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RESEARCH ARTICLE

Mimicking Exercise-Induced Gene Activation: *TPH2* Overexpression Enhances Brain Cell Survival

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ABSTRACT: Physical exercise is known to increase brain function and improve resistance to stress by activating genes. Among many genes, *tryptophan hydroxylase 2* (*TPH2*) plays a key role in serotonin synthesis. This study proposed that this gene is one of the key genes that are activated after exercise, linked to mood regulation and neuronal survival. Therefore, this study aimed to investigate whether *TPH2* overexpression could mimic the neuroprotective effects of exercise in human brain-derived A172 cells under oxidative stress. After the *TPH2* plasmid was transfected into A172 cells, oxidative stress was induced using hydrogen peroxide (H_2O_2) at concentrations of 0, 10, and 20 μM. Cell viability and morphology were subsequently analyzed. Then, cell viability and morphology were analyzed. *TPH2* overexpression significantly increased cell survival in both normal and oxidative stress conditions (0, 10, and 20 μM H_2O_2). Additionally, *TPH2* overexpression increased the average cell size. This result suggests enhanced metabolic activity or survival pathways. Overall, these findings demonstrate that *TPH2* overexpression can improve brain cell viability under stress conditions. This suggests that the exercise-activated gene *TPH2* is one of the key genes that serve as potential therapeutic targets for oxidative stress-related neurological disorders and neurodegeneration.
KEYWORDS: Neuroscience, Cell Biology, Exercise-Induced Genes, *TPH2*, Oxidative Stress.

Introduction

Physical exercise has been extensively documented to confer numerous benefits to brain health, including improvements in learning, emotional regulation, and memory.[1] It helps with various functions, including learning, controlling emotions, and remembering. A study reported that cognitive decline was more prevalent among inactive adults than active adults.[2] Exercise can enhance the brain's plasticity and its resilience to damage while promoting cognitive health. It is also well known that exercising can contribute to reducing depressive symptoms in patients.[3]

The brain consists of three major parts: the cerebrum, brainstem, and cerebellum.[4] The cerebrum is the front part of the brain and includes gray matter and white matter. Its primary function is to control movement, learning, decision-making, and emotions.[5] The brainstem is the middle part of the brain. It consists of the midbrain, the pons, and the medulla. The midbrain controls motor movement, hearing, and vision.[6] The pons controls the sleep cycle and pain signals while also connecting to the cerebellum to control body movements. The medulla, or the back of the brainstem, regulates body activities such as heart rhythm and breathing. Finally, the cerebellum is located at the back of the head. Its known function is to control muscle movements and to help maintain posture and balance.[7]

These parts of the brain can all benefit from exercising. For example, aerobic fitness training is known to increase the volumes of white and gray matter in the cerebrum, which are crucial for dealing with information and managing movement, memory, and emotions.[8] Exercising also has positive effects on the prefrontal cortex, which is located in the cerebrum, and can improve attention, learning, and memory.[9] Furthermore, voluntary exercise modulates the brainstem serotonergic systems, increasing stress resistance.[10] Exercising also improves cerebellum function, leading to positive effects such as decreased oxidative stress.[11]

During cells' consumption of oxygen and cellular metabolism, hydroperoxides are produced in high quantities. Production and removal of hydroperoxides are especially important in the brain, as the brain consumes a high proportion of the oxygen used by our bodies. To do so, the brain prevents damage from hydroperoxides through its antioxidative defense mechanisms.[12]

The effect of hydrogen peroxide on the brain is substantial. Hydrogen peroxide damages cells through oxidation of lipids, proteins, and DNA, and excessive exposure to hydrogen peroxide leads to damage in brain tissue. Additionally, H_2O_2 exposure induces vacuolization of neuronal tissue and triggers apoptotic pathways through oxidative damage to cellular macromolecules.[13]

TPH2 is a rate-limiting enzyme that plays an important role in the synthesis of serotonin, a neurotransmitter that regulates behavior, mood, memory, etc.[14] A Change or decrease in *TPH2* activity has been associated with depression and suicidal activities.[15]

Previous research shows that exercising has a substantial effect on *TPH2* levels. [16] Knee loading and treadmill exercise in mice have led to an increase in their *TPH2* level, showing that simple physical actions can increase *TPH2*, helping to make more serotonin. The research showed that physical exercises stimulate the brain, activating *TPH2* and facilitating the production of serotonin.

DOI: 10.36838/IJHSR815.42

First, we selected genes that are activated in times of exercise, which were brain-derived neurotrophic factor (*BDNF*), *TPH2*, Catechol-O-Methyltransferase (*COMT*), *C-Fos*, activity-regulated cytoskeleton-associated protein (*ARC*), and *EGR-1*. Among the genes, *TPH2* was selected as it appeared to have the most direct effect on serotonin production, and therefore, on mood regulation and depression as well.

To mimic the effect of exercising, we prepared *TPH2* overexpression through plasmid transfection in human brain cells. Also, H_2O_2 was treated in the brain cells to create oxidative stress in the cells. Finally, we measured cell viability to see if *TPH2* overexpression can protect the brain cells from oxidative stress. Since *TPH2* is known to produce serotonin and help with mood regulation, we hypothesized that overexpression of *TPH2* would improve cell viability when cells are exposed to oxidative stress.

Methods

Cell culture:

Human brain-derived A172 glioblastoma cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% antibiotic–antimycotic solution. Cells were maintained at 37 °C in a humidified incubator with 5% CO_2.

Plasmid transfection and transfection efficiency assessment:

Tryptophan Hydroxylase 2 (TPH2) was cloned into the pCMV3 expression vector to generate pCMV3-TPH2. Cells were transfected using Lipofectamine reagent according to the manufacturer's protocol. Two groups were prepared: (1) empty vector control and (2) TPH2 overexpression. Transfection efficiency was assessed by quantifying TPH2 mRNA expression using RT-qPCR 24–48 h post-transfection and comparing expression levels between control and TPH2-transfected cells. Each RT-qPCR analysis was performed in triplicate technical measurements per biological sample. Overexpression of TPH2 relative to control confirmed successful transfection.

Experimental replicates and study design:

All experiments were performed using three independent biological replicates (cells cultured and transfected on different days). Within each biological replicate, measurements (cell counting, size analysis, and viability staining) were performed in technical triplicates to reduce measurement variability. Data shown represent averages from independent experiments.

Oxidative stress induction:

Hydrogen peroxide (H_2O_2) was used to induce controlled oxidative stress in A172 cells because it reliably increases intracellular reactive oxygen species (ROS) and produces quantifiable changes in viability. To evaluate whether TPH2 overexpression confers protection across a graded oxidative burden, cells were treated with 0, 10, or 20 μM H_2O_2. The 0 μM condition served as the negative control to define baseline post-transfection behavior. The 10 μM dose was selected as a moderate, sublethal stress level expected to reduce viability without causing extensive nonspecific cytotoxicity, enabling detection of protective effects. The 20 μM dose was selected as a higher oxidative stress condition to test whether TPH2-mediated protection persists under stronger ROS challenge and to maximize separation between experimental and control groups. H_2O_2 was prepared as a fresh working solution in complete medium and applied at the indicated final concentrations (μM). Cells were incubated with H_2O_2 for a fixed exposure duration (consistent across all conditions) prior to downstream viability and morphology measurements, and the same concentration units (μM) were used consistently.

Cell viability assay:

Cell viability was assessed using the Luna-FL™ fluorescence cell counter following dual-fluorescence live/dead staining. Cells were stained with acridine orange (AO) to label live cells and propidium iodide (PI) to label membrane-compromised (dead) cells, according to the manufacturer's protocol. After staining, cell suspensions were loaded into Luna counting slides, and automated fluorescence imaging was used to quantify total cell number, live cell count, dead cell count, and viability percentage. AO-positive/PI-negative cells were classified as viable, whereas PI-positive cells were classified as non-viable. Measurements were performed for each technical replicate and averaged for analysis.

Morphological analysis:

Cell diameter and morphology were measured using Luna-FL automated imaging analysis to evaluate changes associated with TPH2 overexpression.

Statistical analysis:

Data are presented as mean ± SEM from three independent biological replicates. Comparisons between control and TPH2-overexpressing groups were performed using an unpaired two-tailed Student's t-test. Statistical significance was defined as $p < 0.05$.

Results and Discussion

Table 1: List of genes that are associated with exercise in the brain, which are *BDNF, TPH2, COMT, C-Fos, Arc, EGR-1*, and their function and importance. Gene name, function, and why it's important in the brain were analyzed in this table.

Gene Name	Function	Why It's Important in the Brain
BDNF (Brain-Derived Neurotrophic Factor)	Helps neurons grow, survive, and make new connections (plasticity)	Supports learning, memory, mood, and protects against diseases like Alzheimer's and Parkinson's
TPH2 (Tryptophan Hydroxylase 2)	Makes serotonin, the "feel-good" brain chemical	Boosts mood, reduces depression, helps brain cells survive stress
COMT (Catechol-O-Methyltransferase)	Breaks down dopamine and other neurotransmitters	Regulates emotions, attention, memory, and behavior
C-Fos	Early response gene that activates when brain cells are stimulated	Marks active brain regions, helps brain respond to stress and drugs, aids in memory and repair
Arc	Helps brain cells strengthen connections for long-term memory	Supports learning, memory, and adaptability to new experiences
EGR-1	Controls brain cell growth, repair, and response to stimuli	Important for memory, learning, and recovery after brain injury

To select the gene to be investigated for the research, a table was created to list the genes related to exercise and the brain (Table 1). Such genes and their importance were researched in

previous papers. As a result, six genes were chosen as potential subjects of the experiment. First, *BDNF* is a protein that is important for neurons' growth, survival, and plasticity.[17] It helps with learning, memory, and mood, protecting against diseases such as Alzheimer's and Parkinson's disease. *TPH2* is an enzyme that helps with synthesizing serotonin, which regulates mood and depression. Therefore, the enzyme itself also has a direct effect on mood and depression.[18] *COMT* is an enzyme that breaks down neurotransmitters such as dopamine.[19] Its role is to regulate the emotions, attention, memory, and behavior of humans. *C-Fos*, as a gene, is activated when brain cells are stimulated.[20] It primarily helps the brain's response to stress and drugs, memory, and repair. *Arc* strengthens brain cells' connections, helping with long-term memory. It supports overall learning and adaptability to new experiences as well.[21] *EGR-1* controls brain cells' growth, repair, and response to stimuli. Therefore, it aids in memory, learning, and recovery from injuries.[22] Ultimately, *TPH2* was selected as the gene to be used in this study. The primary goal of the experiment was to discover the effect of exercising on the brain. Since *TPH2* showed the most positive effect on the brain when exposed to exercise, it was selected as the main target gene for this study.

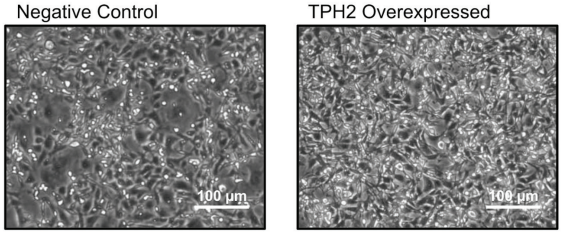

Figure 1: TPH2 overexpression increases the viability of A172 cells under baseline conditions. A172 human brain-derived (glioblastoma) cells were transfected with pCMV3-TPH2 (TPH2 overexpression) or empty vector control, cultured for 7 days, and viable cell counts were quantified using a Luna-FL fluorescence cell counter with acridine orange/propidium iodide (AO/PI) live–dead staining. Data are presented as mean ± SEM from n = 3 independent experiments. Statistics: unpaired two-tailed t-test comparing TPH2 vs. control. $p < 0.01$.

The experiment aims to discover how *TPH2* helps with neuroprotection by mimicking the positive effects of exercising on the brain. To do so, we experimented on whether the TPH2 gene, which is activated during exercise, can increase the survival rate of A172 human brain cells (Figure 1).

As shown in Figure 1, the experimental group in which *TPH2* was overexpressed has a higher number of A172 cells than the control group. Therefore, *TPH2* might have a positive effect on increasing the cells' survival rate. As *TPH2* plays a crucial role in the synthesis of serotonin, which helps with mood regulation and the survival of nerve cells, overexpression of the gene might reduce harm to the cells. The result of the experiment was similar to that of previous studies, which have shown that *TPH2* activation increases brain functionality and stress resistance.

The experiment result showed how *TPH2*, which is expressed during exercise, can help with neuroprotection. In addition, the result shows that *TPH2* can be used as a possible treatment option for neurodegenerative diseases or depression symptoms.

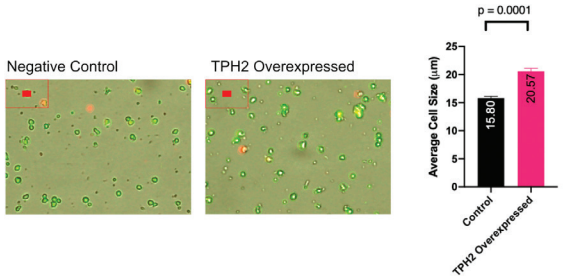

Figure 2: TPH2 overexpression increases average A172 cell size. Following transfection with pCMV3-TPH2 or empty vector control, cell diameter (µm) was measured using the Luna-FL system to assess morphological changes associated with TPH2 overexpression. Data represent n = 3 independent experiments (as stated in Methods/Results). Statistics: unpaired two-tailed t-test comparing TPH2 vs. control. $p = 0.0001$.

The experiment aimed to discover the effect of *TPH2* overexpression on the A172 cells' morphological characteristics, especially cell size (Figure 2). When the average cell diameter was measured through Luna-FL analysis, it was shown that *TPH2* overexpression significantly increased the cell size from 15.80 µm in the control to 20.57 µm ($p = 0.0001$). As shown in Figure 2, pictures also show that cells exposed to *TPH2* overexpression are larger than the control group. Since the increase in cell size is often related to the metabolism or activation of survival signals of the cells, the result shows that *TPH2* can help with the growth and metabolism of brain cells. In conclusion, *TPH2* overexpression increases the overall size of the A172 brain cells. This shows that *TPH2* increases cell survival and functionality, aligning with previous experiments that claimed exercise stimulates the gene and improves the health of brain cells.

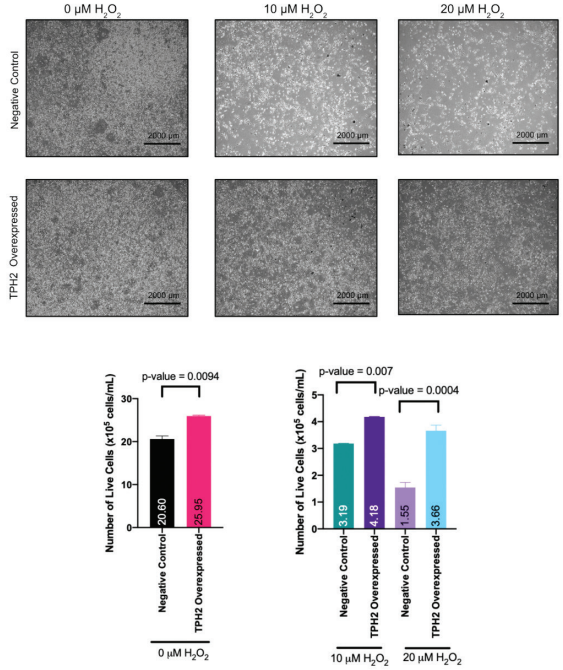

Figure 3: TPH2 overexpression enhances A172 survival across oxidative stress levels induced by H_2O_2. A172 cells transfected with pCMV3-TPH2 or empty vector control were exposed to H_2O_2 (0, 10, 20 µM), and live cell concentration (cells/mL) was quantified using Luna-FL AO/PI analysis. Data reflect n = 3 independent experiments. Statistics: unpaired two-tailed t-test comparing TPH2 vs. control within each H_2O_2 concentration (three pairwise comparisons).

DOI: 10.36838/IJHSR815.42

Cells were exposed to H_2O_2 with concentrations of 0, 10, and 20 μM (Figure 3). Their survival rate was compared to determine if cells with *TPH2* overexpression have a higher survival rate than others in an oxidative stress condition. First, in the 0 μM condition where cells were not exposed to H_2O_2, 2.855×10^6 cells/mL survived when exposed to *TPH2* overexpression, showing a significant increase from the negative control group (2.680×10^6 cells/mL) ($p = 0.0094$). This shows that *TPH2* overexpression itself has a positive effect on the cells' survival rate. Furthermore, in the condition where cells were exposed to 10 μM H_2O_2, 4.18×10^6 cells/mL survived when exposed to TPH2 overexpression, while the negative control group recorded 3.19×10^6 cells/mL ($p = 0.007$). Therefore, the *TPH2* gene can have a positive effect even in mid-range oxidative stress conditions. In the highest oxidative stress condition, where cells were exposed to 20 μM H_2O_2, the negative control group had 1.55×10^6 cells/mL surviving, showing a significant decrease. On the other hand, cells exposed to *TPH2* overexpression showed a significantly higher survival rate with 3.86×10^6 cells/mL ($p = 0.0004$). Microscopic analysis corroborated these quantitative findings, revealing that *TPH2*-overexpressing cells maintained characteristic morphology and higher cell density under both 10 μM and 20 μM H_2O_2 conditions compared to controls, which exhibited increased cellular debris and reduced confluence. The result of this experiment shows that the *TPH2* gene's positive effect on the cells' survival rate is significant in oxidative stress conditions as well as normal conditions.

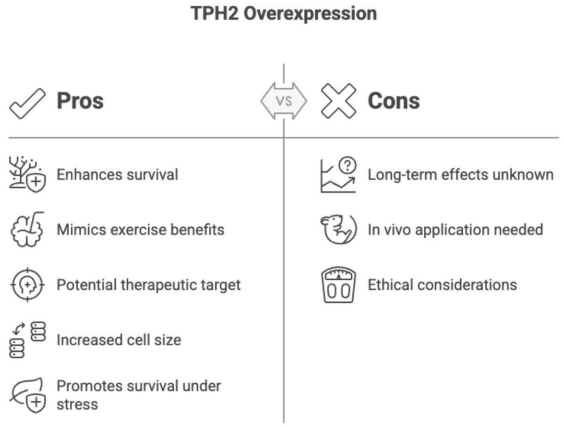

Figure 4: Summary schematic of TPH2 overexpression effects and study limitations. Conceptual overview synthesizing the study's main findings: increased baseline viability (Figure 1), increased cell size (Figure 2), and enhanced survival under oxidative stress (Figure 3), alongside key limitations (single cell line, serotonin not directly quantified, potential plasmid/off-target effects, limited dose-response and long-term assessment, and lack of *in vivo* validation).

The experiment displays how the *TPH2* gene can positively affect brain cell survival, similar to exercising (Figure 4). However, the experiment has several limitations, which are as follows: First, the experiment utilized only one type of brain-originated cell line (A172), which may not accurately reflect the diversity of brain cells or various body conditions. Second, although *TPH2* overexpression is presumed to have a positive effect on serotonin production, we were unable to verify the actual concentration of serotonin. Therefore, whether *TPH2* overexpression and serotonin production are correlated remains unknown. The experiment also does not include the potential off-target effects of plasmid overexpression yet, so having a control experiment for addressing such effects is another possibility. The experiment lacks dose-response data for *TPH2* overexpression levels as well; comparing the effect between low and high overexpression of *TPH2* is another potential future research. Finally, the experiment only involved short-term responses from the cells and did not show the long-term effect of *TPH2* overexpression or the cells' response to stress exposure. The follow-up study plans to use various brain-originated cell lines and primary neuronal cells to evaluate the reproducibility and generalization of the experiment. In addition, the next experiment plans to analyze the amount of serotonin as well as the actual amount of serotonin produced after *TPH2* overexpression. Finally, it plans to use animal models to check if *TPH2* overexpression has a positive effect on depression alleviation or cognitive function.

This study has several limitations that should be addressed in future work. First, although *TPH2* overexpression is expected to increase serotonin synthesis, serotonin levels were not directly quantified, and therefore, the functional biochemical impact of *TPH2* upregulation remains inferred rather than experimentally confirmed. Second, plasmid-driven overexpression may introduce off-target or non-physiological effects, including cellular stress responses or unintended gene regulation changes, which could contribute to the observed survival benefits independently of *TPH2* activity. Third, the study evaluated a single overexpression condition and did not include a dose–response analysis of *TPH2* expression levels, preventing assessment of whether neuroprotective effects scale with expression magnitude or reach a functional plateau. Addressing these limitations through serotonin quantification, vector control, pathway-specific validation, and graded expression studies will strengthen mechanistic interpretation and improve translational relevance.

Conclusion

TPH2 gene overexpression led to an increased survival rate of the A172 human brain-originated cell line, showing that the gene can protect neuronal cells from oxidative stress. Cells exposed to *TPH2* overexpression also showed an increase in average cell size, which is correlated with increased cellular metabolic activities and survival signals. Even in oxidative stress conditions caused by H_2O_2, *TPH2* overexpression increased the cells' survival rate, displaying its neuroprotective role as a gene activated through exercise. The experiment showed potential for genetically re-creating the physiological effect of exercising while also proving that the *TPH2* gene can potentially be used for targeting depression, stress, or neurodegenerative disease treatment in the future. The follow-up experiment plans to assess the correlation between *TPH2* and other exercise-related genes, the long-term effect of the gene, and its application in an actual living body to use the gene as a method for neuronal protection.

Acknowledgments

I want to thank Prof. Woo Rin Lee for supporting this project by teaching experimental methods and assisting my process throughout the experiment.

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DOI: 10.36838/IJHSR815.42