The physiological effects of acute exposure to MPTP on the mammalian lumbar central pattern generator

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Introduction

MPTP is a pharmacological agent used to induce parkinsonism within primates and mice (Przedborski & Vila, 2001). When MPTP crosses the blood brain barrier, it is up taken by glial cells and oxidized into MPP^+ by localized MAO-B enzymes. MPP^+, the active form of the neurotoxin, is released into the synaptic cleft where it is taken up by presynaptic neurons that express dopamine transporters (DAT) at their synaptic bouton (Tan et al., 2022). Once inside, MPP^+ can interact with complex I of the mitochondria, triggering ATP depletion and a buildup of reactive oxygen species (ROS) (Przedborski & Vila, 2001). Moreover, MPP^+ can also interact with Vesicular monoamine transporter protein 2 (VMAT2) to disrupt the packaging of monoamine transmitters (Przedborski & Vila, 2001). MPTP induces dopamine depletion within the substansia nigra pars compacta (SNpc), a key pathophysiology of Parkinson's disorder. Histological evidence shows that MPTP triggers motor neuron death (Vivacqua et al., 2020). However, MPTP effects on neural circuits that control motor activity within the spinal cord remain unknown. Notably, motor neurons localized in the lumbar region of spinal cord have been shown to express DAT. We investigate how acute exposure to MPTP affects the central pattern generator (CPG) network in the isolated spinal cords of neonatal mice. The CPG is a circuit of interneurons capable of generating rhythmic outputs without brain signals. Additionally, we assess the combinatorial effects of dopamine and MPTP on the CPG. We expect to find a decrease in amplitude of electrical discharges termed bursts. Moreover, we see an increase burst duration and cycle period, signaling a decrease in excitability and speed on the CPG network, respectively.

Methods

We isolate the spinal cords of neonatal mice (P0-P6) via ventral laminectomy while preserving flexor and extensor related ventral roots, L2 and L5-respectively. Using serotonin and NMDA, we activate the CPG network to generate rhythmic outputs termed fictive locomotion and electrophysiological techniques are sued to record electrical discharges (Acevedo et al., 2016). After an established stable rhythm, a control recording is records after which MPTP is applied alone or in the presence of dopamine (9 μM) at three concentrations: 50 μM, 75 μM, 100μM. After drug application, we conduct a wash condition. To analyze data, use a custom-made script (provided by Dr. Thomas Cleland, Cornell University) to observe changes in the three main parameters: burst amplitude, burst duration, and cycle period. After, EXCEL and Graph Pad prism are used to quantify and generate graphs.

Results

Current findings indicate that MPTP application alone induces variable results in burst amplitude at 50 μM. However, at 75 μM, MPTP decreased amplitude and obliterated locomotor rhythm at 100 μM. At all concentrations, MPTP decreased the network speed with minimal effect on the CPG's excitability. In the presence of dopamine, at 50 μM and 75 μM, MPTP decreased amplitude. At 50 μM, MPTP decreased burst duration and cycle period. Conversely, at 75 μM, MPTP increased burst duration and cycle period.

Preliminary conclusion and future directions

Our findings suggest that a co-application of MPTP with dopamine offers more replicable results. Overall, our results suggest a drug dependent effect and mechanism of action of MPTP on CPG activity, but MPTP seems to consistently reduce motor neuron recruitment as indicated by a decrease in burst amplitude. In the future, we hope to increase the number of experiments across all concentration groups and conduct patch-clamp recordings. Through patch clamp recordings, we investigate MPTP's effect on excitatory post synaptic potentials (EPSPs), to further understand how MPTP is impacting synaptic transmission and thus motor neuron recruitment.

References

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