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Article

Reducing tremors in LRRK2-G2019S genetically-mutated Parkinson's flies with a lovastatin–levodopa combination

Amelia Foell[1], Courtney Rivet-Noor[2], Andrew Bramante[1]
[1] Greenwich High School, Greenwich, Connecticut
[2] Duke University, Durham, North Carolina

SUMMARY

Parkinson's disease (PD) is a major neurodegenerative disease, impacting millions of people worldwide. One of the most common and problematic symptoms of PD is tremors, or uncontrollable movement. Tremors are a result of a reduced concentration of dopamine in the brain and can generally be treated with the drug combination carbidopa–levodopa. Levodopa replaces the missing dopamine while carbidopa prevents levodopa from being broken down before it reaches the brain. However, research suggests that this chemical combination is not always successful and sometimes worsens symptoms for patients, suggesting that more effective drug combinations could be tested. Lovastatin, an inhibitor typically used to lower cholesterol, has demonstrated neuroprotective properties that may offer a novel mechanism for Parkinson's symptom relief that traditional decarboxylase inhibitors like carbidopa cannot provide. We investigated the effectiveness of a lovastatin–levodopa combination compared to carbidopa–levodopa in reducing tremors in a *Drosophila melanogaster* model of PD (LRRK2-G2019S, PD-L). We hypothesized that the lovastatin–levodopa combination would work to eliminate tremors better than a carbidopa–levodopa combination. Wild-type (WT) and PD-L *Drosophila* activity was recorded over time in the *Drosophila* activity monitor, with lights on or off to represent their circadian rhythms. Our results showed that lovastatin–levodopa was the more optimal drug combination, suggesting that the classic combination of carbidopa–levodopa may not be the most effective at reducing tremors in this model system and may be more beneficial when carbidopa is replaced with lovastatin. Further studies should be aimed at supporting these results in mammals and optimizing the concentration of these drugs in animal systems.

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative diseases, affecting over 10 million people worldwide (1). The rate of PD is increasing due to a large aging population, in which the cells' natural disposal systems—specifically autophagy and the lysosomal pathway—gradually decline as the body ages, causing neurodegeneration (1). PD is characterized by unintentional movements, including shaking, stiff limbs, and struggles with balance and coordination (2). Tremors, or uncontrollable movements, are the most common and debilitating symptom of PD (3). Tremors can significantly impact a patient's daily activities (i.e., drinking from a cup). Tremors usually start in one hand before spreading to the rest of the arm, and after several years they can spread to the other side of the body (4). In some cases, patients have an internal tremor, where they feel the tremor inside their body, but it is not noticeable by others (5). Tremors typically worsen over time—the progression rate varies for each individual, but motor impairments tend to become noticeably disruptive five to ten years after diagnosis of PD (6). PD tremors can significantly impact patients' lives, so it is critical to find the best treatments for these uncontrolled movements. While there are some therapies and medicines that can reduce symptoms, as of now, there is no cure for tremors (7).

The main cause of tremors is a reduction of dopamine in the patient's brain, which can affect the entire body (6). Dopamine is a neurotransmitter that affects one's behavior, movement, memory, sleep, and positive emotions, which is why its reduction has a significant impact on one's mental and physical health (8). Dopamine is produced by neurons in the substantia nigra pars compacta—an area of the midbrain primarily responsible for housing the specialized neurons that produce dopamine—and dopamine loss in PD is often caused by the death of these dopaminergic neurons (i.e., nerve cells that send and receive messages throughout the body, enabling day-to-day actions) (9, 10). Neurons die in PD due to an accumulation of abnormal proteins that kill off these brain cells (11). One of the most common causes of neurodegeneration in PD is a gene mutation of a G2019S variant—a glycine (G) has been replaced by a serine (S) at amino acid number 2019—in LRRK2, a leucine-rich repeat kinase. This mutation causes an increase in LRRK2 activity, which disrupts critical intracellular processes within dopaminergic neurons and surrounding glial cells—including mitochondrial dysfunction that leads to a toxic accumulation of misfolded proteins—and also triggers neuroinflammation by overactivating microglia (12–16). Furthermore, dopamine is harder to produce as one gets older (typically age 60+) because according to a study, the activity of an enzyme called monoamine oxidase B increases, which accelerates the breakdown of available dopamine (17). Taken together, these changes in the levels of dopamine (i.e., mediators of motor function), often result in the tremors seen in PD patients (18). Thus, attempting to increase dopamine levels has been the main form of PD treatment.

Although natural therapies such as walking and stretching can boost dopamine levels in the brain, neurons that have lost the ability to produce dopamine, such as in aging and PD, cannot benefit from these therapies (8–10, 17, 18). Therefore, medications are often used to manage dopamine loss. One of the most common treatment methods used to counter dopamine loss and tremors is a combination of two drugs:

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carbidopa–levodopa, which has been reported to successfully reduce tremors in 78% and 70% of patients with mild and significant baseline resting tremors, respectively (19, 20). The chemicals within this medicine interact with neuro-transmitting enzymes in the brain to create dopamine (21). Levodopa replaces the missing dopamine, while carbidopa prevents levodopa from being broken down before it reaches the brain (22). Carbidopa inhibits aromatic L-amino acid decarboxylase, which reduces the peripheral conversion of levodopa to dopamine, resulting in an increased amount of levodopa entering the brain (23). However, in high concentrations, carbidopa can inhibit the conversion of levodopa to dopamine (23, 24). In addition, this combination is not always successful in reducing tremors, and using more than the recommended amount has been shown to cause dyskinesia, a different type of uncontrollable movement, in up to 20% of patients (25, 26). Because levodopa remains the most potent therapeutic agent for managing Parkinson's tremors, there is more focus on identifying alternative adjunctive compounds that can be co-administered with levodopa to maximize its therapeutic efficiency while mitigating these severe secondary motor complications. Another treatment option is "dopamine agonists," which have been shown to mimic the effects of naturally-produced dopamine (27). However, this method is more common in younger patients who want to delay taking carbidopa–levodopa, as the agonists often do not work as long-term treatments (27, 28). Based on this evidence, there is room for improvement in the types of medications available for PD tremors, especially regarding a replacement to stop levodopa from breaking down before reaching the brain.

The goal of our research was to identify a novel levodopa combination for the treatment of Parkinson's tremors, using an alternative drug (statin) in replace of carbidopa. Statins have neuroprotective qualities that can prevent harmful side effects such as dyskinesia that carbidopa may induce while helping levodopa cross the blood-brain barrier (BBB) (29). Lovastatin was chosen as the model statin due to its high lipophilicity (ClogP = 4.196) for passively diffusing across the BBB and its notable neuroprotective qualities (30). Lovastatin activates neurogenesis (the growth and development of nervous tissue) and induces neuroprotection via its anti-inflammatory mechanisms in the brain (29, 30). In this powerful combination, levodopa still replaces the missing dopamine, and lovastatin decreases the phosphorylation of ERK1/2 which has been associated with side effects from levodopa (31). Additionally, lovastatin can also easily pass through the BBB with a positive effect of preventing toxic protein aggregation, therefore protecting against neuronal death (29, 30, 32). Based on this information, we hypothesized that the lovastatin–levodopa combination will work to eliminate tremors better than a carbidopa–levodopa combination by preventing levodopa induced dyskinesia.

To test this, we used a *Drosophila melanogaster* (hereafter referred to as *Drosophila*) model of PD that contains an LRRK2 mutation (p.Gly2019Ser) that causes the flies to display the tremor movements commonly associated with PD. *Drosophila* was chosen as the model organism for this experiment as they have relatively short generation time, have a high reproductive rate, are easy to maintain in a school-lab environment, and share 62% of the genes that cause Parkinson's disease development in humans (33). We compared the effects of carbidopa–levodopa against lovastatin–levodopa on *Drosophila* tremor behavior, which was determined by the *Drosophila* activity monitor (DAM). Our work demonstrated that the lovastatin–levodopa combination was more successful than the carbidopa–levodopa combination in treating LRRK2-mutation PD ("PD-L") tremors in *Drosophila*, thus introducing a new potential therapy for PD patients.

RESULTS

Our experiment documented a total of 32 wild-type (WT) (n=16) and PD-L (n=16) *Drosophila*, and we recorded the activity of each fly per minute with different chemical-in-food combinations, including carbidopa–levodopa and lovastatin–levodopa (**Table 1**). We recorded overall activity of each fly type (PD-L vs. WT control), and their circadian rhythm, driven by the lighting within the DAM. PD in *Drosophila* causes significant locomotor dysfunction, resulting in reduced climbing ability and less stable movement, which are the equivalents to tremors in humans (34, 35).

We recorded *Drosophila* activity when the lights were both on and off (~13 hours on and ~11 hours off) in the DAM as a representation of day and night, respectively, to consider the possible side effects that the different chemical combinations may have on sleep. This instrument measures the locomotor activity of 32 individual flies at a time by recording the number of times an infrared beam is interrupted as each fly walks back and forth in their respective 5mm-diameter tube (36). A more stable sleep rhythm that is aligned with the day and night cycle would demonstrate a less harmful chemical combination. This would mean that the number of times a fly crosses the tube would be expected to be 0 or a number close to 0 when the lights are off. In other words, the fly is expected to sleep at night and therefore not be as active (**Figure 1**).

Locomotor activity tracking revealed distinct behavioral differences across the two *Drosophila* variants and their chemically-induced foods (**Figure 2**). Baseline controls on untreated food established that healthy WT *Drosophila* exhibited significantly higher movement velocity than the baseline PD-L *Drosophila*, who displayed severe motor disability (0.491±1.512 mpm vs. 0.106±1.347 mpm; unpaired Student *t*-test, p=0.4198). When treated with 100 µM levodopa, WT movement slightly decreased while PD-L activity increased, narrowing the gap in the average movement differences between the two (0.484±1.378 mpm vs. 0.225±1.147 mpm, p=0.0968). Introducing lovastatin to make the combination with levodopa yielded the most

Treatment Group	Lovastatin	Levodopa	Carbidopa
Regular Food	-	-	-
Lovastatin Only #1	0.1 µM	-	-
Lovastatin Only #2	0.5 µM	-	-
Levodopa Only	-	100 µM	-
Lovastatin–Levodopa #1	0.1 µM	100 µM	-
Lovastatin–Levodopa #2	0.5 µM	100 µM	-
Carbidopa Only	-	-	55.3 µM
Carbidopa–Levodopa	-	55.3 µM	100 µM

Table 1: Chemical Combinations. The different chemical combinations and concentrations that were put into the fly food.

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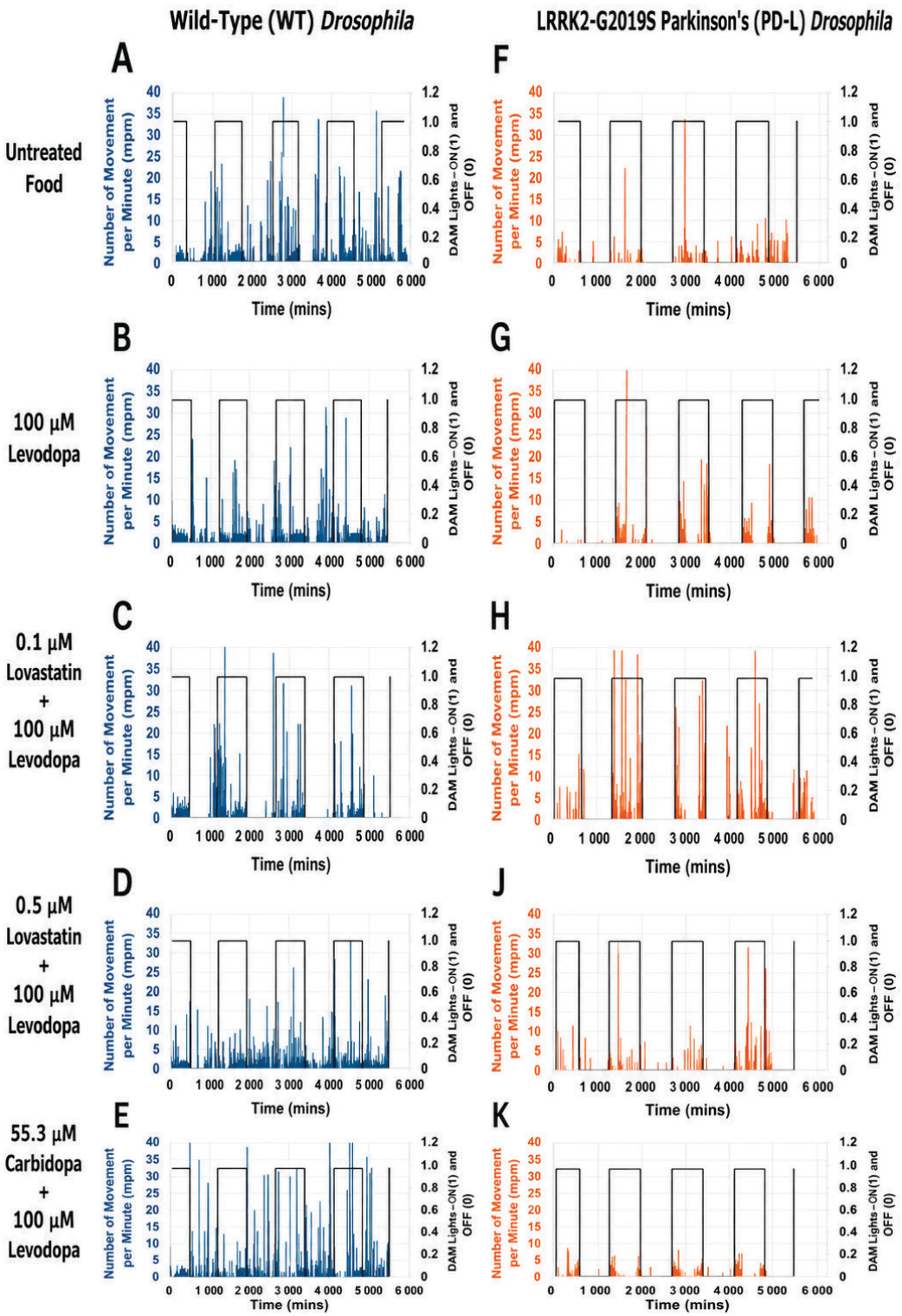


Figure 1: Comparing daily fly activity between wild type (WT) and Parkinson's *Drosophila melanogaster*. The graphs in this figure represent the locomotor activity of one representative fly from each genotype and drug treatment group (i.e. WT fly in untreated food) that demonstrated behavior closest to the average of the respective genotype and treatment type, measured by the *Drosophila* activity monitor (DAM). The data in blue represent the activity of the WT flies **(A-E)** and the data in orange represents the activity of the PD-L flies **(F-K). (A)** WT fly in untreated food. **B)** WT fly in 100 µM levodopa. **C)** WT fly in 0.1 µM lovastatin with 100 µM levodopa. **D)** WT fly in 0.5 µM lovastatin with 100 µM levodopa. **E)** WT fly in 55.3 µM carbidopa with 100 µM levodopa. **F)** PD-L fly in untreated food. **G)** PD-L fly in 100 µM levodopa. **H)** PD-L fly in 0.1 µM lovastatin with 100 µM levodopa. **J)** PD-L fly in 0.5 µM lovastatin with 100 µM levodopa. **K)** PD-L fly in 55.3 µM carbidopa with 100 µM levodopa. The data in the black-outlined boxes represent the day cycle with lights on (1 on right axis), and the data outside of the boxes represent the night cycle with lights off (0 on right axis).

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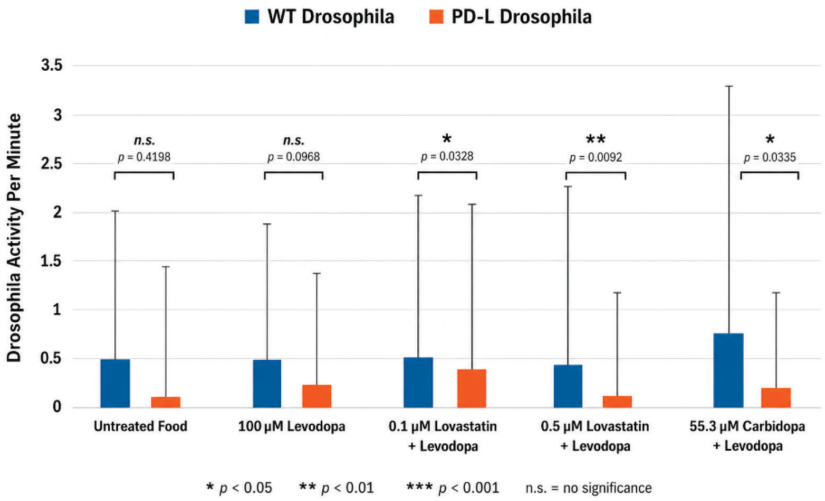


Figure 2: Wild type (blue) and Parkinson's (orange) *Drosophila melanogaster* activity based on different medication combinations. Average movement per minute as measured by the *Drosophila* activity monitor (DAM) activity between WT and PD-L *Drosophila* being treated with different drug combinations. Differences in the average movement of WT and PD-L flies for each treatment group were compared using an unpaired Student's *t*-test. Error bars represent standard deviation. N = 32 flies total; N = 16 flies per group.

therapeutic motor recovery in the PD-L models. 0.1 µM–100 µM lovastatin–levodopa significantly elevated PD-L locomotor activity to near-WT levels, marking the highest motor activity among the PD-L groups (0.495±1.676 mpm for WT vs. 0.384±1.652 mpm for PD-L, p=0.0328). Conversely, adding a higher concentration of lovastatin in the 0.5 µM–100 µM lovastatin–levodopa combination appeared to suppress the locomotion in both *Drosophila* groups (0.442±1.955 mpm for WT vs. 0.114±1.035 mpm for PD-L, p=0.0092). Finally, the standard 55.3 µM–100 µM carbidopa–levodopa combination induced a hyperactive locomotor response in WT but offered only a little improvement for PD-L (0.747±2.411 mpm for WT vs. 0.199±0.925 mpm for PD-L, p=0.0335). These above data indicate that the 0.1 µM–100 µM lovastatin–levodopa combination optimizes locomotor recovery more effectively than the traditional carbidopa–levodopa standard in this *Drosophila* model.

In the WT Drosophila, the 0.1 µM lovastatin with 100 µM levodopa was the only combination that did not disrupt circadian sleep rhythm, as represented by the "lights on/off" areas of the graph (**Figure 1C**). The averages of movement during both day and night were also the most similar between the 0.1 µM lovastatin–100 µM levodopa combination and the regular food in the WT flies—being 0.495 mpm and 0.491 mpm, respectively — which indicated that this lovastatin–levodopa combination altered movement behavior the least for healthy flies (**Figure 2**). While the difference in average movement between WT and PD-L flies on regular food was not statistically significant (p > 0.05), a clear trend in the average was observed. The large p-value is likely due to the small sample sizes used in the experiment.

In the PD-L *Drosophila*, it was also evident that the 0.1 µM lovastatin with 100 µM levodopa combination resulted in the most improvement in general motor activity. The average activity of PD-L *Drosophila* in regular food was 0.106 mpm, which is relatively low as the PD tremors inhibit proper movement. In all three drug combinations (0.1 µM lovastatin with 100 µM levodopa, 0.5 µM lovastatin with 100 µM levodopa, and 55.3 µM carbidopa with 100 µM levodopa) the circadian sleep rhythms were mostly stable and activity overall corresponded according to the lights on/off patterns. However, PD-L flies in 0.5 µM lovastatin with 100 µM levodopa and in 55.3 µM carbidopa with 100 µM levodopa had lower levels of activity (averages of 0.114 mpm and 0.199 mpm, respectively) than the 0.1 µM lovastatin with 100 µM levodopa, which had an average of 0.384 mpm. This suggests that the lovastatin–levodopa combination helps increase PD-L Drosophila activity better than carbidopa–levodopa.

Analysis of night and day activity patterns revealed distinct variations in time-of-day-dependent behavior between the WT and PD-L *Drosophila* (**Figure 3**). While all activity appeared to be relatively the same during the day for WT *Drosophila*, regular-food fly activity and 0.1 uM lovastatin–levodopa fly activity were most similar, indicating that this combination is most effective in not disrupting WT fly behavior (**Figure 3**). For PD-L *Drosophila* activity at night, activity across all drug treatment groups appeared to be relatively the same, indicating that the chemical combinations have little to no impact on sleep rhythm (**Figure 3**). During the day, 0.1 µM lovastatin–levodopa caused the greatest increase in activity compared to untreated food, which shows that this combination successfully improves general motor activity in PD-L *Drosophila* (**Figure 3**).

DISCUSSION

The purpose of our experiment was to determine if a lovastatin–levodopa combination would reduce tremors more potently than the current chemical combination used in clinic (carbidopa with levodopa) in reducing LRRK2-G2019S PD tremors. The results of this experiment support our hypothesis that lovastatin–levodopa is a better chemical combination for improving motor behavior in *Drosophila* than

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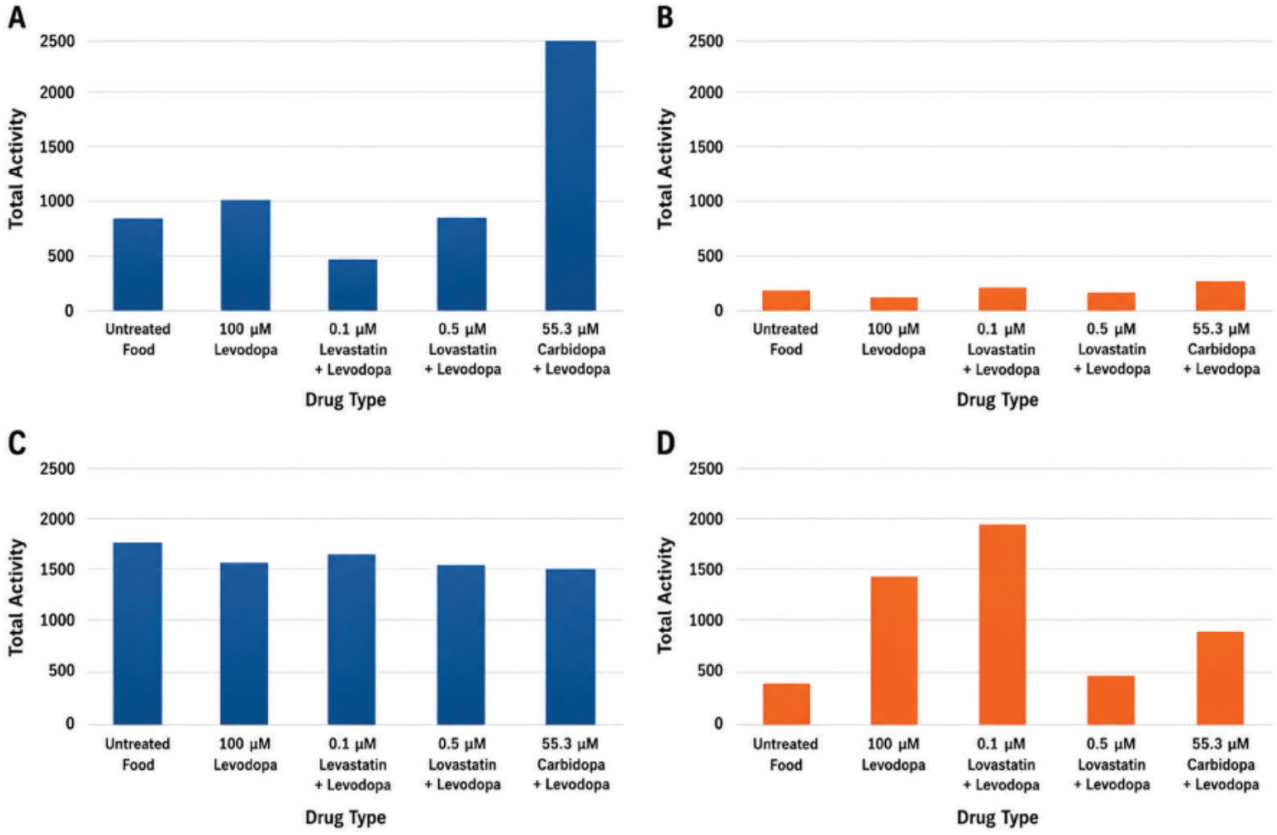


Figure 3: Wild type and Parkinson's *Drosophila melanogaster* total activity when lights are OFF vs. ON. Total activity as measured by DAM activity (mpm) between WT and PD-L *Drosophila* being treated with different drug combinations during lights OFF (night) and lights ON (daytime). **A)** WT *Drosophila* (blue) total activity when lights are OFF. **B)** PD-L *Drosophila* (orange) total activity when Lights are OFF. **C)** WT *Drosophila* total activity when lights are ON. **D)** PD-L *Drosophila* total activity when lights are ON. Each bar on the graphs represents a different chemical combination: untreated food, 100 µM levodopa, 0.1 µM lovastatin with 100 µM levodopa, 0.5 µM lovastatin with 100 µM levodopa, and 55.3 µM carbidopa with 100 µM levodopa (from left to right). Each bar represents data from 1 fly, whose activity has been observed to be closest to the average of all the flies in each chemical treatment group.

carbidopa–levodopa.

WT *Drosophila* activity with carbidopa–levodopa was evidently fluctuant and high during both day and night phases, which indicates that the sleep rhythm of WT flies was disrupted by the carbidopa–levodopa combination (**Figure 1E**). Although carbidopa's low lipophilicity is not a disadvantage, lovastatin's higher lipophilicity (ClogP = 4.196) enables this chemical to pass easier through the BBB and provide additional benefits such as reducing the severity of abnormal movements that may be side effects of levodopa (37, 38). Furthermore, higher doses of carbidopa can cross the BBB and inhibit brain aromatic amino acid decarboxylase, causing insomnia-related behaviors (23, 39). Excess carbidopa also reduces the effectiveness of levodopa, which may explain the little to no change in the activity of the PD-L *Drosophila* in untreated food versus in the carbidopa–levodopa combination (24).

In addition, when looking at the WT fly in 0.5 µM lovastatin combined with levodopa, it appeared to have lower average movement than the graph of the WT fly in carbidopa–levodopa (**Figure 1D, 1E**). The sleep rhythm was relatively unstable, most likely because 0.5 µM lovastatin was too high of a concentration when combined with 100 µM levodopa, and resulted in disrupted sleep. As for the PD-L flies in 0.5 µM lovastatin with levodopa, the change in *Drosophila* activity for flies in untreated food versus in this combination demonstrates the ineffectiveness of this lovastatin concentration with levodopa in reducing tremors.

Finally, when evaluating the WT versus PD-L *Drosophila* in 0.1 µM lovastatin with 100 µM levodopa, both had activity that nearly aligned with the lights on and off times, which provides evidence of this statin concentration's ability to maintain stable sleep cycles for the *Drosophila* (**Figure 1, Figure 3**). This combination had the least adverse effect, with minimal change in the activity of the wildtype flies in regular food compared to the 0.1 µM lovastatin with 100 µM levodopa. The 0.1 µM lovastatin combination resulted in the biggest increase from the regular food out of the three chemical combinations, suggesting that the lovastatin–levodopa combination is more effective in reducing PD-L tremors in *Drosophila* than carbidopa–levodopa (**Figure 2**).

Our work had the following limitations. Not all of the flies, both WT and PD-L, were placed into the DAM at the same time, meaning that the ages of the flies varied when each

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fly's activity was recorded. This limitation occurred because there were only ten *Drosophila* of each kind (WT and PD-L), and since our work required at least thirty flies, there was a two-week period to allow the flies to breed and let the new fly eggs hatch. To use the limited time in the research lab efficiently, both the two-week old (at least) and the newly-hatched flies were used in the research. Like any other species, flies generally become less active as they get older. Therefore, the younger flies would likely have had higher activity recorded than the older flies, regardless of the type of drug in the food, which makes it hard to compare fly activity. Furthermore, younger flies likely have better immunity and therefore more tolerance to the chemicals put in their food, so making dose adjustments based on fly age should have also been a consideration. Future experimentation could be done on age-matched flies with activity recorded over longer periods of time to address these limitations. Furthermore, increased sample sizes would provide additional confidence to statistical testing.

Our results determined that lovastatin–levodopa may be a better drug combination for treating PD-L tremors in *Drosophila* than carbidopa–levodopa. This novel combination effectively minimizes nighttime hyperactivity while improving daytime locomotor activity in flies. In a more clinical landscape, this combination may help improve the overall quality of life for Parkinson's patients who suffer from disrupted sleep and debilitating, drug-induced dyskinesias.

MATERIALS AND METHODS

Culturing the Fruit Flies in Assay Tubes

Ten WT [stock #5] and ten Parkinson-diseased [stock #34750] *Drosophila melanogaster* (fruit flies) were acquired from Indiana University Bloomington and grown under standard conditions, namely at room temperature (20°C) in assay tubes to the desired age (i.e., 4–10 days old), with standard fly food (a formulated cornmeal-based food mix created by Indiana University Bloomington). The flies were left to breed and produce an ample supply of PD-L larvae that could be recorded for PD-L tremor activity.

Preparing the Chemically-Induced Fly Food

In small glass vials, predetermined concentrations of a chemical were mixed with 1 mL of water. This was then incorporated into 7 mL standard fly food, with either a WT or PD-L fly put into each vial (**Table 1**). The control groups in the experiment were the flies, both WT and PD-L, put in the regular food and the 55.3 μM carbidopa (Sigma Aldrich) combined with 100 μM levodopa (Sigma Aldrich), respectively, while the treatment groups were constituted of flies treated with 100 μM levodopa, 0.5 μM-100 μM lovastatin–levodopa and, 0.1 μM–100 μM lovastatin–levodopa (**Table 1**).

Preparing the WT and PD-L *Drosophila* to Put into the TriTech *Drosophila* Activity Monitor (DAM)

Flies that were all at least two weeks old, namely 2–3 WT flies and 2–3 PD-L flies, were loaded into separate DAM assay tubes for each experimental group. One fly was placed in each tube, with either the standard fly food (control) or food combined with drugs: 0.5 μM lovastatin, 100 μM levodopa, 0.5 μM–100 μM lovastatin–levodopa combination, 0.1 μM–100μM lovastatin–levodopa combination, 55.3 μM carbidopa, or 55.3 μM–100 μM carbidopa–levodopa combination. These tubes were then inserted into the DAM (DAM5H, TriKinetics Inc, USA) (39). The average of the total times crossed was calculated for each fly in its respective tube. The tremor activity was recorded as a function of fly activity over a 5–7-day period, with DAM lights programmed to turn on at 7am, and off at 8pm each day. Drosophila activity was automatically recorded each minute as the number of passes across the tube measured by laser light interruption, which were then downloaded into Microsoft Excel (version 2021) to create graphs of Drosophila activity for the week, with lights on/off. Locomotor counts and circadian activity patterns were continuously monitored for each fly type (WT control vs. PD-L) to quantify the behavioral differences between the experimental groups.

Statistical Analysis

All quantitative behavioral data were analyzed using GraphPad Prism (QuickCalcs *t*-test Calculator, GraphPad Software, Boston, MA, USA). Mean locomotor activity was calculated per individual fly across the 5–7 day monitoring window. Statistical significance was determined using an alpha threshold of $p<0.05$. Calculated values were noted across baseline control conditions and experimental treatments. All graphical variance data were expressed as mean standard deviation (SD).

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