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RESEARCH ARTICLE

Exploring the Neuroprotective Roles of Oxytocin and Estrogen on Human Glial and Neuronal Cells

Justin Kim

Korea International School, Daewangpangyo-ro, 385 beon-gil Bundang-gu, Seongnam-si, Gyeonggi-do, 13543, South Korea; justink121106@gmail.com
Mentor: Woo Rin Lee

ABSTRACT: This study aimed to explore the neuroprotective effects of oxytocin and estrogen on human glial (A172) and neuronal (SHSY5Y) cells by focusing on cellular viability and the expression of the stress-related gene HSPB1. Neurodegenerative conditions often involve cellular stress, where the modulation of stress-response genes like HSPB1 could offer insights into potential therapeutic strategies. Given that oxytocin and estrogen have been suggested to play protective roles in brain function, this research sought to determine their effects on cell survival and gene regulation in cultured brain cells. We investigated various concentrations of oxytocin and estrogen to assess their impact on the activation of HSPB1 and overall cell viability. Initial experiments demonstrated that higher hormone concentrations (5 nM, 10 nM) induced cell death in both A172 glial and SHSY5Y neuronal cells, indicating the importance of optimizing hormone concentrations. Specifically, we identified that both hormones' lower concentrations (0.1 nM) showed promise in protecting the cells from stress-induced death. Moreover, the co-administration of Retinoic Acid (20 μL), which is known to influence differentiation, was found to exacerbate cell death, indicating a possible detrimental interaction with these hormones. Further analysis through live/dead assays suggested that oxytocin and estrogen could enhance cell survival at lower concentrations, particularly in the A172 glial and SHSY5Y neuronal cells. Gene expression analysis revealed a significant downregulation of HSPB1 in response to 0.1 nM estrogen, suggesting that this concentration may activate a protective mechanism by reducing stress-related gene expression. These findings indicate that oxytocin and estrogen, at optimized concentrations, may offer neuroprotective benefits and enhance cellular viability. This study provides a foundation for further investigations into the therapeutic potential of these hormones in neuroprotection and stress regulation.

KEYWORDS: Cell and Molecular Biology; Oxytocin; Estrogen; Human Glial Cells; Human Neuron Cells.

Introduction

The human brain is an extraordinary organ that plays a critical role in cognition, emotion, and motor function. The brain's intricate network of billions of neurons and glial cells constitutes the foundation of human identity and consciousness.[1] However, the brain is constantly exposed to stressors, toxins, and diseases that can change its structural and functional properties. To counter these threats, the brain has developed a defense mechanism regulated by hormones in the human body.[2]

Recent research highlights the neuroprotective effects of human hormones.[3] Besides their well-known roles in regulating physiological processes and maintaining homeostasis, hormones such as IGF-1 can protect human neuronal cells from damage and degeneration.[4] This highlights the hormone's functional role in potential therapeutic interventions in neurological disorders and age-related cognitive decline.

This research paper comprehensively explored the neuroprotective effects of oxytocin and estrogen. We select oxytocin and estrogen because of their well-established roles in the brain, diverse mechanisms of action, and clinical implications. Oxytocin is a peptide hormone typically produced in the hypothalamus portion of the brain. It serves various functions in the human body, affecting human behavior. Oxytocin is primarily known to be the "love hormone," mainly facilitating childbirth and other aspects of the reproductive system.[5] However, recent studies have shown that the hormone can also regulate excitatory/inhibitory balance, which is important in different brain regions and neurodevelopment.[6] Scientific research in the recent decade has revealed that Oxytocin has effects on an individual's social behavior, including anxiety, social memory, bonding, emotional recognition, trust, empathy, and mentalization.[7]

Estrogen is a steroid hormone that involves the development of female reproductive organs and sexual characteristics.[8] However, estrogen is not only limited to these two physiological functions. It also contributes to cognitive health, bone health, the cardiovascular system, and other processes.[9] Three different estrogen types exist: estrogen, estradiol, and estriol. Estrogen is a female sex hormone commonly known as the weakest form of estrogen. This specific type is found to be increased after a woman's menopause. Estradiol is found in men and women as the common form of estrogen in the female reproductive years. Estriol levels rise during pregnancies and foster the growth of the uterus, preparing the body for delivery. Estrogen exerts evident effects on specific brain regions, such as the hippocampus and prefrontal cortex. It instigates synaptogenesis, sporogenesis, and a complex set of signal transduction pathways in these two regions through the estrogen receptors.[10]

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Glial cells are crucial in communication between neurons, inflammation regulation, and blood-brain barrier formation. Because each glial cell has a specific function in the central and peripheral nervous system, a dysfunctional glial cell may result in the blooming of neurological conditions.[11] There are four major types of glial cells in the central nervous system (CNS). Astrocytes, the most copious glial cells in the CNS, control neurotransmission, create blood-brain barriers, and regulate brain metabolism. Another type of glial cell is oligodendrocytes. They create myelin, a fatty material around a nerve cell called the axon, to foster faster electrical conduction. Microglia are small, star-shaped glial cells that protect the CNS. They are immune cells that the body uses as the first line of defense against pathogens. Lastly, ependymal cells grow in the fluid-filled compartments of the CNS. They are conducive to lining these fluid-filled compartments and transporting and forming cerebrospinal fluids.[12]

Neuron cells communicate messages throughout the body, allowing humans to do everything from thinking to breathing, walking, and eating. Neurons carry information using electrical and chemical signals that make up an incredibly complex communication network.[13] These cells can be split into three parts: Soma (cell body), dendrites, and axons. The soma is the part of the neuron cell that receives information and contains the neuron's nucleus. Dendrites are thin filaments that transport the information from one neuron to another's soma. Axons are the long projections from the axon that send information off to other neurons' somas. They contain axon terminals, typically the sites where synapses, a point of contact where data from one neuron is passed on to another, are found. Synapses can both be electrical or chemical. In the case of a chemical synapse, a signal reaches a synapse and then triggers the release of chemicals into the gap between the two neuron cells, which is called the synaptic cleft. These chemicals (neurotransmitters) diffuse across the synaptic cleft, triggering a response by interacting with the membrane of the postsynaptic neuron. In the case of an electrical synapse, the synaptic cleft is much narrower, meaning electric currents can pass through directly. Thus, they work much faster than chemical synapses, so they are found in locations requiring quick actions, such as defensive reflexes.[14]

Previous research has revealed that human growth hormones may help with cell viability and act as an agent for neuroprotection.[15] This research investigated oxytocin and estrogen's protective effect on human glial and neuronal cell viability. We researched the effect of oxytocin and estrogen on HSPB1 gene expression, activated by various human brain stresses. We hypothesize that these human growth hormones will increase human glial and neuronal cell viability by increasing the expression of the HSPB1 gene.

Methods

Cell Culture and Maintenance:

Human glial A172 cells and SHSY5Y neuronal cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin to ensure cell growth and prevent contamination. SHSY5Y cells were cultured in a 1:1 mixture of DMEM supplemented with 10% FBS and 1% penicillin-streptomycin. Both cell lines were incubated at 37°C in a humidified atmosphere containing 5% CO_2, ensuring an optimal environment for cell growth. Media changes were performed every 2–3 days to maintain proper nutrient levels. Cells were subcultured when they reached approximately 80% confluency, using 0.25% trypsin-EDTA to detach cells from the culture plates. These conditions were strictly followed to maintain cell viability and prepare for subsequent treatments with oxytocin, estrogen, and retinoic acid.

Estrogen and Oxytocin-induced Cell Death in A172 Glial Cells:

A172 human glial cells were exposed to four experimental conditions: 5 nM Estrogen, 10 nM Estrogen, 5 nM Oxytocin, and 10 nM Oxytocin, followed by a 7-day incubation period. The cellular outcomes were observed and documented through imaging, illustrating the effects of estrogen and oxytocin on A172 cell viability.

Estrogen and Oxytocin-induced Cell Death in SHSY5Y Neuronal Cells:

SHSY5Y neuronal cells underwent the same experimental conditions as A172 cells. Cells were exposed to 5 nM Estrogen, 10 nM Estrogen, 5 nM Oxytocin, and 10 nM Oxytocin, followed by a 7-day incubation period. Cellular outcomes were observed through imaging to assess the impact of estrogen and oxytocin on SHSY5Y cell viability.

Oxytocin and Estrogen-induced Cell Death in SHSY5Y Neuronal Cells Treated with Retinoic Acid (RA):

SHSY5Y neuronal cells were treated with four conditions: RA 20 μL, RA 20 μL + Estrogen 1 nM, RA 20 μL + Oxytocin 1 nM, and RA 20 μL + Estrogen 1 nM + Oxytocin 1 nM, followed by a 7-day incubation period. The effects of oxytocin and estrogen in combination with RA on SHSY5Y cell viability were examined through imaging.

Analysis of Live and Dead Cells in A172 Glial Cells Treated with RA and Co-Treated with Oxytocin or Estrogen:

A172 glial cells were subjected to five treatment conditions, including a no-treatment control, RA only, RA + Oxy (0.1 nM), RA + Est (0.1 nM), and RA + Oxy + Est (0.1 nM), followed by a 2-week incubation. Fluorescence microscopy was employed to analyze live (green) and dead (red) cells, evaluating the impact of oxytocin and estrogen on cell survival.

HSPB1 Gene Expression Analysis:

RT-PCR and agarose gel electrophoresis were utilized to investigate the impact of estrogen and oxytocin on HSPB1 gene expression. Cells were treated with RA + Est (0.1 nM), and the resulting gene expression levels of HSPB1 and GAPDH were compared to control conditions. This sheds light on the potential protective effect of estrogen on SHSY5Y neuronal cells under stressed conditions.

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Results and Discussion

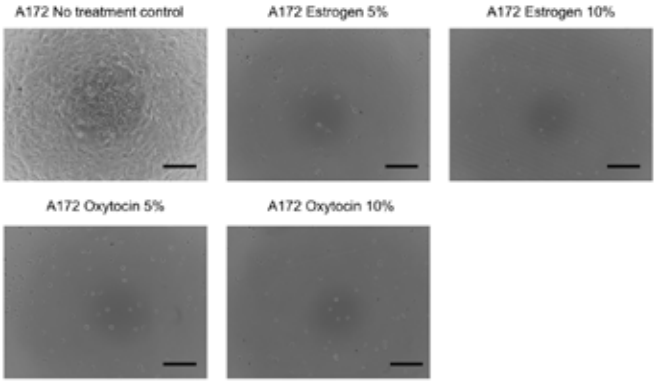

Figure 1: Estrogen and Oxytocin growth hormones induced cell death on A172 human glial cells. A172 cells were subjected to four experimental conditions: 5 nM Estrogen, 10 nM Estrogen, 5 nM Oxytocin, and 10 nM Oxytocin, followed by a 7-day incubation period. The cell image illustrates the cellular outcomes after incubation. High concentrations of Estrogen and Oxytocin induced human glial cell death.

This experiment was conducted to test the effects of the growth hormones estrogen and oxytocin on the cells A172, human glial cells. The cells were placed in 5nM Estrogen, 10nM Estrogen., 5nM Oxytocin, and 10nM Oxytocin. These concentrations were injected into the cell plates and were incubated for seven days. Figure 1 shows the conditions of the A172 cells after seven days of incubation with the growth hormones. After the incubation, it was observed that A172 cells placed in estrogen and oxytocin were all detached from the surface of the plate, signifying their death. A172 cells of the no treatment were in healthy condition, as 100% confluency of the live cells was observed, with the cells in the healthy shape of a rod. It can be deduced that the high concentration of the growth hormones caused the death of most A172 cells. A decreased concentration will be needed for a more accurate representation of the effect of the growth hormones.

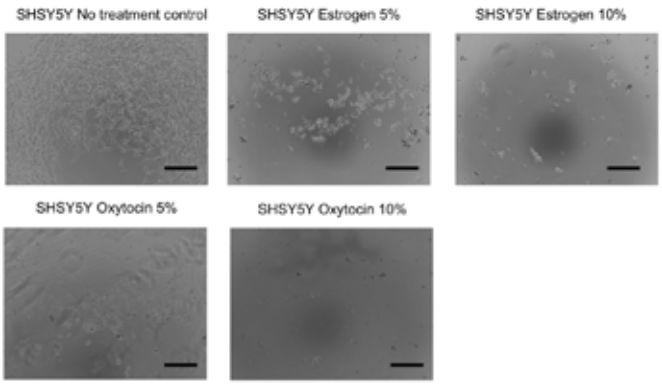

Figure 2: Estrogen and Oxytocin growth hormones induced cell death on SHSY5Y neuronal cells. SHSY5Y cells were subjected to four experimental conditions: 5 nM Estrogen, 10 nM Estrogen, 5 nM Oxytocin, and 10 nM Oxytocin, followed by a 7-day incubation period. The cell image illustrates the cellular outcomes after incubation. High concentrations of Estrogen and Oxytocin induced human neuronal cell death.

This experiment was conducted to test the effects of the growth hormones estrogen and oxytocin on the cells SH SY5Y, which are human neuron cells. The cells were placed in 5 nM Estrogen, 10 nM Estrogen, 5 nM Oxytocin, and 10 nM Oxytocin. These concentrations were injected into the cell plates and were incubated for seven days. Figure 2 shows the SH SY5Y cells' conditions after seven days of incubation with the growth hormones. Similar to the A172 cells, the SH SY5Y were mainly detached from the surface of the plate and clumped together, signifying the death of the cells. Though the 5nM hormone concentrations showed less cell death, there were still too many dead cells to get an accurate representation of the effect of the hormones. It can be deduced that the high concentration of the growth hormones caused the death of most SH SY5Y cells. A decreased concentration will be needed for a more accurate representation of the effect of the growth hormones.

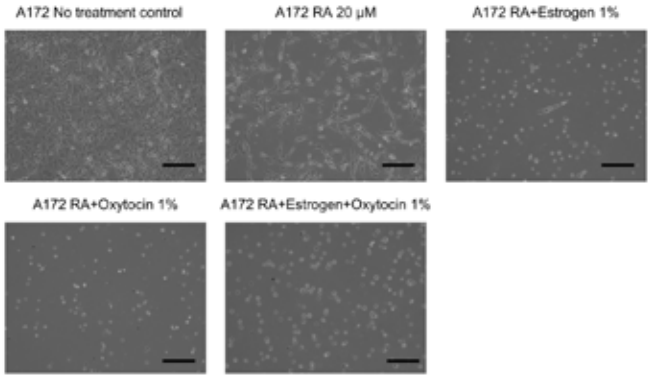

Figure 3: Oxytocin and Estrogen growth hormones on A172 glial cells treated with retinoic acid (RA) induced cell death. A172 cells were subjected to four distinct conditions: RA 20 µL, RA 20 µL + Estrogen 1 nM, RA 20 µL + Oxytocin 1 nM, and RA 20 µL + Estrogen 1 nM + Oxytocin 1 nM. Following injection into cell plates for a 7-day incubation. The image illustrates A172 cell conditions after incubation with growth hormones and RA. RA successfully differentiated A172 glial cells, but oxytocin and estrogen still induced cell death even in lower concentrations.

This experiment investigated the effect of the growth hormones Oxytocin and Estrogen on glial cells after treatment with Retinoic Acid. The cells were placed in four different conditions: RA 20 µL, RA 20 µL + Estrogen 1nM, RA 20 µL + Oxytocin 1nM, and RA 20 µL + Estrogen 1nM + Oxytocin 1nM. These concentrations were injected into the cell plates and were incubated for seven days. Figure 3 shows the A172 cells' conditions after seven days of incubation with the growth hormones and Retinoic Acid. The A172 cells showed some confluency of live cells for the Retinoic Acid environment. It was visible that about 20 µM of cells survived and attached to the surface. However, as the growth hormones were added, the survival of the cells was drastically reduced, showing clumps of cells floating, indicating the death of cells. This showed that the concentration still had to be reduced even more. It can be deduced that the high concentration of the growth hormones caused the death of most A172 cells. A decreased concentration will be needed for a more accurate representation of the effect of the growth hormones.

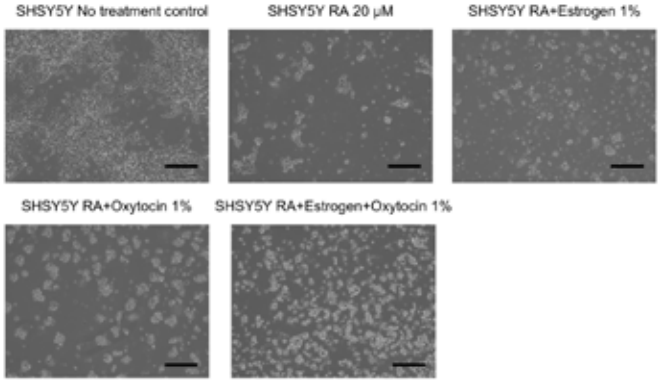

Figure 4: Oxytocin and Estrogen growth hormones on SHSY5Y neuronal cells treated with retinoic acid (RA) induced cell death. SHSY5Y cells were subjected to four distinct conditions: RA 20 µL, RA 20 µL + Estrogen 1nM, RA 20 µL + Oxytocin 1nM, and RA 20 µL + Estrogen 1nM + Oxytocin 1 nM. Following injection into cell plates for a 7-day incubation. The image illustrates SHSY5Y cell conditions after incubation with growth hormones and RA. RA successfully differentiated SHSY5Y neuronal cells, but oxytocin and estrogen still induced cell death even in lower concentrations.

This experiment investigated the effect of the growth hormones Oxytocin and Estrogen on neuron cells after treatment with Retinoic Acid. The cells were placed in four different conditions: RA 20 µL, RA 20 µL + Estrogen 1nM, RA 20 µL + Oxytocin 1nM, and RA 20 µL + Estrogen 1nM + Oxytocin 1nM. These concentrations were injected into the cell plates and were incubated for seven days. Figure 4 shows the SH SY5Y cells' conditions after seven days of incubation with the growth hormones and Retinoic Acid. In contrast to A172 cells, SHSY5Y cells now showed confluency of live cells for the Retinoic Acid environment. It was visible that most cells were not attached to the surface. As the growth hormones were added in, the survival of the cells was similar to that of cells in RA, showing clumps of cells floating, indicating the death of cells. This showed that the concentration still had to be reduced even more.

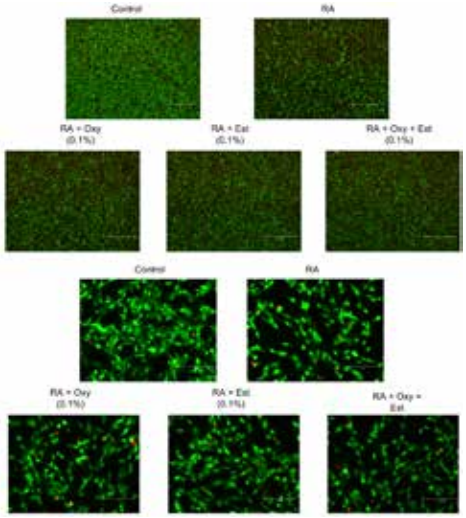

Figure 5: Analysis of live and dead cells in A172 glial cells treated with RA and co-treated with Oxytocin or Estrogen. A172 cells were subjected to five treatment conditions and incubated for two weeks. The conditions include no treatment control, RA only, RA + Oxy (0.1nM), RA + Est (0.1nM), and RA + Oxy + Est (0.1nM). The fluorescence microscopy image depicts live cells in green and dead cells in red. Oxytocin and estrogen may protect the differentiated A172 glial cells.

Next, we aim to analyze the live and dead cells after treatment of RA and co-treatment of RA with either oxytocin or estrogen. We used A172 cells prepared in five conditions and incubated for two weeks. The five conditions are indicated in Figure 5: no treatment control, RA only, RA + Oxy (0.1nM), RA + Est (0.1nM), and RA+Oxy+Est (0.1nM). The green fluorescent cells indicate the live cells, and the red fluorescent cells indicate the dead cells (Figure 5). Interestingly, compared to RA-treated A172 cells, co-treatment of oxytocin or estrogen individually and co-treatment of oxytocin with estrogen showed a higher number of green fluorescent cells. However, there was no difference in red cell numbers between the RA-treated sample and oxytocin or estrogen-treated A172 samples. This result indicates that oxytocin and estrogen may protect the differentiated A172 glial cells.

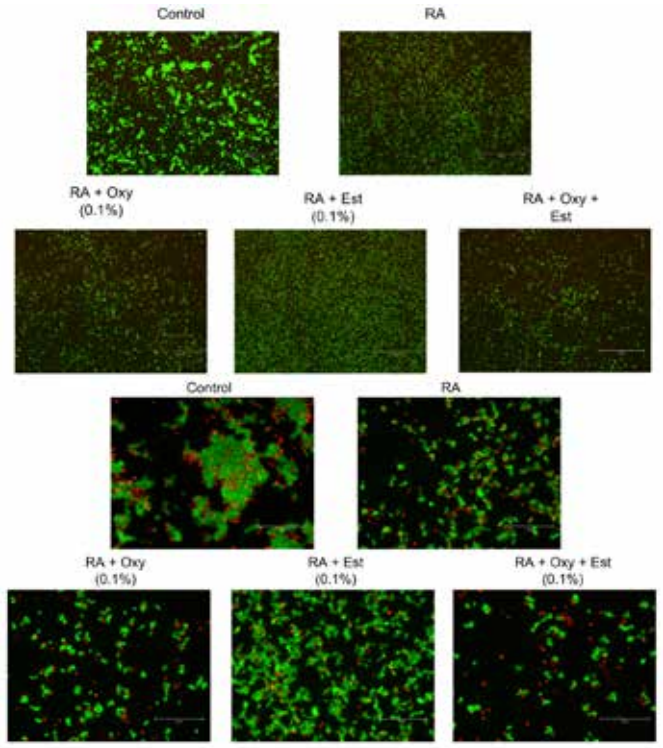

Figure 6: Analysis of live and dead cells in SHSY5Y neuronal cells treated with RA and co-treated with Oxytocin or Estrogen. SHSY5Y cells were subjected to five treatment conditions and incubated for two weeks. The conditions include no treatment control, RA only, RA + Oxy (0.1nM), RA + Est (0.1nM), and RA + Oxy + Est (0.1nM). The fluorescence microscopy image depicts live cells in green and dead cells in red. Estrogen (0.1 nM) protects neurons and may increase brain integrity.

Here, we analyze the live and dead cells after treatment of RA and co-treatment of RA with either oxytocin or estrogen. We used SH SY5Y cells prepared in five conditions and incubated for two weeks. The five conditions are indicated in Figure 5: no treatment control, RA only, RA + Oxy (0.1 nM), RA +Est (0.1 nM), and RA+Oxy+Est (0.1 nM). After the results of previous experiments, we discovered that even a 1 nM concentration of the growth hormones can be toxic to the cells, leading to cell deaths. Thus, we reduced the concentration to 0.1nM to mitigate the effect of the hormones on the cells. The green fluorescent cells indicate the live cells, and the red fluo

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rescent cells indicate the dead cells (Figure 6). As visible in the figure, compared to RA-treated A172 cells, co-treatment of estrogen increased the number of live cells drastically. The figure displays an increase in the number of green cells compared to any other condition, including the one only treated with RA. The number of red cells is homogenous in all conditions except for the estrogen-treated cells, showing that estrogen protects neurons and increases brain integrity.

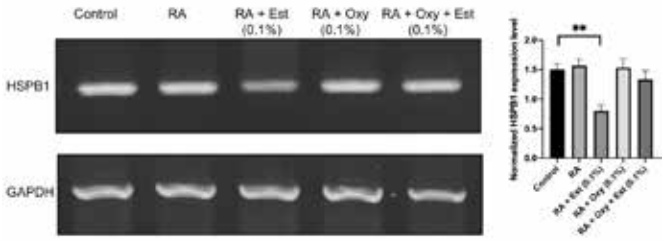

Figure 7: HSPB1 gene expression level was decreased in the RA+Est (0.1nM) treated condition. RT-PCR and agarose gel were used to visualize the gene expression of HSPB1 and GAPDH.

Next, we aim to explore the impact of estrogen and oxytocin on the neuron stress marker HSPB1. A prior study has demonstrated elevated expression of the HSPB1 gene in stressed brain cells. Consequently, we hypothesized that either estrogen or oxytocin could reduce the expression level of HSPB1. Figure 7 presents the results of the RT-PCR analysis of HSPB1 and GAPDH. Compared to the control sample, RA, RA + Oxy, and RA + Oxy + Est-treated samples exhibited no significant change in the band intensity of HSPB1. However, the RA + Est (0.1nM) treated condition displayed a lower band intensity than the control sample, indicating a decreased expression level of HSPB1. This outcome suggests that estrogen might have a protective effect on SHSY5Y neuronal cells under stressed conditions.

In this study, a deeper investigation into the interactions between oxytocin and estrogen and their combined effects on cellular viability and stress response reveals a complex interplay that influences both neuroprotection and cellular stress mechanisms. Oxytocin, known for its roles in social behavior and stress modulation, interacts with estrogen, a hormone involved in synaptogenesis and neuroprotection, to regulate cellular responses to external stressors, such as oxidative stress and inflammation. The combined treatment of oxytocin and estrogen has been shown to influence key stress markers, such as HSPB1, a gene associated with cellular protection under stress. Both hormones can enhance cell survival at optimal concentrations by mitigating cellular stress pathways, including those mediated by reactive oxygen species (ROS). Their neuroprotective effects are likely mediated through estrogen receptor pathways and oxytocin's modulation of neurotransmission, with both hormones contributing to improved cellular resilience, particularly in glial and neuronal cells. However, their synergistic impact at higher concentrations can lead to adverse effects, including cellular apoptosis, highlighting the necessity for precise concentration optimization in therapeutic settings. These findings suggest that oxytocin and estrogen not only provide a protective role but also modulate the cellular stress response in ways that could inform future neuroprotective therapies for degenerative neurological diseases.

Conclusion

This research examines the neuroprotective effects of oxytocin and estrogen on human glial and neuronal cells, focusing on their impact on the HSPB1 gene associated with brain stress. The study was conducted on A172 glial cells and SHSY5Y neuronal cells, and the results showed that high concentrations of estrogen and oxytocin resulted in cell death. This highlights the importance of optimizing hormone concentrations to represent their effects accurately. Co-treatment of SHSY5Y neuronal cells with retinoic acid (RA) reduced cell survival when estrogen and oxytocin were added, indicating the need for lower hormone concentrations. In A172 glial cells treated with RA and co-treated with oxytocin or estrogen, live and dead cell analysis indicated a potential protective role for these hormones at lower concentrations. Gene expression analysis showed that estrogen at 0.1nM significantly reduced HSPB1 expression, supporting the hypothesis of a protective mechanism.

While the findings of this study provide valuable insights, it is essential to acknowledge its limitations. The study primarily focused on *in vitro* experiments using A172 glial cells and SHSY5Y neuronal cells, which may not fully represent the complexity of the human brain. Further investigation is needed to extrapolate the findings to *in vivo* scenarios and clinical applications. The study also utilized high concentrations of hormones in some experiments, leading to significant cell death, highlighting the need for careful optimization of hormone concentrations. The research is also constrained by the specific cell lines and conditions chosen, which may limit the generalizability of the findings to diverse cell types or neurological contexts. The study did not explore potential interactions between oxytocin and estrogen, which could influence their combined effects. Addressing these limitations in future studies will enhance the applicability and robustness of the findings in the broader context of neuroprotection and therapeutic development.

This research sheds light on the potential therapeutic avenues for neurological disorders and age-related cognitive decline by understanding the neuroprotective effects of oxytocin and estrogen on human glial and neuronal cells. When administered at optimal concentrations, these hormones may play a protective role in enhancing cell viability. The study's results indicate that estrogen reduces the expression of the brain stress marker HSPB1, suggesting a specific molecular mechanism underlying its neuroprotective effects. This knowledge has implications for the development of targeted interventions that leverage the potential of oxytocin and estrogen to mitigate cellular damage and promote brain health. The study's impact extends beyond the laboratory, offering insights that could influence future research directions and the development of novel therapeutic strategies for neurodegenerative conditions.

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Authors

Justin Kim, a student at Korea International School, plans to major in environmental science and is interested in biology.

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