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*Review Article*

# Assessment of the level of apoptosis in differentiated pseudo-neuronal cells derived from neural stem cells under the influence of various inducers

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**Abstract:** Development and maintenance of the nervous system are governed by a scheduled cell death mechanism known as apoptosis. Very much how neurons survive and function depends on the degree of death in differentiating pseudo-neuronal cells produced from neural stem cells. Different inducers can affect the degree of death in these cells: hormones, medicines, growth factors, and others. Developing inventive therapies for neurodegenerative illnesses depends on a knowledge of how these inducers impact mortality in differentiated pseudo-neuronal cells. Using flow cytometry, Western blotting, and fluorescence microscopy among other techniques, the degree of death in many pseudo-neuronal cells is evaluated. Flow cytometry generates dead cell counts from measurements of cell size, granularity, and DNA content. Whereas fluorescence microscopy visualizes dead cells using fluorescent dyes or antibodies, Western blotting detects caspases and Bcl-2 family proteins. This review attempts to offer a thorough investigation of present studies on death in differentiated pseudo-neuronal cells produced from neural stem cells under the effect of different inducers. Through investigating how these inducers influence death, the review aims to provide information that might direct the next studies and support treatment plans for neurodegenerative diseases. With an eye toward inducers like retinoic acid, selegiline, cytokines, valproic acid, and small compounds, we examined research to evaluate death rates. The findings offer important new perspectives on the molecular processes guiding death in these cells. There is still a complete lack of understanding of how different factors affect the molecular processes that lead to death, so understanding these processes can contribute to new therapeutic approaches to treat neurodegenerative diseases.

**Keywords:** Apoptosis, brain disorders, inducers, therapeutic approaches, neurodegenerative diseases, neural stem cells

## Introduction

Neural stem cells (NSCs) show significant potential for regenerative medicine because of their amazing self-renewal capacity, which lets them proliferate and generate more stem cells as well as their predisposition to specialize into many cell types within the central nervous system (CNS). These cells are mostly located in specific brain areas, including the sub ventricular zone (SVZ) and the dentate gyrus. Moreover, researchers can obtain NSCs from diverse sources, including embryonic tissues and induced pluripotent stem cells (iPSCs). Researchers utilize neural stem cells (NSCs) as a major element in the treatment of several central nervous system (CNS) disorders, such as stroke, traumatic brain injury, and neurodegenerative diseases like Parkinson's and Alzheimer's, owing to their adaptability [1, 2]. There is much optimism that NSCs can assist individuals in these circumstances. Research indicates that motor performance and tissue viability markedly enhance following NSC transplantation in ischemic stroke models.

Furthermore, NSCs are integral to drug discovery and screening, enhancing their appeal.

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NSCs obtained from Huntington's disease patients have been pivotal in discovering new therapeutic agents, underscoring their significance in personalized medicine. The capacity to genetically alter NSCs to improve their viability or to express therapeutic genes broadens their clinical potential. This component is deemed essential for enhancing therapy alternatives for neurodegenerative disorders [3].

Though NSCs have great promise for regenerative medicine, we have to overcome certain obstacles to properly utilize their features. Ensuring that NSCs develop properly into the relevant neuronal types, improving transplanting methods, and avoiding immunological rejection will help us to solve these problems [4]. Scholars always create fresh ideas to solve these problems. They are using small molecules, for example, to control the growth of brain stem cells and creating biomaterials that improve the survival and integration of transplanted cells [5]. Solving these problems is essential for the effective use of NSCs in clinical settings.

Understanding the functional relevance of differentiated pseudo-neuronal cells formed from NSCs depends on an evaluation of death in these cells. A basic step in forming the nervous system, apoptosis - also known as programmed cell death - is connected to dysregulated death linked to many CNS diseases including Alzheimer's and Parkinson's diseases [6]. Developing sensible therapeutic approaches depends on an awareness of the regulatory systems controlling death in these cells [7].

Standard aspects of many central nervous system diseases, oxidative stress, inflammation, and DNA damage can all cause death. Examining how these inducers influence death in NSC-derived pseudo-neuronal cells helps us to understand the fundamental causes of many disorders and point possible therapy targets [8]. You are absolutely vital in this understanding and will help to bring about major changes in treatment choices, therefore contributing to the development of the field.

Moreover, the efficacy of stem cell treatments depends on the important function of death. After transplantation, NSCs encounter many difficulties including immunological responses and ischemia that can cause death and compromise their survival and integration into host tissues. Developing plans to improve the life of transplanted NSCs or preconditioning the cells or applying immunosuppressive medications depends on an evaluation of death in these cells. This evaluation will help to improve the outcomes of stem cells-based therapy [9, 10].

Many inducers have been investigated for their effect on death in pseudo-neuronal cells derived from NSC. Selegiline is a monoamine oxidase inhibitor noted for its neuroprotective properties and ability to stop death in neurodegenerative animals. Retinoic acid can induce both pro-apoptotic and anti-apoptotic reactions in neural stem cells under suitable timing and dosage of treatment. Changing death pathways helps to promote cell survival by means of growth factors such as epidermal growth factor (EGF) and necessary fibroblast growth factor (bFGF). Sonic hedgehog (Shh) signaling has been observed as protection against oxidative stress-induced mortality. Concurrently, bone morphogenetic proteins (BMPs) may display diverse effects on death based on their modulation of apoptotic signaling channels. Moreover, neurotrophins have a major role in cell survival and differentiation, therefore affecting the death process. Cytokines have two functions in control of death: some induce cell death while others increase survival by affecting apoptotic proteins. Furthermore, certain tiny compounds are known to either induce or promote survival by changing the expression of apoptotic proteins, hence modulating death.

Harnessing the therapeutic possibilities of NSCs in the treatment of neurological diseases depends on an awareness of how these inducers influence death. This review attempts to fully evaluate the present knowledge on apoptosis in differentiated pseudo-neuronal cells originating from NSCs, thereby guiding future investigations and highlighting the critical need of more study to create successful therapeutic options in this developing field.

### Differentiation of neural stem cells into pseudo-neuronal cells

The development of cell-based therapeutics for neurological diseases depends on differentiating neural stem cells into pseudo-neuronal cells [11, 12]. Stem cell research has advanced to expose the intricate interaction among envi-

ronmental elements, genetic programming, and signaling pathways affecting this process. Essential in cell fate determination and neuronal differentiation are key pathways including Notch, Wnt, and Sonic Hedgehog (Shh) [13-15]. With features similar to embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) present a fascinating direction for study [16]. Their ability to separate into neural stem cells and neuron-like cells offers a special chance to investigate elements influencing brain development, including signaling pathways and hormones such as thyroid hormone (T3) [17]. The production of particular neuronal types by microplasma exposure highlights even more the possibilities of iPSCs in both studies and treatments [18]. Modern approaches, including single-cell calcium imaging, are transforming our knowledge of brain development. They provide exact control over the process and analysis of elements influencing neuronal growth. These methods improve neuronal growth and lower variability by changing signaling pathways and using specified reagents. Further emphasizes the importance of these cutting-edge methods in the encouragement of neuronal differentiation by soluble cues, cell-cell contacts, electrical stimulation, and growth factors [19-21].

Not only is the creation of cell-based treatments dependent on an awareness of the differentiation process, but also the degree of death in brain stem cells under the effect of different inducers [22, 23]. Identification of possible therapeutic approaches and guarantee of the safety and effectiveness of these treatments depend on this knowledge.

Understanding neuronal development in neural stem cells (NSCs) requires first investigating substrate features, cell-cell interactions, and extracellular matrix proteins [24]. NSCs are quite helpful for a variety of uses in neuroscience research and tailored therapy approaches since of their regenerative character and multilineage potential [25]. For example, IL-6, an inflammatory cytokine, controls neuronal differentiation, suggesting that changing the inflammatory milieu can increase neurogenesis and support brain regeneration [26].

Different combinations of growth factors, cytokines, and signaling molecules help neural stem cells to develop into pseudo-neuronal cells with great efficiency and specificity. While FGF2 and IGF1 direct astrocyte development [19, 22, 25, 26], FGF2, EGF, and LIF cause neuronal differentiation. Three-dimensional (3D) cell culture and organoid development are two advanced cell culture methods that help neural stem cells differentiate into pseudo-neuronal cells mimicking in vivo circumstances. These methods enhance cell survival, function, and complex neural network building [27-29]. Different inducers, such as chemical, physical, or biological factors [30, 31], as well as the differentiation process itself, can affect the degree of death in differentiated pseudo-neuronal cells. Thus, it is crucial to find the ideal conditions for converting neural stem cells into pseudo-neuronal cells and to pinpoint the inducers that might control death in these cells [32].

### The process of differentiating neural stem cells into pseudo-neuronal cells

Understanding neural stem cell (NSC) differentiation into pseudo-neuronal cells and the elements driving this intricate process has advanced significantly recently. With their fate decided by a complex interaction of signaling pathways, genetic instructions, and many environmental elements, NSCs show extraordinary capacity for self-renewal and differentiation into several brain cell types, including neurons and glia [33, 34].

Manipulating transcription factors such as Ascl1, Smad7, and Nr2f1 has shown several studies of the guided differentiation of NSCs into particular neuronal subtypes, such as GABAergic and pyramidal neurons. YAP and other essential proteins help adipose-derived MSCs to develop into neural progenitors and neural cells [35, 36]. Emphasizing the need of knowledge of molecular control, better techniques for producing and analyzing mutant neurons open the path for possible cell replacement treatments in neurodegenerative illnesses.

Studying neuronal network formation and identifying developmental neurotoxicity has been much aided by in vitro techniques using neural progenitor cells [37, 38]. With controlled differentiation producing the expression of neural-associated genes and proteins confirming neuronal features, using growth factors, cytokines,

and other signaling molecules efficiently promotes NSC differentiation into pseudo-neuronal cells [39, 40]. The multipotential differentiation of NSCs emphasizes their capacity for migration and glial and neuronal cell differentiation [41, 42].

Small chemicals like STC2, valproate (VPA), and purmorphamine among other elements affect NSC differentiation by altering important pathways [43, 44]. The activation of neurogenesis in response to focal cerebral ischemia helps to repair brain tissue, therefore pointing up possible treatment targets for neurological diseases [45].

Providing a useful instrument for investigating stem cell activity, Bizy and Sacri R. Ferrón (2015) explained the development of neurospheres from undifferentiated NSCs [46]. J. Kriska (2021) underlined the fascinating part several signaling pathways, including Wnt/β-catenin, play in inducing neuron-like cell development over glial cells, thereby providing possible therapeutic targets for neurological diseases [47].

Like electric fields, external elements encourage NSC differentiation into neurons in 3D settings, so creating opportunities for 3D-engineered neural tissues and thus improving therapies for neurological diseases. Using markers for tracking neural cell development and evaluating the impact of microglial cells on neuronal differentiation, studies by Ramila Joshi (2016), Y. Hirano (2023), and Ulrica Englund Johansson (2002) significantly contribute to our understanding of the differentiation process and molecular regulation, identifying markers for tracking neural cell development and assessing the effects of microglial cells on neuronal differentiation [48, 49].

### Types of inducers used to promote differentiation and their mechanisms of action

Recent research has shown how crucial it is to comprehend the processes underpinning varying neural stem cell differentiation into pseudo-neuronal cells. Though each possesses a different mode of action, these systems can be categorized as chemical, physical, or biological. Maximizing the differentiation process and improving regenerative therapies depend on your knowledge of and contributions to these systems.

Retinoic acid, forskolin, valproic acid, tiny compounds like all-trans retinoid acid (ATRA), and chemical inducers all help to alter particular signaling pathways engaged in neuronal development and support transdifferentiation. While forskolin stimulates the cAMP pathway, retinoic acid promotes the Wnt pathway, fostering neuronal development [50, 51]. Inhibiting histone deacetylases, valproic acid stimulates astrocyte differentiation [52]. In leukemia cells, ATRA restores autophagy, a mechanism for eliminating damaged cells and preserving cellular homeostasis, therefore fostering granulocyte differentiation [53].

Mechanical and electrical stimuli, among other physical inducers, help neural stem cells develop into pseudo-neuronal cells. Shear or cyclic stress applied to neural stem cells causes astrocyte and neuron differentiation [54, 55]. Simultaneously, electrical and deep brain stimulation fosters the differentiation of several cell types and neuronal development [56, 57].

Growth factors and cytokines are among biological inducers that activate particular signaling pathways and help to transdifferentiate cells. Interleukins activate B lymphocyte and bone marrow stem-cell differentiation [58]. Whereas BMP4 and IGF-1 foster astrocyte differentiation, FGF2, EGF, and LIF cause neuronal differentiation. Dopaminergic and cholinergic neurons are partly developed by GDNF and BDNF. Exosomes and other extracellular vesicles help cells to communicate for self-renewal and differentiation [59-61].

Apart from these elements, transdifferentiation also results from Basic Fibroblast Growth Factor (bFGF), Wnt proteins, Smoothened agonist (SAG), and B27 supplement. While Wnt proteins change cell proliferation and differentiation by β-catenin-dependent signaling [62], bFGF increases neuronal differentiation by upregulating NGFβR and NRP1 following stimulation [63]. SAG targets genes [64] and induces Indian Hedgehog (Ihh) expression by modulating the Hedgehog (Hh) pathway (**Figure 1**). B27 supplement enhances neural stem cell development and proliferation as well as neuronal cell survival [65].

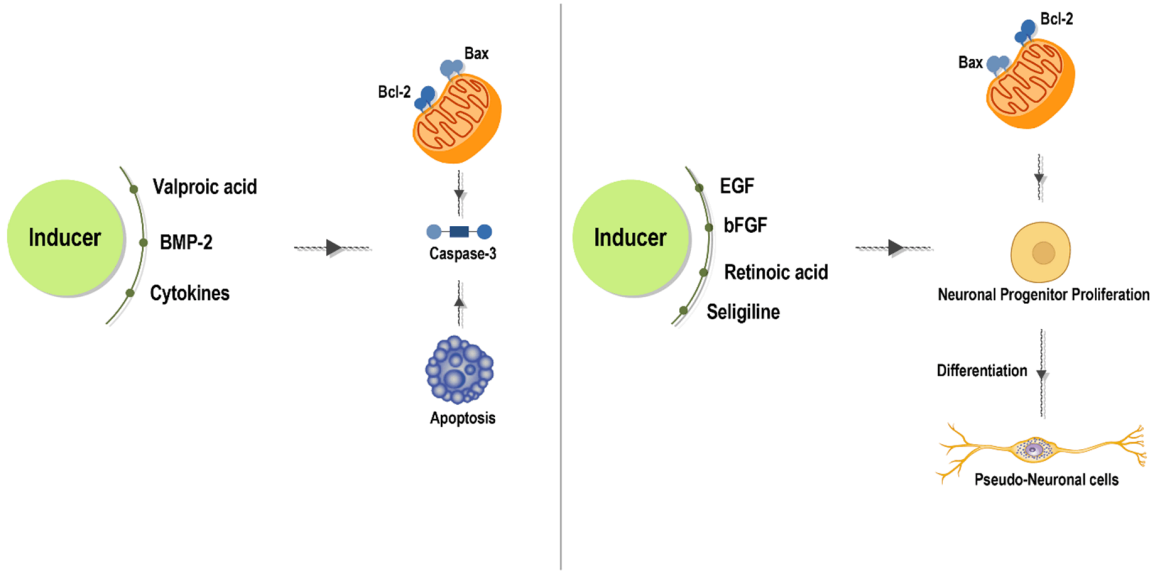


**Figure 1.** Chemical, physical, and biological inducers illuminate key mechanisms guiding neural stem cells' transformation into pseudo-neuronal cells, enhancing therapeutic.

## Mechanisms of apoptosis

Apoptosis, a planned cell death process, is essential for the growth and maintenance of the nervous system. Different pseudo-neuronal cells, particularly sensitive to death, originate from neural stem cells. Many elements can affect this process, including inducers that support differentiation. Developing sensible plans to prevent or treat neurodegenerative illnesses depends on an awareness of the molecular mechanisms underlying death in these cells. The intrinsic pathway, set off by cellular stress and DNA damage, is one of the key paths in death in differentiated pseudo-neuronal cells. The Bcl-2 family of proteins controls this mechanism; members of both pro- and anti-apoptotic (e.g., Bax) varieties [66]. Unbalances in the expression or activity of these proteins can activate caspases, which are proteases that cut important cellular proteins and finally cause cell death. The function of caspases in cell death emphasizes our study's need to create efficient treatments or preventive measures against neurodegenerative illnesses [67]. Death ligands (e.g., TNF-α, Fas ligand) attach to their specific receptors on the cell surface to start the extrinsic route, another important actor in death. This event sets caspases into action, which finally causes death [68]. Crucially, the extrinsic pathway is not a single process since it can interact with the intrinsic system, enhancing the death signal (**Figure 2**) [69]. This complicated interaction between the two routes clarifies death's several characters and helps us regulate it. By changing the activation of these pathways, inductors - which guide the differentiation of neural stem cells into pseudo-neuronal cells - have a major impact on death. For example, retinoic acid, a promoter of neuronal development, has been found in certain studies to raise Bcl-2 expression and lower Bax expression, lowering death [70]. On the other hand, valproic acid has been shown to raise Bax and caspase-3 expression as a promoter of astrocytic differentiation, hence increasing apoptosis [71]. These results highlight the interesting part inducers play in controlling death.

## Assessment of apoptosis

Understanding how various variables and inducers impact differentiated pseudo-neuronal cells derived from neural stem cells requires knowing how much death occurs in these cells. To evaluate the degree of death in these cells, we have applied flow cytometry, Western blotting, and fluorescence microscopy among other approaches. These strong approaches can produce notable knowledge of the complex and many molecular pathways controlling death in these cells. Your knowledge is vital in further investigation employing these approaches to

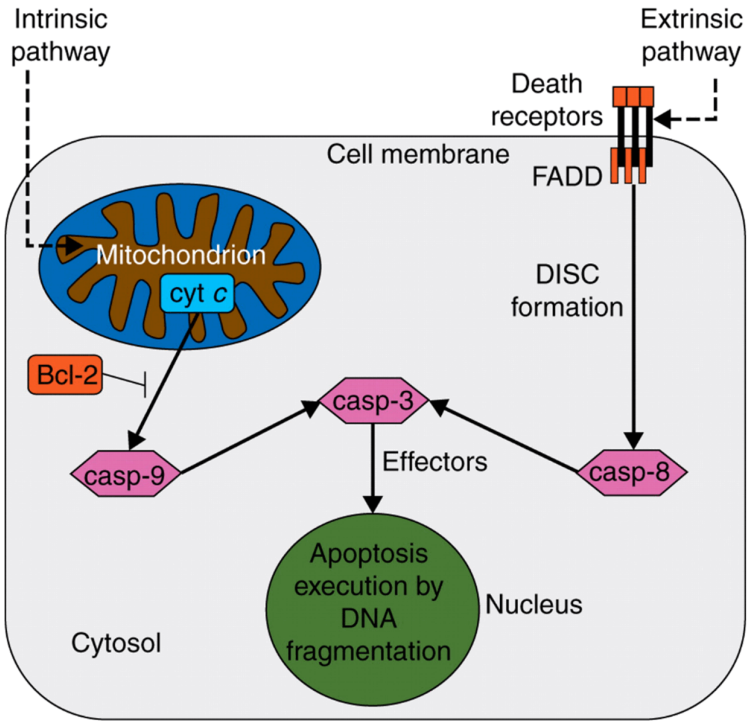


**Figure 2.** The two major pathways of apoptosis. The intrinsic or mitochondrial path of apoptosis (left side) affects mitochondrial dysfunction, the liberation of cytochrome c (cyt c), and the next activation of caspase-9 (casp-9) at the apoptosome. The anti-apoptotic protein Bcl-2 deters the discharge of cytochrome c from the mitochondrion. The extrinsic or death receptor pathway (right side) is begun via the binding of death ligands to the death receptor and subsequent recruitment of the adapter protein FADD and caspase-8 (casp-8) into the death-inducing signaling complex (DISC). Both apoptosis paths link at the activation of effector caspase-3 (casp-3), which cleaves several cellular proteins, ultimately showing the usual changes of apoptosis such as DNA fragmentation in the nucleus.

completely grasp the effect of diverse inducers and variables on apoptosis in differentiated pseudo-neuronal cells (**Figure 2**). A fundamental occurrence in cellular biology, apoptosis occurs through two main signaling channels: intrinsic and extrinsic ones. The intrinsic process consists of opening the mitochondrial membrane, synthesis of the apoptosome, and caspase activation. This process depends heavily on BCL-2 proteins. Understanding the fundamental processes of death initiation depends on this pathway. Conversely, the extrinsic pathway distinguishes the activation of death receptors, the recruitment of adaptor proteins with death domains, and the processing of procaspases, therefore activating caspase-8 and inducing death. Clarifying the environmental stimuli triggering death depends on grasping these channels. Flow cytometry is a widely used method to quantitate apoptotic cells by measuring changes in cell size, granularity, and DNA content. It uses fluorescent dyes that label apoptotic cells and distinguish them from viable cells based on their fluorescence intensity. Scientists have used this method to check the amount of apoptosis in neural stem cells that had been treated with different chemicals, such as sevoflurane, hydrogen peroxide, and genistein [72-75]. Another method for assessing apoptosis is western blotting, which involves detecting the expression of apoptotic markers like caspases and Bcl-2 family proteins. Researchers have employed this method to investigate the mechanisms of apoptosis in neural stem cells treated with various inducers, such as cyclosporine A and tanshinone I [76, 77]. Fluorescence microscopy is a powerful technique for visualizing apoptotic cells using fluorescent dyes or antibodies that bind to apoptotic markers. Scientists have used this method to investigate how neural stem cells change shape during apoptosis when treated with various inducers such as basic fibroblast growth factor and insulin-like growth factor-1 (**Figure 3**) [78, 79].

### The function of inducers in pseudo-neuronal cell apoptosis

A carefully controlled process, programmed cell death - also known as apoptosis - plays a vital part in many physiological and pathogenic disorders. Many years of neuroscience studies have focused on the triggering of death in pseudo-neuronal cells. Non-neural cells displaying certain functional and physical characteristics of neurons are pseudo-neuronal cells, including glial cells and neuronal progenitor cells. This review will cover the various inducers of apoptosis in pseudo-neuronal cells, along with their respective modes of action.

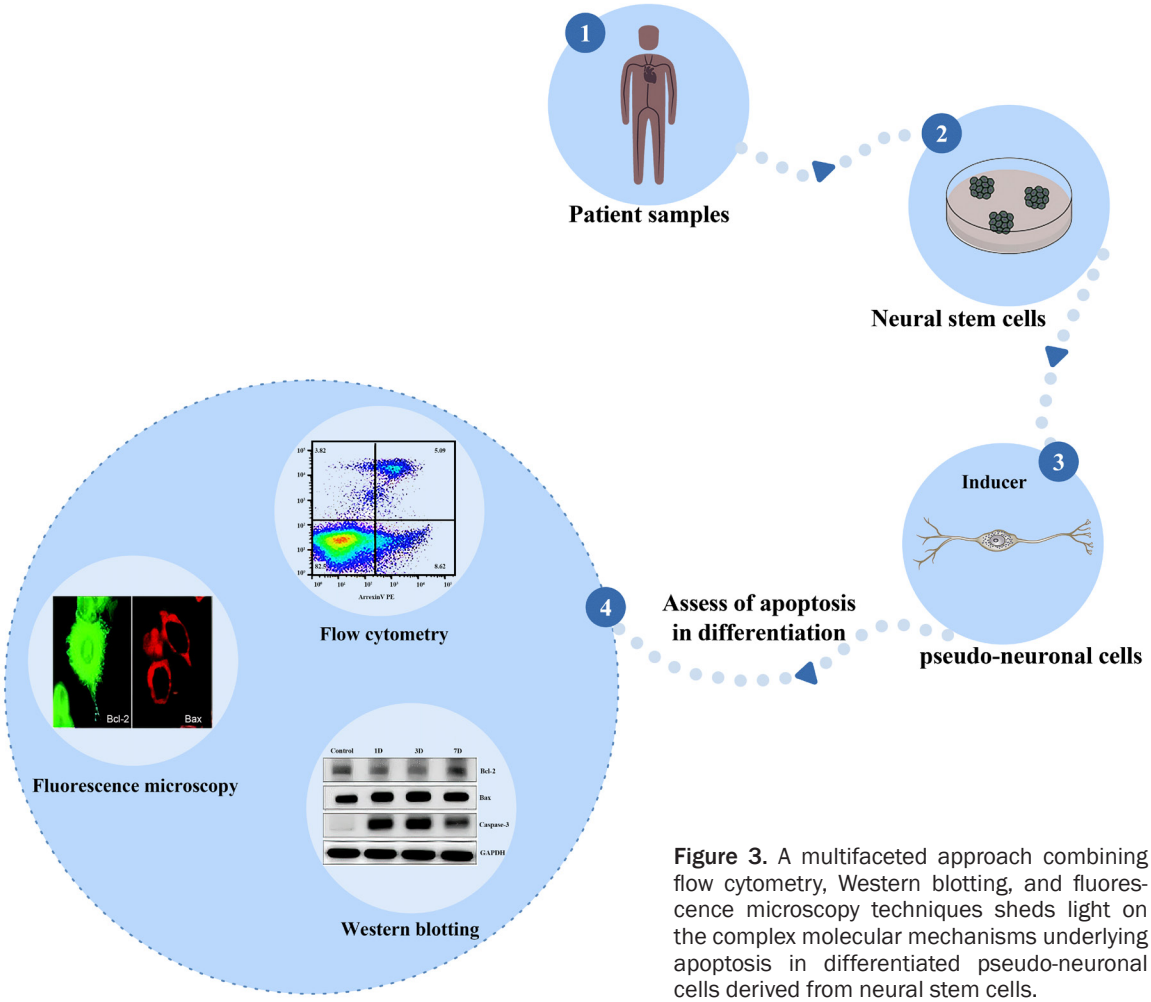


**Figure 3.** A multifaceted approach combining flow cytometry, Western blotting, and fluorescence microscopy techniques sheds light on the complex molecular mechanisms underlying apoptosis in differentiated pseudo-neuronal cells derived from neural stem cells.

Oxidative stress is one of the main causes of death in pseudo-neuronal cells. Reactive oxygen species (ROS) can be produced during normal cellular metabolism or in response to environmental stresses, leading to cellular damage and death. Researchers have found that oxidative stress can kill pseudo-neuronal cells. They have found that this is caused by the activation of the caspase cascade and the upregulation of pro-apoptotic genes, such as Bax and Bad [80, 81].

Another important way to kill pseudo-neuronal cells is to activate death receptors such as Fas, TNF-R1, and TRAIL-R1/2. These receptors initiate caspase cascades, leading to the death of cells. A study of what sets off death receptors in pseudo-neuronal cells shows that cytokines, radiation, and chemotherapeutic agents are just a few of the things that can do this [82, 83]. Apoptosis in pseudo-neuronal cells is a complicated process under the effect of several elements. Among these are endoplasmic reticulum (ER) stress, DNA damage, and mitochondrial dispersion. These stressors can thereby set off the intrinsic mitochondrial mechanism of death, the DNA damage response, and the unfolded protein response [84-86]. Furthermore, well studied is the purpose death serves in neurological disorders including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Under these conditions, oxidative stress, β-amyloid and tau in AD, α-synuclein in PD, and mutant huntingtin in HD all play a crucial role in killing off pseudo-neuronal cells, hence slowing down the course of the disease [87, 88]. One feasible therapeutic strategy now is to target death in neurological illnesses. Among the numerous approaches looked at are tiny molecules meant for apoptotic pathways, anti-apoptotic proteins, and

caspase inhibitors. New studies, for instance, have revealed that inhibiting the action of a protein termed mixed lineage kinase domain-like (MLKL) can prevent pseudo-neuronal cells from dying [89].

### The impact of various inducers on apoptosis levels in pseudo-neuronal cells

Apoptosis is an essential process in the development of the nervous system that affects what happens to differentiated pseudo-neuronal cells that come from neural stem cells. Various factors, such as MAPKs, cytokines, and neurotransmitters, modulate this process [90-92]. For instance, retinoic acid, a known inducer, reduces apoptosis by increasing the expression of the anti-apoptotic protein Bcl-2 and decreasing the pro-apoptotic protein Bax. On the other hand, valproic acid, another inducer, promotes apoptosis by increasing the expression of Bax and the activation of caspase-3 [93-95]. Neuroprotective agents like BDNF and EPO also reduce apoptosis, highlighting their therapeutic potential [96]. Viral products from HIV-1-infected cells contribute to neuronal apoptosis, emphasizing the need to explore their role in neurodegeneration [97]. Sphingolipid metabolism is crucial in neuronal survival during stress, providing another therapeutic target. The impact of chemicals on cell proliferation and apoptosis underscores the importance of understanding cell-specific toxic responses [98, 99]. Neuronal apoptosis is affected by levodopa, beta-amyloid inducers, and retinoic acid. This shows the importance of understanding apoptotic pathways for targeted therapies [100, 101]. Proinflammatory cytokines, oxidative stress, and compounds that move calcium ions around also affect apoptosis, meaning there are more therapeutic targets [102]. Various apoptosis-inducing agents contribute to neuronal cell death in neurodegenerative diseases. Of particular interest is IL-1β, which primes neurons for apoptosis by regulating p75NTR expression [103]. Changing the expression of proteins in sphingolipid metabolism affects the survival of neurons, and DNA damage causes apoptosis, which shows how important it is to keep the mitochondrial membrane potential stable [104, 105]. Protective compounds like NAC (N-acetyl cysteine) promise to mitigate these effects [106].

Human neural progenitor cells (NT2, hNP1) and neuroblasts (SH-SY5Y) show different apoptotic responses to GSNO and STS, with NT2 and hNP1 cells experiencing mitochondrial hyperpolarization followed by depolarization under short-term STS treatment [107]. CDK and cysteine aspartase inhibitors activate distinct apoptotic pathways, offering varied neuronal protection [108]. Silica nanoparticles induce apoptosis through reactive oxygen species-activated endoplasmic reticulum stress pathway [109]. Additionally, a combination of N2 supplement, retinoic acid, and nerve growth factor enhances neuronal characteristics and reduces apoptosis in HT22 cells, providing an optimized model for gene expression studies [110].

Prostaglandin D2 synthase induces apoptosis in PC12 neuronal cells through caspase-3 activation [111, 112]. In contrast, induced neural stem cells (iNSCs) protect against apoptosis in cortical neurons by activating the Akt and ERK pathways [113]. The gravity of the situation is underscored by the fact that high-LET radiation more effectively induces apoptosis in human neuronal progenitor cells than low-LET radiation [114, 115], while neuro progenitor cells are more sensitive to chemical-induced apoptosis than differentiated neurons [116].

Lastly, inducers like EGF and bFGF promote neural differentiation but may have time-dependent effects on apoptosis and neural cell markers. Protein phosphorylation and calcium homeostasis modulators also influence apoptosis by affecting Bcl proteins and caspase processing [117, 118].

### Revealing novel understanding of powerful inducers in apoptosis of pseudo-neuronal cells and their mechanism of action

The degree of death in neural stem cells can be changed by inducing their differentiation into pseudo-neuronal cells. Among the several inducers under investigation are selegiline, retinoic acid, epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), sonic hedgehog, bone morphogenetic proteins (BMPs), neurotrophins, cytokines, and small compounds. We have grouped the conversation according to inducer type, giving a clear, orderly approach, and including examples of current studies look-

ing at death in reaction to each inducer in **Table 1**.

*Selegiline*

Through a thorough knowledge of its mechanisms, selegiline - a complicated but interesting topic in neuropharmacology - affects death in differentiated pseudo-neuronal cells. Crucially for the survival of neurons, it selectively inhibits monoamine oxidase B (MAO-B), therefore lowering dopamine breakdown and stopping the accumulation of hazardous metabolites [119, 120]. Selegiline also prevents the absorption of dopamine and increases its release, therefore preserving higher dopamine levels that support cell survival and fight mortality [121]. Furthermore, selegiline's antioxidant qualities should help to greatly lower oxidative stress, a main factor causing death in neural cells [122]. Its capacity to stabilize mitochondria and raise the expression of neurotrophic factors, such as Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) [123] could inspire next research and development in the field of neuroprotection, so igniting interest and motivation among researchers. Finally, selegiline stimulates the expression of thioredoxin (Trx) [124], thus increasing the levels of the antioxidant MnSOD and the anti-apoptotic protein Bcl-2, thus improving the cell's capacity to fight oxidative damage and stop death. Using these combined activities, selegiline is quite important in preventing death in neuronal-like cells, thereby offering hope and confidence in its possible therapeutic value for neurodegenerative illnesses [125, 126].

*Retinoic acid*

Retinoic acid (RA) modulates death in differentiated pseudo-neuronal cells via multiple pathways. It stops the AP-1 transcription factor from working, which lowers the expression of genes that stop cells from dying. This causes death even when serum levels are low or nerve growth factor (NGF) is present [127]. In SH-SY5Y neuroblastoma cells, RA plays an intriguing role by encouraging differentiation into neuron-like cells, lowering P2X7 receptor expression, and preventing receptor-mediated death. The key actor in this process is the p38 MAPK pathway, which inhibits caspase-3 activation [128]. While BCL-2 overexpression in undifferentiated cells can prevent death, RA also downregulates the anti-apoptotic protein BCL-2 in differentiated NT2/D1 cells, thereby increasing cell death [129]. Fascinatingly, RA can show anti-apoptotic effects in retinal progenitor cells by upregulating particular protein kinase C (PKC) isoforms and protein kinase A (PKA), thereby simulating its protective action when PKA is active [130]. An intriguing field of study that keeps the audience interested and captivated is the part RA plays in stopping death. RA is concentration-dependent; hence, when mixed with bone morphogenetic proteins (BMPs), it can synergistically cause death [131]. Retinal pigment epithelium (RPE) lessens the specific death that RA causes in rod photoreceptors during retinal development [132]. RA also increases death by PKC activation, which works in concert with RA to further drive mortality [133]. Furthermore, RA is necessary for neural development and encourages stem cell differentiation into neurons, although its processes in embryos are yet mostly unknown [134].

*EGF, bFGF*

Our studies on EGF and bFGF have revealed fresh pathways of cell survival. Using tyrosine kinase-dependent pathways unique to the well-known protein kinase A (PKA) or protein kinase C (PKC), eGF and bFGF reduce death in differentiated pseudo-neuronal cells [135]. One interesting observation is that EGF increases the β1-integrin location on the surface of neuroepithelial cells (NECs), fostering cell survival. To cause β1-integrin expression and increase cell proliferation, both EGF and bFGF depend on the mitogen-activated protein kinase (MAPK) pathway [136, 137]. Moreover, a fresh understanding of cell survival mechanisms comes from bFGF's activation of the PI3K/Akt pathway, producing phosphorylation of the pro-apoptotic protein Bad and inhibition of caspase-3 [138]. Whereas EGF reduces oxygen-induced death in cultured rat cerebral cortical neurons in a dose-dependent manner, bFGF reduces death in PC12 cells via the Ras/MAPK and PKC delta pathways. Together, these growth factors show complementary and sequential activities that support cell survival and proliferation [139].

*Sonic hedgehog (Shh)*

As an inducement in neural-like cells, sonic hedgehog (Shh) signaling is absolutely important. It accomplishes this by controlling death

**Table 1.** Types of inducers and their effect on apoptosis

| Inducer | | Anti-apoptotic protein | Pro-apoptotic protein | Signaling pathway | Result | Ref. |
|---|---|---|---|---|---|---|
| Selegiline | | Increase of Bcl-2 | Decrease of Bax | Wnt/β-catenin | Reduced apoptosis | [187] |
| Retinoic acid | | Increase of Bcl-2 | Decline of Bax | - | Reduced apoptosis | [93] |
| Valproic acid | | Decline of Bcl-2 | Increase of Bax and caspase-3 | - | Increased apoptosis | [188] |
| Epidermal growth factor (EGF) | | Increase of Bcl-2 | Decrease of Bax | - | Reduced apoptosis | [189] |
| Basic fibroblast growth factor (bFGF) | | Increase of Bcl-2 | Decrease of Bax | PI3K/Akt | Reduced apoptosis | [190] |
| Sonic hedgehog | | Increase of Bcl-2 | Decrease of Bax | - | Reduced apoptosis | [191] |
| Bone morphogenetic proteins (BMPs) | BMP-2 | Decline of Bcl-2 | Increase of Bax and caspase-3 | - | Increased apoptosis | [192, 193] |
| | BMP-4 | Increase of Bcl-2 | Decrease of Bax | - | Reduced apoptosis | |
| Neurotrophins | | Increase of Bcl-2 | Decrease of Bax | - | Reduced apoptosis | [194] |
| Cytokines | | Decline of Bcl-2 | Increase of Bax | - | Increased apoptosis | [195] |

and proliferation via a multifarious process [140]. The pathway starts when Shh interacts with Patched (Ptc), which, without Shh, reduces the activity of Smoothened (Smo) [141]. Once Shh hooks to Ptc, Smo turns active and starts a signaling cascade that affects Gli transcription factors, including Gli1 [142]. This activation both suppresses pro-apoptotic elements like p53 [143] and increases the expression of genes in charge of cell survival and proliferation. Mostly by helping the transition from the G1 to the S phase, which is essential for proliferation, Shh signaling is key in guaranteeing the survival of neural-like cells by avoiding death and facilitating cell cycle advancement [144]. Shh generates a gradient in brain development to control the differentiation and proliferation of neural progenitor cells, therefore guaranteeing appropriate tissue patterning. Shh's effects are context-dependent, though; even if it encourages the development of brain progenitor cells, it can also cause cell cycle arrest and death in differentiated cells [145]. Shh thus balances survival, proliferation, and differentiation in a finely controlled way, so acting as a crucial regulator of neural-like cell fate.

*BMPs*

Bone morphogenetic proteins (BMPs), particularly BMP2 and BMP4, govern death in differentiated pseudo-neuronal cells when coupled with retinoic acid (RA), in a manner that outperforms either one alone. BMPs alone have little influence on death. When combined with RA, however, they cause notable death (up to 40% of cells), therefore limiting the generation of fully developed neurons and glial cells and rather fostering smooth muscle cell differentiation [146]. By means of DNA fragmentation and cell shrinkage, BMP2 and BMP4 induce death; caspase and endonuclease inhibitors prevent this process. These BMPs demonstrate an apoptotic impact varying with dosage and render brain cells dependent on survival elements such as FGF and NGF [147]. Particularly BMPR-IA and BMPR-IB, BMP receptors regulate the two-stage fate of neural progenitor cells. Key actor BMPR-IA promotes early precursor proliferation while BMPR-IB induces death or terminal differentiation, hence regulating the generation of dorsal neural precursors [148]. In the neuroectoderm, BMP co-expression stunts development and promotes death. Simultaneously, BMP signaling dynamically affects neural fate by first encouraging neuronal differentiation, then switching toward astrocyte differentiation, and so preventing future neural development [149]. Moreover, BMPs such as BMP-6 and BMP-7 are quite crucial for preventing death of neurons. This demonstrates how specifically BMPs regulate neuronal survival, development, and death [150].

*Neurotrophins*

Two main processes underlie neurotrophin control of death in differentiated pseudo-neuronal cells. First, mature neurotrophins like BDNF and neurotrophin-3 bind to Trk receptors. This sets off important signaling pathways like PI3K-Akt and MAPK/ERK. These pathways either raise or lower levels of the anti-apoptotic protein Bcl-2 [151-154], which either helps cells stay alive or stops them from dying. Second, pro-neurotrophins cause death even in cases of Trk receptor activation by binding to the p75NTR receptor. Pro-neurotrophins induce cell death, while mature neurotrophins sustain survival utilizing a mechanism including proteolytic cleavage [155]. For example, pro-neurotrophins produced from astrocytes can induce death in p75NTR-positive neurons under situations such as convulsions [156]. By inhibiting Trk receptors, endogenous NT-3, which is produced by p75NTR, can also cause death in axotomized corticospinal neurons [157]. Therefore, depending on the particular receptor and cellular environment, neurotrophins have opposite effects in either enhancing survival or causing death [158]. The work with differentiated SH-SY5Y cells showed that neurotrophins improve the health of neurons and their ability to respond to mechanical stimuli. This has immediate relevance for diseases like Alzheimer's [159].

*Cytokines*

Cytokines influence death in differentiated pseudo-neuronal cells via several survival and death-regulating processes. By activating the NF-κB and JNK signaling pathways, pro-inflammatory cytokines such as TNF-α and IL-1β boost the expression of pro-apoptotic proteins such as Bax and lower levels of anti-apoptotic proteins such as Bcl-2, therefore enhancing cell death [160]. By JNK1 and JNK2 activation, TNF-α causes death in differentiated PC12 cells (dPC12), hence downregulating anti-apoptotic signals [161]. On the other hand, anti-

inflammatory cytokines like TGF-β and IL-10 boost survival through the PI3K-Akt pathway, hence suppressing lethal signals [162]. Moreover, essential for triggering NF-κB, which ensures neuron survival in the presence of cytokines, are cytokines such as CNTF, LIF, CT-1, and IL-6. This highlights in immunology and neurology how important their goals are. It is not merely a need; we have to understand it as a basic one [163].

*Small molecules*

Small molecules, with their potential to influence apoptosis in differentiated pseudo-neuronal cells through several key signaling pathways, offer a reassuring prospect. They modulate NF-κB signaling, which promotes anti-apoptotic factor expression in neurons, enhancing survival. However, prolonged NF-κB activation can lead to neurodegeneration and apoptosis, while in glial cells, NF-κB contributes to neuroinflammation, exacerbating neuronal death [164]. In the context of diabetic retinopathy, small molecules targeting the VEGF/BDNF/NF-κB pathway have shown promise; anti-VEGF treatment or VEGF siRNA increases BDNF levels in Müller glial cells exposed to high glucose, which reduces pro-inflammatory cytokines (IL-1β, TNF-α) by inhibiting NF-κB [165]. Activation of TrkA/NTRK1 in neuroblastoma cells impairs the G2/M checkpoint in response to ionizing radiation, increasing apoptosis susceptibility through suppression of the ATM-Chk2 and ATR-Chk1 pathways. Small-molecule inhibitors, with their potential to prevent neuronal loss by targeting apoptotic pathways such as caspases, JNK, p38 MAPK, cell cycle proteins, and GSK3, emerge as promising therapeutic agents against neurodegenerative disorders [166]. In addition, they can generate small-molecule neural precursor cells (NPCs), a significant progress that, absent expensive growth inputs, can develop into neuronal lineages relevant to neurodegenerative diseases [167]. By means of research on their mechanisms and viable treatments, this practical application advances our knowledge and approach to diseases. Retinoic acid, for example, increases pro-apoptotic protein expression [168], which causes death in neural stem cells; valproic acid, on the other hand, enhances anti-apoptotic protein expression [169], therefore promoting survival. Through GSK3β suppression [170], lithium reduces death; curcumin increases survival by altering death pathways [171]; P7C3 boosts neural stem cell survival [172], Isx-9 accelerates neuronal differentiation [173], and KHS101 improves cell survival [174].

## Conclusion

Recently, researchers have thoroughly investigated the effect of several inducers on the death of pseudo-neuronal cells produced from neural stem cells. These studies reveal a complex interplay in which inducers can exhibit both pro- and anti-apoptotic effects, contingent on the specific biochemical pathways they influence. For instance, studies have demonstrated that drugs such as selegiline, retinoic acid, and resveratrol can lower death rates by altering the expression of vital proteins like Bcl-2 and Bax [175-177]. The scientific community's cooperation has led to the discovery that selegiline protects human neural stem cells from oxidative stress-induced death by stimulating the Wnt/β-catenin signaling pathway [178]. On the other hand, inducers such as BMP-2 and IL-6 cause death through Bax and caspase-3 [179], highlighting the need for continued collaboration in understanding these processes. Collective research also yields growth factors such as EGF, bFGF, and BDNF, which can control death in brain stem cells. BDNF helps neural stem cells live longer and grow by activating the PI3K/Akt and MAPK/ERK signaling pathways. EGF and bFGF, on the other hand, stop cell death by turning on the PI3K/Akt pathway and controlling Bcl-2 family proteins [180, 181]. Resveratrol is a natural substance that lowers the death rate of neural stem cells by controlling the expression of Bcl-2 and Bax. This helps the cells differentiate through AKT and p38 signaling. Moreover, the intricate relationship between mortality and neurodegenerative illnesses is widely known, which emphasizes the significance of our common knowledge to guide therapeutic innovations [182, 183]. The ability of neurotrophic factors to regulate mortality emphasizes even more their possible therapeutic target status in neurodegenerative diseases [184, 185]. These findings highlight the complicated balance of death control in brain stem cells and the possible evolution of targeted therapies for neurodegenerative diseases. Modulating death in pseudo-neuronal cells, a potential path for therapeutic innovation could help stop or slow down the development of

such disorders. Advancement of this discipline depends on an awareness of the several ways in which various inducers influence death [186]. More research is critically required to completely understand these pathways and identify fresh intervention targets, as death is a main regulator of brain stem cell survival and development. Fresh techniques to tackle neurodegenerative illnesses revealed by this continuous study should improve patient outcomes.

## Disclosure of conflict of interest

None.

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