigidity, bradykinesia, and postural instability. In addition, PD patients suffer from non-motor symptoms such as cognitive impairments and mood disorders. The disease is caused by the death of dopamine cells in the substantia nigra pars compacta. The exact cause of this cell death is not well understood. While there is no cure for PD, dopamine replacement therapy can only treat motor symptoms in the early stages but have side effect and fluctuation in medical treatment, especially in advanced stages.

Deep brain stimulation (DBS) is a surgical procedure involving implanting electrodes in specific brain regions to apply an electrical impulse that can improve motor symptoms in PD patients. In the past, traditional surgical approaches were used to treat these conditions. However, they were abandoned due to their irreversible nature and the availability of more effective drug treatments. Advancements in neurosurgery have led to improvements in stimulation equipment and neuroimaging techniques, making targeting brain structures more precise. Furthermore, intraoperative electrophysiology techniques have also improved the targeting of brain regions, particularly the subthalamic nucleus (STN). High-frequency stimulation (HFS) of the STN, discovered in 1993, is now a standard treatment for PD.

Monoaminergic neurotransmitter systems are essential for regulating various functions of the central nervous system, such as mood, behavior, and movement. The primary monoaminergic neurotransmitters involved are dopamine, noradrenaline and serotonin. Dopaminergic neurons primarily project to the basal ganglia, which are involved in movement regulation, while serotonergic neurons project to several brain areas, including the basal ganglia and prefrontal cortex. In addition, noradrenergic neurons projects to cortical, subcortical, and spinal structures. Dysregulation of these systems can lead to neurological like PD. The cholinergic system may also interact with the monoaminergic systems, particularly in movement regulation. Understanding the involvement of these systems in neurological will help optimize treatment options to improve patient healthcare.

Monoaminergic neurotransmitters, such as dopamine, noradrenaline and serotonin, play an essential role in DBS's therapeutic and side effects. In **Chapter 2**, the literature review the DBS effects on the activity of the striatal and mesolimbic dopaminergic systems, locus coeruleus (LC) noradrenergic, dorsal raphe nucleus (DRN) serotoninergic system, and the pedunculopontine nucleus (PPN) cholinergic system. DBS has been shown to improve motor symptoms and increase dopamine release in the striatum. However, it can also cause non-motor side effects such as mood disorders, which might be related to its impact on the DRN serotonergic and LC noradrenergic systems. Recent research has shown that external stimuli can drive neurotransmitter switching in the mature brain, providing evidence for

DBS-induced neurotransmitter respecification. Understanding the effects of DBS on the monoaminergic systems is essential for optimizing its benefits and minimizing its side effects.

Recent approaches such as optogenetic, chemogenetic, and transgenic animal lines can address the limitations of detecting real-time transmitter release and neurotransmitter-related changes in distant neural locations. In addition, these approaches make it possible to target specific cell types. Therefore, in **Chapter 3**, we have conducted optogenetic experiments to examine the precise effects of neuromodulation on neurotransmitter release and evaluate the cumulative and chronic impact of DBS on local and distant neural components. While using a genetically encoded calcium indicator protein using a viral vector, we could assess the neuronal activity and phenotype of serotonergic neurons in the DRN. Our findings suggest that long-term STN-DBS may have a negative impact on the serotonergic system, specifically by inhibiting the activity of DRN serotonergic neurons, which may contribute to mood-related side effects such as depression. The use of a specific cell-type approach using transgenic mice allowed for the assessment of the effects of STN-DBS on DRN serotonergic neurons with greater specificity. The observed reduction in calcium signaling in the DRN is consistent with previous studies that have demonstrated the inhibitory effect of STN-DBS on serotonergic neurons in the DRN.

Additionally, the behavioral despair observed in mice treated with STN-DBS suggests the negative impact of STN-DBS on the serotonergic system. The findings highlight the importance of investigating the long-term effects of DBS on the brain's neuromodulatory systems, particularly those implicated in mood regulation. Post-mortem immunohistochemistry analysis reveals that the STN-DBS may cause a change in the phenotype of DRN serotonergic neurons. This is supported by previous studies showing that STN-DBS can lead to changes in neurotransmitter release and the expression of specific neurotransmitter-related proteins in various brain regions.

Neuroplasticity refers to the ability of the brain to adapt and reorganize in response to environmental stimuli or experiences. There is increasing evidence that neuroplasticity also occurs with DBS, including STN-DBS. As previously mentioned, STN-DBS can affect local neural circuits and distant brain areas, leading to changes in neurotransmitter release and behavioral outcomes. The stimulation-induced changes in neurotransmitter release may cause neuroplastic changes in the target neurons, resulting in the respecification of neurotransmitter phenotypes. This may contribute to the long-term effects of STN-DBS on both motor and non-motor symptoms in PD.

There is no direct connection between STN and DRN, and STN-DBS could bypass through other relay nuclei such as lateral habenula and prefrontal cortex. Nevertheless, a novel link between globus pallidus externus (GPe) and DRN has been discovered. In addition, the known connection of the GPe to STN. As a result, in **Chapter 4,** we assessed the effect of GPe on DRN using a chemogentic approach in mice treated with STN-DBS. Our findings suggest that the GPe does not directly mediate the effect of STN-DBS on DRN serotonergic neurons. Further studies are needed to investigate the precise pathways involved in STN-DBS. In **Chapter 5**, our findings suggest that STN-DBS has no significant effect on the

PPN cholinergic system. These findings indicate that STN-DBS may improve gait in PD through other pathways, including the STN projection and modulation of cortical connectivity.

DBS requires invasive surgery and can lead to complications. In **Chapter 6**, we have reviewed the use of nanomaterial for neuromodulation. Novel approaches are being explored, such as using magnetoelectric nanoparticles (MENPs) to deliver DBS wirelessly. MENPs generate an electric field in response to a magnetic field, which can stimulate the brain without genetic modification. In **Chapter 7**, our findings suggest that magnetoelectric stimulation of the STN may have similar effects as conventional STN-DBS, particularly concerning enhancing locomotion and an increase in the neuronal activity in the motor cortex and paraventricular thalamus. Notably, magnetoelectric stimulation of the STN decreases the activity of the ventral tegmental area (VTA) dopaminergic and DRN serotoninergic neurons, respectively. However, it's important to note that magnetoelectric stimulation did not affect neuron activity in the PPN cholinergic and SNc dopaminergic neurons. These results suggest that the principal monoaminergic neurotransmitter systems may play a role in the mechanisms of magnetoelectric stimulation of the STN. These findings may have implications for developing noninvasive neuromodulation approaches for treating PD. In addition, the increased activity in the PV following magnetoelectric stimulation of the STN may lead to hyperlocomotion due to the relay of information from the subthalamic and brainstem regions to the nucleus accumbens and the amygdala, which are associated with cortical areas.

These findings suggest that magnetoelectric stimulation of the STN may modulate dopaminergic activity in the VTA, which could lead to the observed hyper locomotion. The potential involvement of GABAergic cells in the VTA in this mechanism warrants further investigation. In addition, it is possible that the lack of observed effects on the nigrostriatal network in naïve animals could be due to compensatory mechanisms within the system. Future studies could investigate the long-term effects of magnetoelectric stimulation of the STN on both the mesolimbic and nigrostriatal pathways, as well as potential downstream effects on behavior and cognition. Overall, these findings provide insight into the neural mechanisms underlying the therapeutic effects of magnetoelectric stimulation of the STN and could inform the development of new neuromodulatory approaches for PD. In addition, magnetoelectric stimulation of the STN did not significantly impact the activity of cholinergic neurons in the PPN. This is consistent with previous research on conventional STN-DBS, which also suggests that the therapeutic effect of STN-DBS may be related to other pathways, such as the direct projection to the cortex and the mesolimbic dopaminergic system, despite a known dopaminergic-cholinergic imbalance that exists in axial movement disorder symptoms, especially in PD. However, it appears that magnetoelectric stimulation of the STN did not affect this particular pathway.

Nevertheless, this technology is still new and needs more research to optimize it, including designing a powering device and less invasive delivery routes to the brain. In addition, several challenges must be addressed before nanomaterials can be used in clinical applications. It needs to be explored whether multiple MENPs can be used simultaneously. Delivering nanomaterials to the brain requires noninvasive methods that do not damage neural tissue. Moreover, studying the optimal stimulation parameters and

patterns of MENPs would be essential to optimize their therapeutic effects while minimizing side effects. Overall, further research is needed to understand the potential of MENPs technology for PD treatment.

In summary, These findings provide valuable insight into the mechanisms of action of STN-DBS and its effects on the monoaminergic neurotransmitter system. The role of the serotonergic system in mood regulation and its relationship with STN-DBS-induced adverse mood effects highlight the importance of monitoring and managing the serotonergic system in PD patients. The lack of effect on the cholinergic system suggests that other pathways may be responsible for the therapeutic effects. STN-DBS surgery for PD has overall had a beneficial impact. It must, however, be taken with caution, monitored closely, and individually assessed for each patient while considering possible harmful effects. Future studies must fully detail how to enhance this process, reduce the negative impacts of these procedures, and uncover the precise neurotransmitters mechanism. In addition, developing less-invasive techniques could make it more practical and affordable for patients and healthcare.