Research question: 'Can psychostimulant drugs provoke Parkinson's disease?''

Introduction

Previous studies have linked psychostimulants with neurotoxicity, which poses a serious global health risk. In 2019, there were approximately 47 million global users of amphetamine-type stimulants (Crime, 2021), which emphasises the further need for investigation in order to educate health professionals and the public about the great risks involved. The further study of the important behavioural modifications as well as the molecular mechanisms, upon psychostimulant consumption is vital in filling this gap in the knowledge so that clinical solutions can be devised.

In this study, the link between psychostimulant consumption and neurodegeneration that has recently been observed will be further explored using *Drosophila* in order to learn more about the biology, both on a cellular and on an organism-wide level, of amphetamine consumption. This interdisciplinary research will be important in several different fields of study, using novel approaches and a knowledge of neurology to investigate the effects of amphetamine consumption on the *Drosophila* brain.

Background

Psychostimulants disrupt striatal dopamine neurotransmission through several important modes of action (Sulzer, 2011). AMPH may act through direct interactions with the *Drosophila* vesicular monoamine transporter 2 (dVMAT2) and the *Drosophila* dopamine transporter (dDAT). (Philyaw, Rothenfluh and Titos, 2022). It may also interfere with the vesicular pH gradient and act directly on the MAO inhibitor and the TH activator (Sulzer, 2011). Overall, the molecular basis of the response to amphetamines and other psychostimulants is conserved in flies and mammals, which makes Drosophila the perfect experimental organism, particularly of identification of novel genes and molecular processes.

The behavioural impacts of amphetamine consumption in Drosophila are also important. Using assays of motor-activity (Philyaw, Rothenfluh and Titos, 2022), were able to quantify different responses upon response to cocaine, a psychostimulant drug. However, to date, little has been answered about amphetamine consumption more specifically, especially regarding its effects to neurotoxicity in *Drosophila*.
Another study, (Shin et al., 2017) described that the long-term dopaminergic damage in the brain caused by methamphetamine, a type of psychostimulant, such chronic use of methamphetamine may be related to Parkinson's disease, however more studies are necessary. This research question aims to fill this gap in the knowledge, exploring this link between psychostimulant consumption and Parkinson's disease.

All in all, the complexity of this issue calls for further research, particularly with different types of experimental organisms due to the differences in amphetamine neurotoxicity between species and using different administration routes. Furthermore, although there may be a link between Parkinson's disease and psychostimulants, this is uncertain, and the molecular mechanisms behind this are not fully known. This study will attempt to resolve such questions through the use of several different experimental methods using *Drosophila*.

Objectives

-To use genetic tools in the laboratory to investigate the molecular and cell biology behind amphetamine consumption on the brain.
-To observe the behavioural changes in Drosophila caused by amphetamine consumption, and link these observations to the molecular mechanisms.
-To explore the links between amphetamine consumption and neurodegeneration.
-To explore the possible in field applications of these findings, including the education of patients in rehabilitation centres.

Timeframe
This project will last 6 weeks during the summer of 2022, and it will be mainly laboratory based. Different genetic techniques will be utilised in order to closely observe the mechanisms behind amphetamine-induced neurodegeneration in *Drosophila*. Furthermore, behavioural changes throughout the process will also be monitored.

Intended audience
The intended audience for this project is both academic, as this project includes a posters and presentations to university staff and students. The intended audience is also non-academic, particularly patients in rehabilitation centers.

To give a brief summary of this project to a layperson, I would begin by stating that psychostimulant drugs can influence different reward pathways in the brain, which can lead to several different consequences. In order to investigate such consequences, an example of which would be neurodegeneration, genetic experiments will be conducted on the fruit fly. This will ensure a better understanding of the pathways in the brain that lead to neurodegeneration, which is important in educating health professionals as well as users of such psychostimulant drugs so that they can be made aware of the severe consequences.

Conclusion
In conclusion, this project is of wide importance to global health, and it is vital that more is learned about the link between Parkinson's disease and psychostimulant consumption. The molecular and behavioural effects of amphetamine consumption will be investigated using Drosophila as an experimental organism, using genetic tools in the laboratory to ultimately bridge the gap in knowledge between neurotoxicity, and the consumption of psychostimulant drugs.

References
1. Crime, U., 2021. World Drug Report 2021. *CrimRxiv*.

2. Philyaw, T., Rothenfluh, A. and Titos, I., 2022. The Use of Drosophila to Understand Psychostimulant Responses. *Biomedicines*, 10(1), p.119.

3. Shin, E., Dang, D., Tran, T., Tran, H., Jeong, J., Nah, S., Jang, C., Yamada, K., Nabeshima, T. and Kim, H., 2017. Current understanding of methamphetamine-associated dopaminergic neurodegeneration and psychotoxic behaviors. *Archives of Pharmacal Research*, 40(4), pp.403-428.

4. Sulzer, D., 2011. How Addictive Drugs Disrupt Presynaptic Dopamine Neurotransmission. *Neuron*, 69(4), pp.628-649.