Unraveling the Role of GABAergic Dysfunction in Catatonia: A GABAergic Investigation in Drosophila

Varsha Alladi
Advisor: Kevin Crowthers, Ph.D

Background

- Catatonia is a neuropsychiatric syndrome associated with various medical and psychiatric disorders
  - Most associated with mood or psychotic disorders but it can also occur with other conditions
- Catatonia can be life-threatening but can be treated with medications such as benzodiazepine or electroconvulsive therapy
- Research has shown that the GABAergic pathway is important in the development of catatonia, particularly involving GABA-A receptors
  - However, the exact mechanisms still remain unclear

Research Question

How does Ashwagandha exposure **influence** locomotion and chemosensory responses in Drosophila melanogaster, as a model for understanding **GABAergic dysfunction** in catatonia?

Hypothesis

Ashwagandha exposure will **enhance** locomotion and chemosensory responses in Drosophila melanogaster with reduced **GABAergic activity**.

Purpose

This study aims to evaluate how Ashwagandha exposure impacts behaviors in Drosophila melanogaster with reduced GABAergic activity, modeling catatonia-like symptoms. Specifically, this study examines:

- **Locomotion**: Movement patterns and climbing ability in a negative geotaxis assay.
- **Sensory Responsiveness:** Reaction to sucrose in a two-choice chemosensory assay.

Insights aim to determine whether Ashwagandha enhances GABAergic function and alleviates motor and sensory impairments,

Analysis

- **Negative Geotaxis Assay**:
  - Ashwagandha exposure increased locomotion, particularly at 0.60% and 1.20% concentrations.
  - Higher concentrations showed a dose-dependent effect, enhancing climbing activity more than the control group.
  - Indicates that Ashwagandha may influence GABAergic pathways in low GABA flies, improving motor function.
- **Chemosensory Assay:**
  - Ashwagandha exposure enhanced chemosensory responses, with 0.60% and 1.20% concentrations showing the strongest effect.
  - Flies treated with Ashwagandha were more attracted to sucrose compared to the control, suggesting increased sensory responsiveness.
  - Suggests Ashwagandha modulates chemo responsiveness, impacting sensory behavior.

GABAergic Pathway

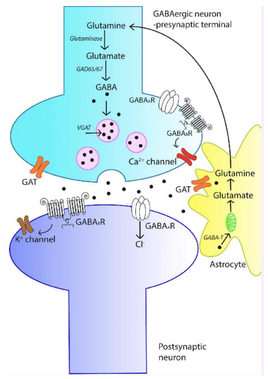


Figure 2: A visual representation of the GABAergic pathway. GABA molecules are transferred from one neuron to another enacting a series of interactions within the body.

- The GABAergic pathway is a network of neurons and synapses in the central nervous system
  - Gamma-aminobutyric Acid (GABA) is a neurotransmitter used to inhibit excessive brain activity
- Dysfunction in the GABAergic pathway disrupts inhibitory signals, leading to overactivity in neural circuits
  - This affects motor and behavioral control
- Since the symptoms of catatonia, such as motor immobility and rigidity are linked to disruptions in motor control, the GABAergic pathway likely plays a role

Main Takeaways

Drosophila with reduced GABAergic signaling exhibit impaired locomotion, mimicking catatonia-like motor deficits observed in humans.

- This makes them a viable model for studying GABA dysfunction in catatonia.

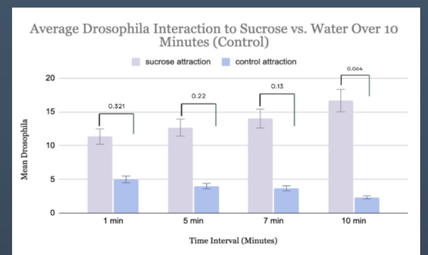
Ashwagandha exposure

- Enhances locomotor activity in Drosophila --> improved climbing performance in the negative geotaxis assay.
- Chemosensory responses improve -->with flies showing an increased preference for sucrose, showing that sensory function returned to normal.

Results will highlight:

- The role of GABAergic dysfunction in behaviors linked to catatonia
- Potential pathways for alternative treatment strategies

Results



Graph 1: This graph shows the average attraction of wild-type Drosophila to sucrose compared to water over a 10-minute period. As expected for the control group, Drosophila exhibited a stronger attraction to sucrose, demonstrating normal chemosensory behavior. The consistent attraction to sucrose over time indicates typical sensory processing, supporting the reliability of the control group in assessing Drosophila's natural response to sucrose.

Conclusion

Low GABA causes catatonia-like symptoms:

- Reduced GABA activity in flies leads to behaviors consistent with catatonia, including impaired motor and sensory responses.

Ashwagandha enhances locomotion:

- Ashwagandha treatment improves motor function in Drosophila with reduced GABA activity, as shown in the negative geotaxis assay.

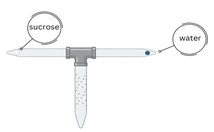
Increased chemosensory responsiveness:

- Leads to higher attraction to sucrose, suggesting improvement in sensory processing.

Potential for GABAergic dysfunction:

- Ashwagandha could help modulate GABAergic pathways involved in catatonia-like symptoms.

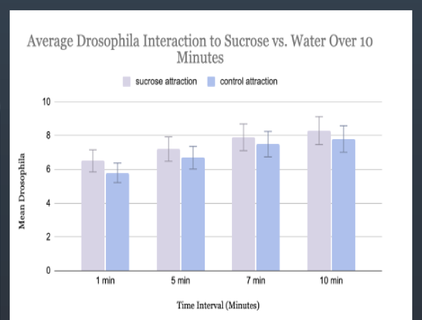
Methodology



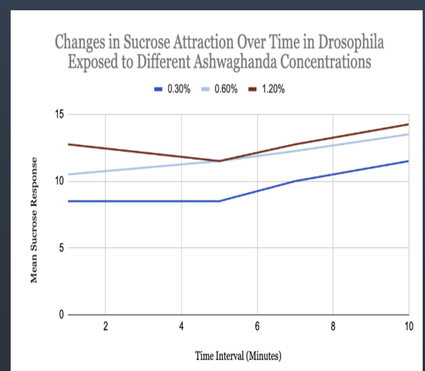
Chemosensory Assay: Assesses sensory function by tracking Drosophila's preference for sucrose over water. Sensory deficits are a feature of catatonia, making this assay relevant for studying GABAergic dysfunction.

Negative Geotaxis Assay: Tests locomotor ability by measuring how quickly Drosophila climb against gravity. Since catatonia involves motor impairments, reduced climbing in low-GABA flies models these symptoms.

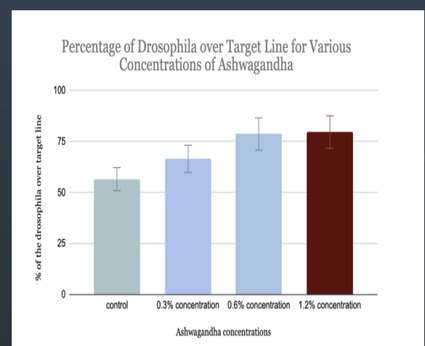
Experimental Setup: Identified low GABA Drosophila as a model for catatonia, divided them into control and Ashwagandha-exposed groups (0.3%, 0.6%, 1.2%).
Negative Geotaxis Assay (Motor Function): Tested climbing ability over 10 seconds to assess locomotion deficits, analyzed using one-way ANOVA.
Two-Choice Chemosensory Assay (Sensory Response): Measured preference for sucrose vs. water to evaluate sensory perception, analyzed using t-tests.
Data Analysis & Relevance: Compared behavioral improvements across groups to assess Ashwagandha's effects, validating Drosophila as a catatonia model.



Graph 2: This graph shows the average attraction to sucrose versus water over a 10-minute period in Drosophila with a mutation in the rdl gene, leading to reduced GABA levels. Unlike the control group, these GABA-deficient flies exhibited a significantly decreased attraction to sucrose, indicating impaired sensory processing. The difference in attraction between sucrose and water highlights the sensory deficits caused by the GABA mutation, supporting the use of rdl mutant Drosophila as a model for studying catatonia-like symptoms.



Graph 3: This line graph shows the change in sucrose attraction of Drosophila with the rdl mutation (low GABA) when exposed to different concentrations of Ashwagandha. The graph demonstrates an increasing trend in sucrose attraction as Ashwagandha concentration rises, indicating a potential improvement in sensory function and mitigation of catatonia-like symptoms in GABA-deficient flies.



Graph 4: This is a bar graph representing the percentage of Drosophila with the rdl mutation (low GABA) that successfully crossed the target line in the negative geotaxis assay at different concentrations of Ashwagandha. The results show a trend of increased climbing ability with higher Ashwagandha concentrations, suggesting a potential improvement in motor function and alleviation of catatonia-like symptoms in GABA-deficient flies.

References

De Jonge, J. C., Vinkers, C. H., Pol, H. E. H., & Marsman, A. (2017). GABAergic Mechanisms in schizophrenia: linking postmortem and in vivo studies. Frontiers in Psychiatry, 8. https://doi.org/10.3389/fpsyt.2017.00118
Edinoff, A. N., Kaufman, S. E., Hollier, J. W., Virgen, C. G., Karam, C. A., Malone, G. W., Cornett, E. M., Kaye, A. M., & Kaye, A. D. (2021). Catatonia: Clinical overview of the diagnosis, treatment, and clinical challenges. Neurology International, 13(4), 570–586. https://doi.org/10.3390/neurolint13040057
Hirjak, D., Kubera, K., Wolf, R., & Northoff, G. (2019). Going back to Kahlbaum's psychomotor (and GABAergic) origins: Is catatonia more than just a motor and dopaminergic syndrome? https://www.semanticscholar.org/paper/Going-Back-to-Kahlbaum's-Psychomotor-(and-Origins%3A-Hirjak-Kubera/9863cd69199674522fc0a522cd83d9a2ea4304d8
Kline, C. L., Suzuki, T., Simmonite, M., & Taylor, S. F. (2022). Catatonia is associated with higher rates of negative affect amongst patients with schizophrenia and schizoaffective disorder. Schizophrenia Research, 263, 208–213. https://doi.org/10.1016/j.schres.2022.09.001
Parekh, P., Gozi, A., Reddi, V. S. K., Saini, J., & John, J. P. (2021). Resting state functional connectivity and structural abnormalities of the brain in acute retarded catatonia: an exploratory MRI study. European Archives of Psychiatry and Clinical Neuroscience, 272(6), 1045–1059. https://doi.org/10.1007/s00406-021-01345-w
Plevin, D., Mohan, T., & Bastiampillai, T. (2017). The role of the GABAergic system in catatonia—Insights from clozapine and benzodiazepines. Asian Journal of Psychiatry, 32, 145–146. https://doi.org/10.1016/j.ajp.2017.12.008
Vang, L. L., Medvedev, A. V., & Adler, J. (2012). Simple ways to measure behavioral responses of drosophila to stimuli and use of these methods to characterize a novel mutant. PLoS ONE, 7(5), e37495. https://doi.org/10.1371/journal.pone.0037495