The Role of Methylphenidate (Ritalin) on Neuronal Development: A Cell Biological Perspective on the Treatment of ADHD

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DISCOVER

Abstract

As one of the most common neurodevelopmental disorders in children, attention deficit hyperactivity disorder (ADHD) is often characterized by persistent inability to focus, increased restlessness and behavioral impulsivity, all of which can impede in daily functioning. Although the true cause of ADHD is unknown, it has long been attributed to genetic, environmental and lifestyle factors. Additionally, ADHD patients have often been found to have sub-optimal norepinephrine and dopamine levels in their pre-frontal cortex, which contributes to the symptoms of ADHD such as reduced executive function. To treat ADHD, physicians often prescribe methylphenidate (MPH), commercially known as Ritalin, which acts as a dopamine re-uptake inhibitor by targeting the dopamine transporter protein (DAT) on pre-synaptic neurons of the pre-frontal cortex. Based on current literature, MPH has been found to be an effective treatment for ADHD in both adult mouse models and humans at varying doses, however, a knowledge gap exists concerning the long-term effects of MPH on juvenile brain development, which this literature-based study aims to address. With a greater understanding of the effects of MPH on adolescent brain development, improved clinical drug treatments can be achieved in the future to improve the quality of life for young patients living with ADHD.

Introduction

Origins

- In 1798, Sir Alexander Crichton made the first discoveries of what would later be described as ADHD by observing adolescent inattention and inability to focus
- However, nearly 200 years later The Diagnostic and Statistical Manual of Mental Disorders (DSM), did not formally recognize ADHD until 1987! [1]

Symptoms and Prognosis

- Typically, these symptoms present before the age of 12 and can manifest as early as age 3
  - **Inattention:** having a difficult time concentrating, staying on task or lacks organization skills
  - **Hyperactivity:** constantly moving around or fidgeting
  - **Impulsiveness:** acting without thinking or sustaining self-control [2]

- Many children diagnosed with ADHD in adolescence can be properly treated with medication and behavioral therapy to lead a normal life
- However, if left untreated into adulthood many difficulties can arise such as: academic/job related difficulties, depression, and substance use disorders

Demographics of ADHD

- Nearly 11% of children in the US have been diagnosed with ADHD, totaling to approximately 6 million as of 2019
- Additionally, Black, non-Hispanic children and White, non-Hispanic children are more often diagnosed with ADHD (12% and 10%, respectively), than Hispanic children (8%) or Asian, non-Hispanic children (3%) [3]

Neurobiological Basis of ADHD

- ADHD primarily effects an individual's pre-frontal cortex, which is responsible for executive function, such as self-monitoring and cognition [4]
- ADHD is caused by dopamine deficiencies caused by increased dopamine transporters (DAT) function
- ADHD is associated with deficiencies in serotonin uptake

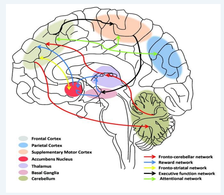

Fig 1. The functional circuits of the brain impacted by the pathophysiology of ADHD

Methylphenidate (MPH) Treatment

- The CNS stimulant, methylphenidate (MPH), commercially known as Ritalin, was first discovered in 1944, and is prescribed to children diagnosed with ADHD
- **Mechanism of Action:** MPH is a re-uptake inhibitor for both dopamine and norepinephrine, thereby increasing dopaminergic concentrations in the synaptic cleft of pre-frontal cortex neurons [5]

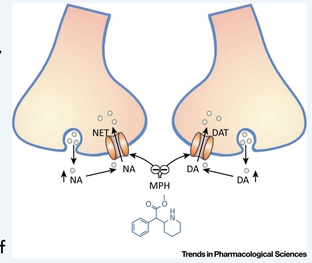

Fig 2. The most probable mechanism of action for methylphenidate (MPH) acting upon both dopamine transporters (DAT) and norepinephrine transporters (NET)

Effect of Neural Stem Cell Differentiation and Neurogenesis during MPH Treatment

- **Chronic methylphenidate exposure was studied in both high and low does to see the effects on neurogenesis**, cells increased in both doses however cells not receiving constant methylphenidate didn't survive past the 28-day mark.
  - This may show some dependency on the drug, high dose groups (10mg/kg) groups experienced cell proliferation, but these cells didn't survive past the 56-day mark most likely due to decreases in VEGF, TrkB and beta-catenin. These studies were performed in mouse models. [7]

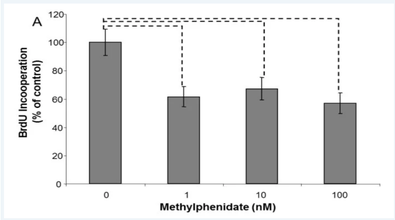

Fig 3: Methylphenidate at varying concentrations enhanced neuronal differentiation into immature neurons in murine neural stem cell (mNSC)

- Murine neural stem cells have been used as models to test the effects of varying dosages of methylphenidate on neuronal differentiation.[10]

Morphological Effects on Sperm and Brain Structures due to MPH Treatments

- **Methylphenidate (MPH) has shown to cause problems with sperm morphology, count, and motility.** Sperm motility decreased by 38.62 units. Sperm count decreased by 14.36 units [9]
- **Free-moving spontaneously hypertensive (SH) rats are a useful model for studying the neurochemical basis of ADHD** and assessing the pharmacological effects of treatment therapies.
  - Using in vivo micro-dialysis techniques, this review synthesizes findings from research on catecholaminergic function in important brain regions of SH rats, including as the **prefrontal cortex (PFC), striatum, and nucleus accumbent**.
  - The findings show a varied neurochemical landscape characterized by **reduced basal norepinephrine efflux in the PFC and hyper-functional dopaminergic neurotransmission in the striatum and mesolimbic system**, which mirrors the hyperactive phenotype of SH rats.
  - Finally, potential medication development directions for ADHD are suggested, based on the findings from these micro-dialysis experiments in SH rats [8].

Research Gaps

Although MPH has been shown to be an effective treatment for ADHD, there are still many unknowns that must be addressed to understand the implications of long-term usage on juvenile brain development:

1) Are there differences in the effects of methylphenidate based on early exposure to those misdiagnosed with ADHD and those with true ADHD?

2) Most research are short-term effects of MPH on brain function, more specifically in adult brains, what is the effect on juvenile brains?

3) What are the negative effects on brain development after long-term methylphenidate treatments?

4) Why are there differences in the expressions of the ADHD in males and females?

Proposed Experimental Approaches

- **Certain genes and regulators in the striatum have been associated with ADHD, as such sequencing using Chip-seq could create targets for further research**
  - Latrophilin-3 (***LPHN3***) is a regulator of synaptic function associated with ADHD.
  - Further sequencing of this receptor using **Chip-Seq** will allow us to further investigate its role in synaptic function.
  - Using this molecular target and previous research that saw reduced synaptophysin immunoreactivity.
  - Studies between high-attention rats and control rats both treated with MPH demonstrated major differences in regulation of several genes including reduction of ***Cfl1*** and dysregulation in ***Glo1*** *the* approach could now focus on differences between the sexes in juveniles. [11]
- An additional new approach would be **to measure the density of synaptophysin with parameters associated with juvenile brains** in mice models, specifically SH rats

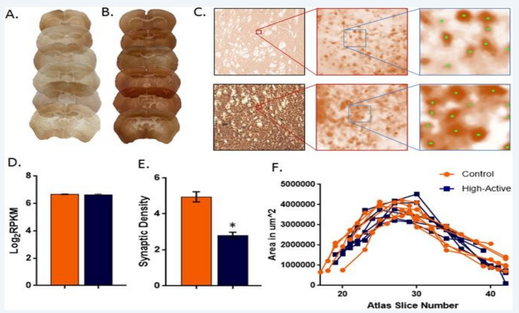

Fig 4: The density of synaptophysin is reduced in hyperactive mice-models

- As part of this approach, the research would use different parameters for density measurement that would account for the developing juvenile brain, with comparisons between male and female brains
- Another potential approach, would be to use SH rats as a model to target specific genes related to ADHD and the effect MPH has on their expression (which can be accomplished by **RNA-Seq**) [12]

Density of synaptophysin

Significance

ADHD, a prevalent lifelong neurodevelopmental disorder, poses significant challenges for individuals in both academic and professional settings. It's crucial to recognize that ADHD often coexists with other disorders. Competing views exist regarding behavioral and pharmacological approaches. MPH is commonly prescribed to manage ADHD symptoms. In fact, 59% of ADHD patients take stimulants such as MPH.[9] While it effectively enhances attention in children and adults, concerns persist regarding misdiagnosis. Gender differences in symptom presentation—females more inclined toward inattentiveness, while males often display hyperactivity and impulsivity—underscore the complexity of accurate diagnosis. However, reliance on methylphenidate is not without risks. Prolonged use may lead to dependence and morphological changes in the brain. Common side effects include difficulty sleeping, nervousness, irritability, and impaired cognitive function and reproductive issues. Research conducted on 71 children, in Iran, revealed that 74% of children on methylphenidate experienced anorexia, 57% exhibited irritability, and 47% reported other adverse reactions over six months.[13] Concerns linger about the long-term impact, particularly on the developing juvenile brain. Given these concerns, further research is imperative to elucidate the full spectrum of physical and mental effects associated with methylphenidate. Such insights could alleviate the burden on families, both in terms of the financial costs associated with long-term medication and the potential health risks posed to children with ADHD.

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Acknowledgements

Our team would like to thank Dr. Piya Ghose for her support, guidance and mentorship throughout the duration of our project.