

Research Article

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COMBINED EFFECTS OF RETINOIC ACID AND SELENIUM ON CELL VIABILITY IN SH-SY5Y NEUROBLASTOMA CELLS



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Abstract

Objective: This study aimed to investigate the individual and combined effects of retinoic acid (RA) and selenium (Se) on cell viability in SH-SY5Y neuroblastoma cells, with a focus on dose- and time-dependent responses.

Materials and Methods: SH-SY5Y cells were treated with varying concentrations of RA (1, 10, or 100 µM) and Se (1, 10, or 100 µM), either alone or in combination. Cell viability was assessed using the trypan blue exclusion assay at 48 and 72 hours. Statistical analyses were performed using one-way or two-way ANOVA followed by Dunnett's post hoc test, as appropriate.

Results: Retinoic acid significantly reduced cell viability in a dose-dependent manner at both time points, with 100 µM RA causing near-complete loss of viable cells. Selenium also decreased viability, but its effect was milder and became significant only at higher concentrations. Notably, the combined application of RA and Se produced a substantially stronger cytotoxic effect than either agent alone, indicating a potential synergistic or additive interaction between the two.

Conclusion: These findings indicate that the simultaneous application of RA and Se can elicit a stronger cytotoxic effect in SH-SY5Y cells than either treatment alone. The results highlight the importance of redox modulation and combination strategies in neuroblastoma cell models. Further studies are warranted to elucidate the underlying mechanisms and therapeutic potential of RA and Se co-treatment.

Keywords Retinoic acid • Selenium • SH-SY5Y • Neuroblastoma • Cytotoxicity • Combination therapy

INTRODUCTION

The SH-SY5Y cell line, originally derived from the bone marrow of a four-year-old girl with metastatic neuroblastoma, remains a widely used model for studying neuroblastoma biology and neuronal differentiation (1, 2). Neuroblastoma (NB)

typically arises from poorly differentiated neural crest-derived cells (3, 4). Retinoic acid (RA), a metabolite of vitamin A, is clinically used in high-risk neuroblastoma treatment protocols to promote the differentiation of tumour cells into a less malignant phenotype (5). SH-SY5Y cells are highly susceptible to apoptosis (6). Notably,

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when these cells are differentiated with RA, they become even more sensitive to hydrogen peroxide (H_2O_2)-induced cytotoxicity than their undifferentiated counterparts (7). Treatment with all-trans RA for 4–7 days induces neuron-like phenotype and leads to a marked increase in apoptosis upon peroxide exposure (7). In RA-treated cells, levels of superoxide and H_2O_2 rise (as shown by ROS-sensitive probes), but this is not matched by increased expression of peroxide-detoxifying enzymes, resulting in H_2O_2 accumulation (8, 9). At typical concentrations ($10\mu M$), RA rapidly drives the transformation from neuroblastic to neuron-like cells and inhibits proliferation (9, 10). These findings indicate that increased ROS is not just a side effect but an integral part of RA-induced differentiation (8). Disruption of redox homeostasis, whether through elevated ROS or impaired antioxidant defence, can shift the balance towards oxidative stress, impeding proliferation or triggering apoptosis (11, 12). In both cancer and neurodegeneration, this imbalance leads to genomic instability, deregulated cell cycle control, and neuronal loss (12). The interplay between pro-oxidant and antioxidant pathways often determines whether a cell survives or undergoes apoptosis (12, 13).

Therapies that selectively increase ROS in cancer cells may take advantage of their heightened sensitivity to oxidative damage, leading to apoptosis (14).

Conversely, differentiation therapies and antioxidant strategies seek to restore redox balance, suppress proliferation, or promote tumour cell maturation (15). For example, RA regulates gene expression through nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), thereby influencing cell growth, differentiation, and apoptosis (16). RA functions through binding to nuclear RARs and RXRs, thereby regulating gene expression and influencing cell growth, differentiation, and apoptosis (16). These pathways are essential for development and neurogenesis, and RA induces cell cycle arrest and neurite outgrowth in human neuroblastoma cells (16).

Selenium (Se) is an essential trace element, present as selenocysteine in at least 25 human selenoproteins, many of which function in redox regulation and antioxidant defence (17, 18). At physiological levels, Se supports redox balance, but at higher concentrations, it can become pro-oxidant (17–19). Excess Se can induce ROS production, mitochondrial dysfunction, and caspase activation, thereby promoting oxidative damage and apoptosis rather than prevention (17–19). Selenium concentrations above a certain threshold have been shown to trigger reactive oxygen species (ROS) production and induce apoptosis in cell culture models (20).

A study on ovarian cancer cells demonstrated that fenretinide (a synthetic retinoid) combined with sodium selenite more effectively suppressed proliferation and induced apoptosis than either agent alone, both in vitro and in vivo (21). These findings suggest that combination approaches may produce synergistic anti-tumour effects (21).

The combined use of RA and Se provides a valuable model for exploring how oxidative stress modulation can influence cell fate. While physiological levels of Se may buffer RA-induced ROS through enhanced antioxidant capacity, higher or pro-oxidant doses of Se may instead amplify oxidative damage and drive cells towards apoptosis (22–24). The SH-SY5Y cell line is particularly well suited for investigating this interaction, as it is highly susceptible to oxidative stress and readily undergoes neuronal differentiation in response to RA (25–27).

This study aimed to compare the dose- and time-dependent effects of RA, Se, and their combination on SH-SY5Y cell viability at 48 and 72 hours. By quantifying the inhibition of proliferation and cell death over time, we aimed to determine whether Se modulates or enhances RA-induced cytotoxicity in this neuroblastoma model. Our findings contribute to understanding how redox modulation affects cell fate and may inform the development of redox-based combination therapies for neuroblastoma and other cancers.

MATERIALS AND METHODS

SH-SY5Y cells were cultured and treated

SH-SY5Y human neuroblastoma cells (ATCC) were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco, USA) supplemented with 10% fetal bovine serum (FBS; Sigma-Aldrich, USA), 1% L-glutamine, and 1% penicillin–streptomycin at $37^\circ C$ in a humidified incubator containing 5% CO_2 . For experiments, cells with >95% viability were seeded into 6-well culture plates (Corning, USA) at a density of 5×10^5 cells per well.

Cells were treated with various concentrations of retinoic acid (RA; 1, 10, 100 μM) and selenium (Se; 1, 10, 100 μM), either individually or in combination. The control groups consisted of untreated and solvent-control cells exposed to ethanol, which was used as the vehicle in RA treatments (28). Selenium stock solutions were prepared in sterile water. All treatments were adjusted so that the final ethanol concentration did not exceed 0.1% in any group. All treatments were performed in triplicate ($n=3$).

All experiments were performed independently for each treatment condition. Single-agent treatments presented within combination experiments represent independent experimental sets and were not derived from the same dataset as those shown in single-treatment analyses.

Cell viability was assessed at 48 and 72 hours post-treatment using the trypan blue exclusion assay. After treatment, cells were detached by trypsinization, collected by centrifugation (5 minutes at 1200 rpm), and resuspended in 1 mL of fresh medium. Each cell suspension was mixed 1:1 with 0.4% trypan blue solution (Gibco, USA). Ten microliters of the mixture were loaded into a Neubauer haemocytometer, and viable (unstained) and non-viable (blue-stained) SH-SY5Y cells were counted manually under a light microscope. Cell viability was



calculated as the percentage of live cells relative to the total number of cells counted. All samples were analysed in triplicate (29-31).

All experiments were performed in triplicate ($n=3$), and results are presented as mean $\pm$ standard deviation (SD). For single-factor dose-response analyses, statistical significance was assessed using one-way ANOVA followed by Dunnett's post hoc test to compare treatment groups against the control. For combined treatment analyses involving dose and time, two-way ANOVA followed by Dunnett's post hoc test was applied. All analyses were conducted using GraphPad Prism (version 10, GraphPad Software, San Diego, CA, USA). A p -value <0.05 was considered statistically significant.

RESULTS

The effects of different concentrations of RA and Se on SH-SY5Y cell viability were assessed at 48 and 72 hours (Figure 1). At 48 hours, RA significantly decreased cell viability in a dose-dependent manner: both 1 μ M and 10 μ M RA reduced viability compared with the control group ($p<0.01$), while 100 μ M RA induced a near-complete loss of viable cells ($p<0.0001$) (Figure 1a). At 72 hours, all RA concentrations significantly reduced cell viability, with 10 μ M and 100 μ M producing highly significant cytotoxic effects ($p<0.0001$) and 1 μ M RA also showing a marked decrease compared with control ($p<0.001$) (Figure 1b).

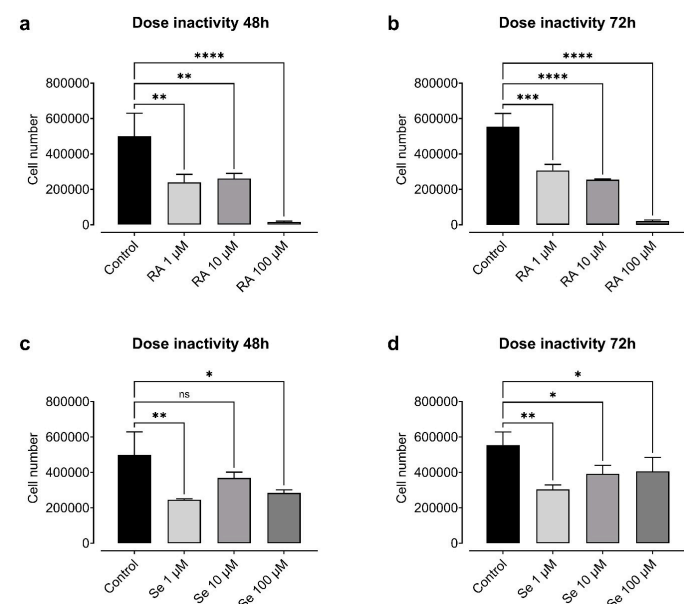


Figure 1. Effects of retinoic acid (RA) and selenium (Se) at different concentrations (1, 10, and 100 μ M) on SH-SY5Y cell viability. SH-SY5Y cells were treated with RA or Se at concentrations of 1, 10, or 100 μ M. Cell viability was assessed by trypan blue exclusion at 48 hours (a, c) and 72 hours (b, d). *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$, ****: $p<0.0001$.

Selenium treatment also resulted in reductions in cell viability, although the effect was less pronounced than that observed with RA. At 48 hours, 1 μ M Se significantly decreased cell viability compared

with the control group ($p<0.01$), whereas 10 μ M Se did not produce a statistically significant effect. In contrast, 100 μ M Se caused a modest but significant reduction in viability ($p<0.05$) (Figure 1c). At 72 hours, all Se concentrations significantly reduced cell viability relative to the control group, including 1 μ M ($p<0.01$), 10 μ M ($p<0.05$), and 100 μ M ($p<0.05$) (Figure 1d).

Although similar treatment conditions were applied, single-agent responses showed variations between independent experiments. The effects of combined retinoic acid (RA, 10 μ M) and selenium (Se, 10 μ M) treatment on SH-SY5Y cell viability were further evaluated at 48 and 72 hours (Figure 2). At both time points, RA alone significantly reduced cell viability compared with the control group ($p<0.0001$). In contrast, Se alone produced a modest but significant decrease in cell viability at 48 hours ($p<0.05$), whereas no significant effect was observed at 72 hours. Combined RA + Se treatment resulted in a significantly greater reduction in cell viability than either single treatment at both time points ($p<0.0001$).

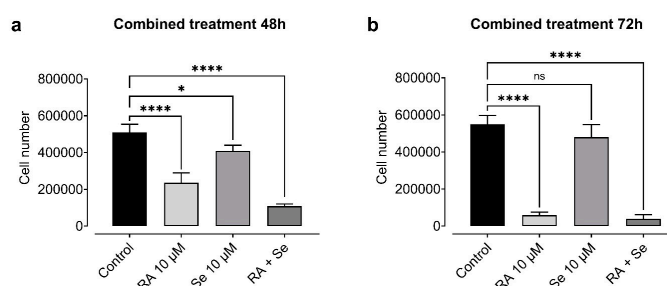


Figure 2. Effects of combined retinoic acid (RA) and selenium (Se) treatment (10 μ M each) on SH-SY5Y cell viability. SH-SY5Y cells were treated with RA (10 μ M), Se (10 μ M), or both in combination for 48 hours (a) and 72 hours (b). Cell viability was assessed by trypan blue exclusion. *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$, ****: $p<0.0001$.

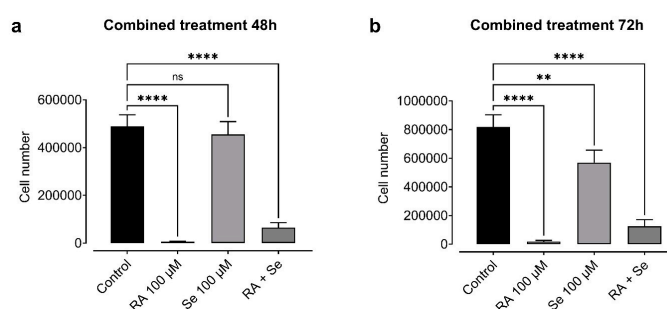


Figure 3. Effects of combined retinoic acid (RA) and selenium (Se) treatment (100 μ M each) on SH-SY5Y cell viability. SH-SY5Y cells were treated with RA (100 μ M), Se (100 μ M), or both in combination for 48 hours (a) and 72 hours (b). Cell viability was assessed by trypan blue exclusion. *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$, ****: $p<0.0001$.

The effects of higher-dose combined treatment with retinoic acid (RA, 100 μ M) and selenium (Se, 100 μ M) were also examined (Figure 3). At both time points, RA alone caused a near-complete loss of cell viability compared with the control group ($p<0.0001$).



Selenium alone did not significantly affect cell viability at 48 hours; however, a significant reduction was observed at 72 hours ($p < 0.01$). The combined RA + Se treatment markedly decreased cell viability at both time points, with the RA + Se group showing significantly lower values than the control and Se-alone groups ($p < 0.0001$). No significant difference was observed between the RA-alone and RA + Se groups.

DISCUSSION

In this study, we investigated the dose- and time-dependent effects of RA and Se on cell viability in SH-SY5Y neuroblastoma cells. Our findings demonstrate that RA induces a pronounced reduction in cell viability at 48 and 72 hours, with cytotoxicity becoming more evident at higher concentrations. Notably, treatment with 100 μM RA resulted in an almost complete loss of viable cells, in agreement with previous reports indicating that high-dose RA can exert cytotoxic effects through oxidative stress-related mechanisms (32). In contrast, Se alone produced a comparatively moderate and variable reduction in cell viability; although most concentrations had limited effects, 100 μM Se significantly decreased viability at 72 hours.

Importantly, the combined application of RA and Se resulted in a greater reduction in cell viability than either agent alone. Rather than conclusively demonstrating synergy, these findings are more appropriately interpreted as indicating an additive or potentiating interaction, particularly given the absence of a formal synergy analysis. In this context, Se did not appear to mitigate RA-induced cytotoxicity and may, under certain dose and time conditions, enhance it. This observation is consistent with reports showing that Se can modulate antioxidant defence systems and sensitise cancer cells to cytotoxic agents (33). Moreover, accumulating evidence suggests that, at supraphysiological concentrations, Se may shift from an antioxidant to a pro-oxidant role, thereby amplifying oxidative stress and promoting cell death (33-35).

The differential effects observed with RA and Se alone further support this interpretation. While RA consistently exerted strong inhibitory effects across all tested concentrations, Se produced a milder, dose-dependent decrease in cell viability. These results highlight the complex and context-dependent nature of redox modulation, whereby agents acting through distinct but intersecting pathways collectively influence cellular fate decisions (36, 37).

The SH-SY5Y cell line represents a well-established and relevant in vitro model for examining the interplay between oxidative stress, neuronal differentiation, and tumour cell survival, particularly in the context of RA signalling (38). Accordingly, our findings contribute to a broader understanding of how redox-modulating agents interact in neuroblastoma cells and may inform future strategies aimed at exploiting redox imbalance or differentiation pathways for therapeutic benefit.

A key limitation of this study is the reliance on cell viability as the primary experimental endpoint. While this approach is suitable for establishing dose- and time-dependent cytotoxic effects, it does not provide mechanistic insight into the underlying cellular processes. Future studies incorporating complementary analyses, such as measurements of oxidative stress markers, mitochondrial function, and differentiation-related endpoints, will be necessary to more fully characterise the biological basis of the observed interactions between RA and Se.

CONCLUSION

In conclusion, this study demonstrates that RA exerts a strong and dose-dependent cytotoxic effect on SH-SY5Y neuroblastoma cells, whereas Se induces a comparatively milder but measurable reduction in cell viability, particularly at higher concentrations and longer exposure times. Notably, combined treatment with RA and Se resulted in a more pronounced reduction in cell viability than either agent alone, consistent with an additive or potentiating interaction. These findings underscore the importance of dose, timing, and combination context when evaluating redox-modulating agents in neuroblastoma models. Further investigations addressing redox balance, mitochondrial involvement, and differentiation status will be essential to clarify the mechanistic basis of these effects and assess the potential translational relevance of RA and Se co-treatment strategies.



Peer Review	Externally peer-reviewed.
Author Contributions	A.B. conceived, designed, and supervised the study. B.Y. performed data analysis, drafted the manuscript, conducted the literature review, and contributed to study concept development. B.B. and M.S. carried out the experiments and contributed to data collection. All authors participated in data interpretation and manuscript revision and approved the final version of the manuscript.
Data Availability Statements	The data underlying this article are available in the article.
Conflict of Interest Statement	The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be understood as a potential conflict of interest.
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