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Article

Quantifying natural recovery of dopamine deficits induced by chronic stress

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SUMMARY

Chronic stress can impair dopamine production, contributing to the development of neurodegenerative and psychiatric conditions, including depression. While interventions such as exercise and diet have shown promise in reversing these effects, the body's natural ability to recover from stress-induced dopamine deficits remains unclear. We aimed to quantify the natural reversibility of dopamine deficits induced by chronic stress in *Caenorhabditis elegans* by measuring changes in the expression of *cat-2* and *sod-2*, known to be associated with dopamine biosynthesis and oxidative stress responses, respectively. *C. elegans* were exposed to starvation or hydrocortisone to simulate chronic stress and then allowed to recover naturally. Gene expression levels were measured using RT-qPCR at pre-stress, stress, and post-stress timepoints. We found that *cat-2* expression was only detectable in select groups, with markedly higher expression following mild stress compared to recovery. *sod-2* expression was highly reversible in starved *C. elegans*, moderately reversible at lower hydrocortisone concentrations, and not reversible at higher doses. These findings suggest that the natural reversibility of dopamine-related gene expression is dependent on the type and severity of stressor. Understanding these mechanisms may help establish biological baselines for recovery and improve treatment strategies for individuals with stress-related dopamine dysfunction. Ultimately, our research contributes to a better understanding of how natural recovery processes could support therapeutic approaches for depression and related disorders.

INTRODUCTION

Chronic stress refers to a prolonged feeling of anxiousness (1). It has adverse effects at multiple levels and contributes to holistic bodily impairments, such as increased inflammation and telomere shortening, a marker of accelerated aging (2–4). Additionally, the effects of chronic stress can extend beyond the period in which a human experiences it. A cross-sectional study on teen recovery from trauma revealed that approximately 26% to 52% reported unchanging or increasing stress about a past, potentially traumatic life event (5).

A major pathway affected by chronic stress is the dopaminergic system. Dopamine is a key neurotransmitter in functions such as mood regulation, learning, movement, and sleep (6). Chronic stress interferes with normal dopamine levels, as shown by decreased reward learning in rats following chronic mild stress (7). This decreased reward learning appears in diseases such as depression (8). Thus, the dopamine deficits caused or associated with chronic stress may play a key role in the development and persistence of depression.

Certain interventions have successfully raised dopamine levels after chronic stress. More behavioral interventions like exercise and diet have both shown success (9, 10). Pharmacological interventions such as amisulpride—an atypical antipsychotic—and quinpirole—a psychoactive drug that serves as an agonist for the dopamine D2 and D3 receptors—also improved cognitive processes associated with dopamine, such as reward learning after chronic mild stress (11).

However, while it has been established that behavioral and pharmacological interventions can restore dopamine deficits caused by chronic stress to some degree, the body's natural capacity to reverse these deficits without intervention is understudied. Such an understanding of the body's natural capacity to reverse dopamine deficits could serve as a baseline to compare the capacity of interventions commonly prescribed in medical settings.

Direct measurement of dopamine levels is technically challenging due to the small quantities involved and the complexity of dopamine signaling, often requiring time-consuming or resource-intensive methods (12, 13). To overcome these challenges, researchers use model organisms like *Caenorhabditis elegans*, a type of nematode worm commonly used in laboratory research due its large capacity for reproduction and high level of genetic similarity to humans (14, 15). In this study, we focused on two genes: *cat-2* and *sod-2*. While dopamine itself is difficult to measure directly in *C. elegans*, expression levels of these genes provide a useful indirect measure of dopaminergic activity under stress conditions. *cat-2* in *C. elegans* encodes for the tyrosine hydroxylase enzyme, a precursor to dopamine synthesis (16). *sod-2* encodes for the protein responsible for detoxifying superoxide, a free radical (17). Additionally, both *cat-2* and *sod-2* in *C. elegans* are functionally similar to *TH* and *SOD2* in humans, respectively, supporting the relevance of this model for studying dopaminergic stress responses (18, 19).

We hypothesized that levels of *cat-2* and *sod-2* expression in stressed *C. elegans* would recover to some extent during post-stress recovery for groups exposed to either starvation or hydrocortisone, with the highest recovery expected in starved *C. elegans*. Hydrocortisone was used as an additional stressor in this experiment because unlike starvation, hydrocortisone exposure is less studied with *C. elegans*. Our

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results partially supported our hypothesis: starved *C. elegans* demonstrated the greatest recovery of gene expression toward pre-stress levels, followed by *C. elegans* exposed to lower concentrations of hydrocortisone. In contrast, *C. elegans* exposed to the highest hydrocortisone concentration showed no reversal and even greater divergence from pre-stress expression levels. These findings suggest that the natural reversibility of dopamine-related gene expression is dependent on both the type and severity of the stressor. Understanding the biological limits of natural recovery may help refine treatment approaches for stress-related dopamine dysfunction, particularly in conditions such as depression where dopaminergic imbalance plays a key role.

RESULTS

We assessed whether dopamine-related gene expression in *C. elegans* naturally recovers following exposure to chronic stressors of varying type and intensity. We allowed *C. elegans* to grow in a pre-stress environment for two days. Then, we exposed the *C. elegans* to two stressors—starvation and hydrocortisone exposure. Separate groups of *C. elegans* underwent either starvation for 2–4 days or one of three hydrocortisone treatments (7.5 mM, 15 mM, or 20 mM). After stress exposure, we gave the *C. elegans* two days to recover. Finally, we used real-time reverse transcription quantitative PCR (RT-qPCR) to detect expression levels of *cat-2* and *sod-2* in pre-stress, stress, and recovery samples. We then used these expression levels to calculate the level of recovery. Recovery was defined as the percent by which post-recovery expression levels could rebound to pre-stress levels. In RT-qPCR, gene expression was assessed using the cycle threshold (Ct) value, which refers to the number of cycles needed for the relative fluorescence units (RFU) to exceed a set background threshold. RFU represents the fluorescence intensity detected during amplification, which correlates with the amount of target gene present. The more cycles needed for detection, the lower the assumed gene expression. This method for measuring recovery of expression levels of these genes allowed for measurement of dopamine levels indirectly and inexpensively. Using both a well-established stressor like starvation and one less studied like hydrocortisone, also allowed for possible simulation of stress accurately and through multiple means.

Out of the 12 groups, only three—7.5 mM hydrocortisone stress, 7.5 mM hydrocortisone recovery, and 15 mM hydrocortisone recovery—showed detectable *cat-2* expression **(Figure 1)**. The remaining nine groups had expression levels too low for detection. Interestingly, we found that expression of *cat-2* in the 7.5 mM hydrocortisone stressed group was sixteen-fold compared to the 7.5 mM hydrocortisone recovery group **(Figure 1)**. This fold change was estimated based on a 4-cycle difference in Ct values between the two groups, using actin as a housekeeping gene and assuming a doubling of expression with each cycle decrease.

For all stressed groups, expression levels of *sod-2* decreased compared to pre-stress levels, but recovery levels varied **(Figure 2, Table 1)**. *sod-2* expression levels for the starvation group recovered almost completely, with approximately 100% reversibility. Among the hydrocortisone groups, the 15 mM hydrocortisone group showed the greatest recovery at 68.34%, followed by the 7.5 mM hydrocortisone group at 7.33%. An unexpected observation was that *sod-2* expression in the 20 mM recovery group was lower than in the 20 mM stressed group, indicating a negative 16.96% change relative to stress levels rather than a reversal toward pre-stress levels **(Figure 2, Table 1)**.

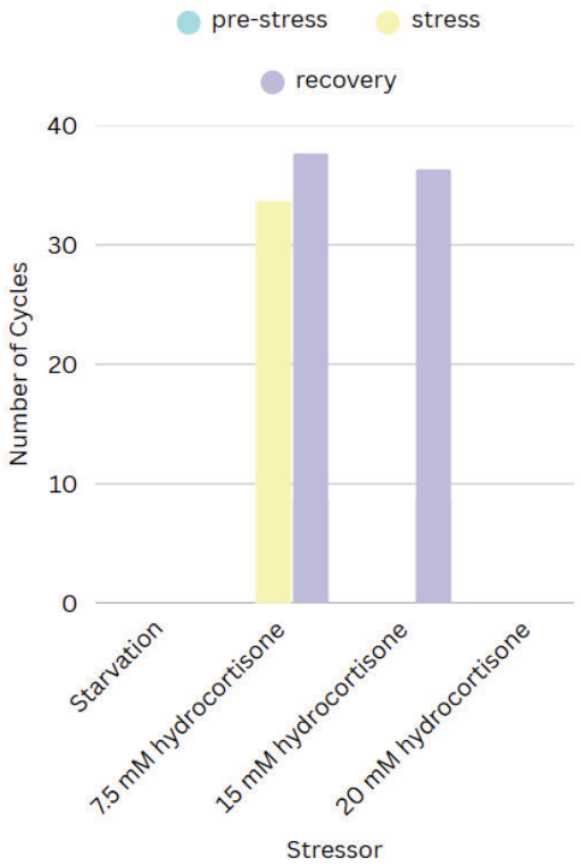

Figure 1: *cat-2* expression in *C. elegans* exposed to starvation and hydrocortisone stressors. The number of cycles required for *cat-2* detection using real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR) in the experimental groups used in this research ($n = 1$ biological replicate per condition). Cultures of *C. elegans* were grown under pre-stress control conditions, stress conditions of either starvation or hydrocortisone treatment (7.5 mM, 15 mM, or 20 mM), and recovery conditions. Expression levels were normalized using the housekeeping gene *actin-1*. Bars are only shown for groups in which *cat-2* expression was detectable; groups without a bar represent samples in which gene expression was too low to produce a valid Ct value (NaN) and were therefore considered undetectable.

DISCUSSION

The goal of our research was to quantify the natural recovery of the dopamine-related effects of various stressors and determine the extent to which it can be reversed in *C. elegans* during recovery. We sought to achieve this goal by exposing *C. elegans* to starvation stress and different concentrations of hydrocortisone and comparing expression levels of *cat-2* and *sod-2* in pre-stress, stress, and recovery conditions, that indirectly serve as indicators of dopamine levels. Notably, only three groups—the 7.5 mM hydrocortisone stressed, 7.5 mM hydrocortisone recovery, and 15 mM hydrocortisone recovery groups—had markedly detectable

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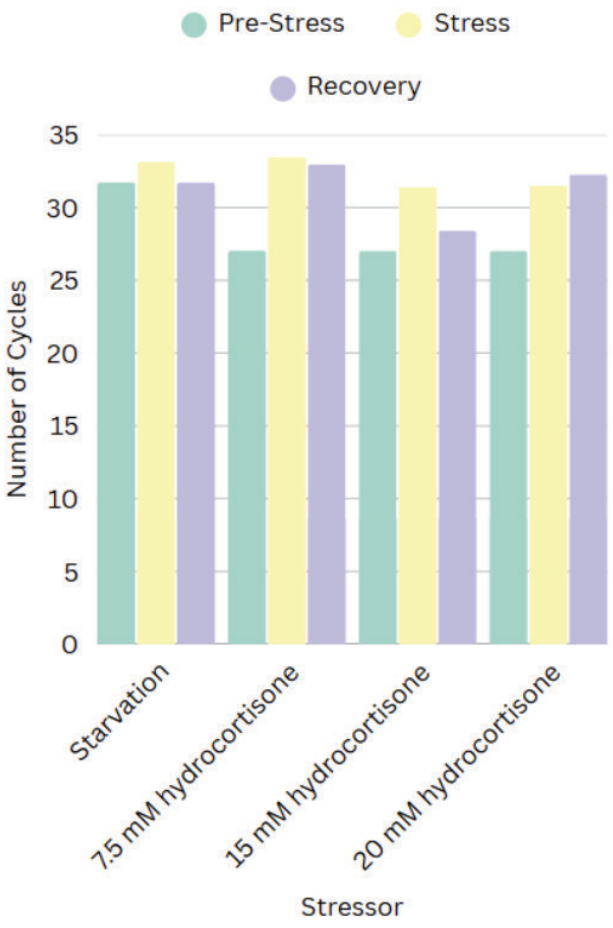

Figure 2: *sod-2* expression in *C. elegans* exposed to starvation and hydrocortisone stressors. The number of cycles required for *sod-2* detection using real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR) in the experimental groups used in this research (n = 1 biological replicate per condition). Cultures of *C. elegans* were grown under pre-stress control conditions, stress conditions of either starvation or hydrocortisone treatment (7.5 mM, 15 mM, or 20 mM), and recovery conditions. Expression levels were normalized using the housekeeping gene *actin-1*.

cat-2 expression levels, with the 7.5 mM hydrocortisone stressed group showing a higher expression level than its recovery counterpart. This unexpected pattern raises questions about how *cat-2* expression reflects dopamine-related stress responses. Similarly, *sod-2* expression decreased across all stress conditions, but the degree of recovery varied. These results indicate that recovery of *sod-2* expression varies with the type and intensity of stress, with higher hydrocortisone concentrations potentially impairing the natural recovery process. Since free radicals contribute to oxidative stress, and oxidative stress is inversely correlated with dopamine levels, free radicals could also have an inverse association with dopamine levels (20). Thus, higher *sod-2* expression may mean more protection from oxidative stress and higher dopamine levels. Levels of expression of these genes may serve as feasible and also reliable markers of dopamine levels.

The semi-detectability of *cat-2* expression in this study could reflect several factors. The 7.5 mM hydrocortisone concentration may represent an optimal level for *cat-2* expression. Gene upregulation to compensate for stress might explain detectable *cat-2* levels in the 7.5 mM and 15 mM recovery groups. However, this compensatory response may not occur at 20 mM, which could be a threshold beyond which dopamine recovery is impaired. Additionally, high cortisol concentrations are known to potentially degrade RNA, which could affect gene expression measurements (21). These findings suggest that after a certain threshold is reached, dopamine deficits may not be reversible.

Gene	Stressor	Reversal Level
cat-2	starvation	—
	7.5 mM hydrocortisone	—
	15 mM hydrocortisone	—
	20 mM hydrocortisone	—
sod-2	starvation	100.7%
	7.5 mM hydrocortisone	7.33%
	15 mM hydrocortisone	68.34%
	20 mM hydrocortisone	-16.96%

Table 1: Reversal levels of *cat-2* and *sod-2* expression following exposure to different stressors in *C. elegans*. Percentage reversal values for *cat-2* and *sod-2* expression levels (n = 1 biological replicate per condition). Cultures of *C. elegans* were grown under pre-stress control conditions, stress conditions of either starvation or hydrocortisone treatment (7.5 mM, 15 mM, or 20 mM), and recovery conditions. Expression levels were normalized using the housekeeping gene *actin-1*.

Additionally, one possible explanation for the notably higher *cat-2* expression in the 7.5 mM hydrocortisone stressed group compared to its recovery counterpart may be that 7.5 mM is a healthy amount of stress that may boost dopamine levels compared to the recovery group. This finding suggests that mild levels of stress may be beneficial (22, 23).

The reduced *sod-2* expression during starvation stress, followed by near-complete recovery, may reflect a controlled oxidative stress response, aligning with findings that short-term fasting methods such as intermittent fasting can mitigate oxidative stress rather than exacerbate it (24). However, it should be noted that the chunk used to propagate the *C. elegans* in this plate may have contained trace amounts of OP50 due to the *C. elegans* in this chunk being extracted from a dish with ample OP50, which could have influenced gene expression results.

Initially, the starvation period used in this research was thought to have been too short to result in stress, as previous experiments have typically used slightly longer starvation durations to produce measurable stress responses in *C. elegans* (25). However, the two-day starvation period may still be a large portion of a typical N2 strain *C. elegans* lifespan, which has a median of about 17 (26). This means the two-day starvation period may be around 12% of the lifespan of

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the *C. elegans* cultured in this research and may indicate that a critical period—a limited window of time during which recovery of *sod-2* expression is most effective—exists for *C. elegans* previously starved.

Differences in *sod-2* recovery across the hydrocortisone-treated groups suggest that the intensity of stress can shape not only the degree of damage but also the capacity for recovery. Notably, *C. elegans* exposed to 15 mM hydrocortisone showed the highest level of *sod-2* recovery, while those in the 7.5 mM group recovered far less. This contrast raises the possibility that certain levels of stress may be more effective in triggering adaptive recovery mechanisms. However, recovery appeared to drop again at 20 mM, indicating that excessively high stress may suppress this process altogether. These patterns point to a possible "optimal zone" of stress intensity for genetic recovery. Identifying this zone of stress exposure that promotes recovery could provide insight into how organisms modulate stress responses. In humans, understanding such a range could inform treatment approaches that use controlled stressors to enhance resilience or recovery at the molecular level. Further testing may be necessary to determine whether this trend reflects a consistent biological pattern or results from confounding variables.

Furthermore, the stress period used in this research began during *C. elegans* adolescence (27). Starvation during adolescence may induce physiological changes that improve recovery after stress. This adolescent timing of starvation could explain why previously starved *C. elegans* showed better *sod-2* expression recovery compared to other stress groups. Although the impact of hydrocortisone on *C. elegans* may require more study, this conclusion may also shed light on how adolescence and related neural changes influence stress outcomes.

Moreover, although *C. elegans* shows a high level of genetic similarity to humans, the differences may differentiate to some degree how the *C. elegans* nervous system works from that of humans (15, 28). More research has to be conducted to analyze these sequences and how they can limit generalization to human populations.

Our research may also point to the need for more direct yet affordable methods of measuring dopamine. While *cat-2* in *C. elegans* is known to drive dopamine synthesis through tyrosine hydroxylase, higher *cat-2* expression may not always reflect higher dopamine levels. For instance, *cat-2* expression was 16 times higher in the 7.5 mM hydrocortisone stressed group compared to the 7.5 mM recovery group. This suggests that under certain, still poorly understood conditions—such as stress—*cat-2* expression might signal the body's perceived demand for dopamine rather than a direct marker of dopamine itself. In this way, *cat-2* expression could potentially serve as an indicator that dopamine production may need to be increased.

Due to time constraints, this experiment could not be repeated with multiple sets of groups to produce results to conduct significance testing. Further research must consist of this replication. Despite this limitation, this experiment was valuable because it was one of the few attempts to quantify chronic stress recovery with a dopamine-focused approach. Existing research has primarily focused on demonstrating that various interventions can reverse the effects of chronic stress, but few studies have measured the extent of this recovery or provided precise quantification of how much stress is reversed. Specifically, the procedures used to simulate chronic stress and recovery and the measurement of gene expression as an indirect quantification of stress effects may enable future studies to further generalize the results of this experiment to humans. Understanding the effectiveness of various interventions in reversing dopamine deficits caused by different chronic stressors could enable healthcare professionals to treat chronic stress more personally and effectively.

MATERIALS AND METHODS

Starvation Stress Experimental Setup

The N2 Bristol strain of *C. elegans* was used for this experiment. All *C. elegans* used were originally obtained from the Caenorhabditis Genetics Center (CGC).

The control starvation group (pre-stress) consisted of a petri dish of unknown size, likely within the standard 60–100 mm range used for *C. elegans* cultivation, containing plain fresh agar and 60 µL of OP50 *Escherichia coli* spread across the surface. Approximately 100–300 L4-stage *C. elegans* were transferred from a mature control starvation plate to a freshly prepared plate using chunking. The new plate was then sealed and left to incubate at room temperature (22°C) for 2 days and then removed from the incubator. The starvation stress group was created in the same manner as the control group with one exception: no OP50 was added.

To create the starvation recovery group, a chunk of agar containing *C. elegans* from the starvation group (which had no food) was transferred to a fresh plate containing food (60 µL of OP50 *E. coli*), identical to the pre-stress control conditions. This simulated recovery by removing the stressor—food deprivation—and reintroducing nutrition. This new plate was then incubated at room temperature for 4 days and subsequently removed from the incubator.

Hydrocortisone Stress Experimental Setup

Hydrocortisone was used as an additional stressor in this experiment. Chunking was used to obtain four chunks of *C. elegans* from the same source used to create the starvation groups. Each chunk was transferred to one of four dishes, each containing 50 µL of OP50 with varying concentrations of hydrocortisone—0 (the control concentration), 7.5, 15, or 20 mM. While 60 µL was used in the control starvation group, 50 µL was used here to evenly divide the available OP50 across experimental groups without significantly affecting bacterial availability or experimental results. After transferring the four chunks to one of the separate plates, we incubated these plates at 22°C for 4 days to ensure proper stress exposure and then removed them from the incubator.

The hydrocortisone recovery groups were then created. Chunking was used to transfer pieces of agar from each hydrocortisone treatment group to recovery plates with conditions identical to the pre-stress controls: 60 µL of OP50 and no hydrocortisone exposure. This simulated recovery by removing the stressor. Each hydrocortisone group had its own corresponding recovery plate. For example, a chunk from the 7.5 mM hydrocortisone group was transferred to a plate specifically designated for recovery from that concentration. All recovery plates were incubated at 22°C for 2 days before being removed from the incubator.

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RNA Isolation

RNA samples were isolated from each group per manufacturer's protocols with the TRIzol reagent (Thermo Fisher Scientific). To begin this process, a chunk was taken from each of the groups and was suspended in a solution of 10 mL of phosphate-buffered saline (PBS). Each of the solutions were then vortexed briefly and transferred to another tube to remove the agar from the samples. Next, the solutions were centrifuged for 20 minutes at 3900 x g, the supernatant was removed, and 1 mL of TRIzol reagent was added. The samples were left to incubate for five minutes, after which, 0.2 mL of chloroform was added to help separate the solution into a bottom phenol-chloroform phase, an interphase, and an upper aqueous phase. The three solutions were centrifuged for 15 minutes at 12,000 x g before the aqueous phase was separated from each solution. 0.5 mL of isopropanol was added to each aqueous phase, incubated for 10 minutes, and centrifuged for 10 minutes at 12,000 x g . The supernatant was removed, and 30–50 µL of diethylpyrocarbonate (DEPC) water was added to each of the fully isolated RNA samples for preservation. The samples were then frozen at -20°C overnight. RNA concentration was measured with a nanospectrometer.

Preparation of RT-qPCR Wells

RNA samples were reverse transcribed into cDNA as per manufacturer's instructions (Takara Bio, Cat# RR047B). The concentrations of ssDNA were measured using a nanospectrometer, and each solution was adjusted to 200 µL at 100 ng/µL. For each gene (*cat-2*, *sod-2*, and *actin-1*), a primer mix was first prepared by combining 12 µL of forward primer and 12 µL of reverse primer. For each RT-qPCR reaction, this primer mix was added to 12 µL of RNase-free water and 60 µL of a 2X SYBR Green master mix, following manufacturer instructions. While the manufacturer and stock concentrations of the primers were not recorded, the same proportions were used across all conditions.

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