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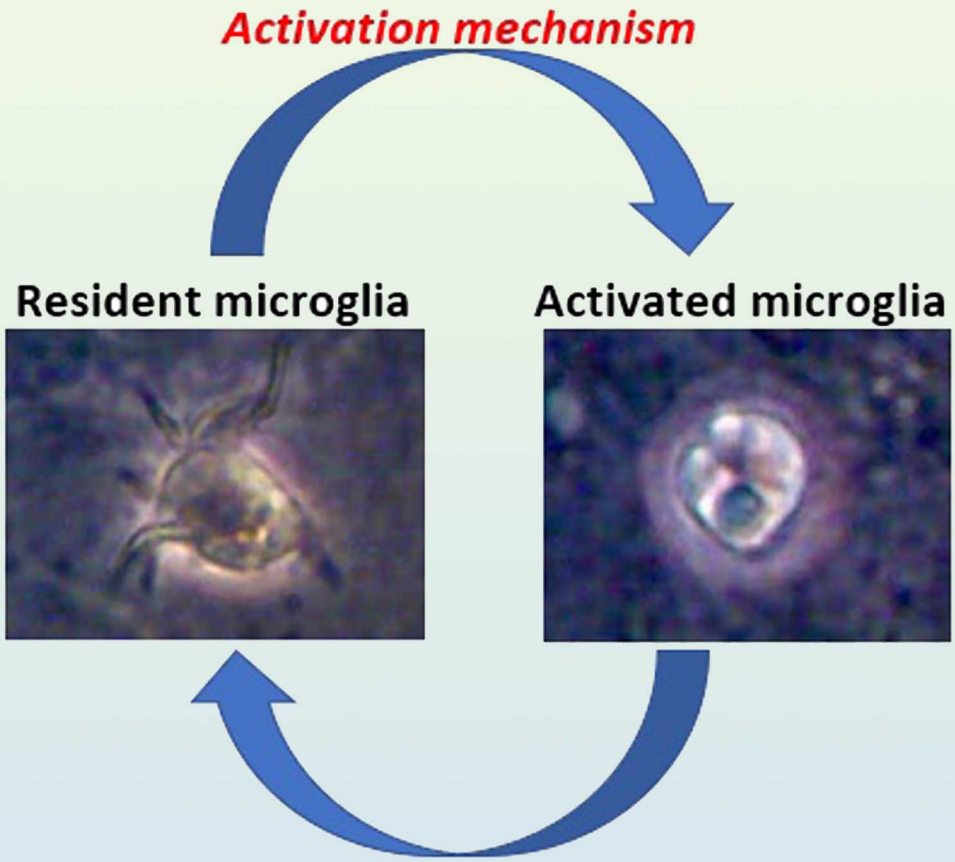

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

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C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

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REVIEW ARTICLE

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Experimental cell culture models for investigating neurodegenerative diseases

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Abstract

Neurological disorders (NDs) are an important cause of mortality and constitute 11.84% of total deaths globally according to WHO data 2015. It is estimated to increase up to 12.22% in year 2030. Most common NDs can be account for four main groups such as Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and Parkinson's disease (PD). Among these diseases, only AD is the seventh common death cause worldwide and until recently the therapeutic approaches are still lack to decrease of prevalence. Hence, developing new strategies to understand molecular targets or break down to cascade of cellular degenerative process in the neurodegeneration should be investigated by future studies. In cell culture studies, many types of tissues and cells can be cultivated to be a minimized model to normal or pathophysiological status of disorders. There are lots of methodology or technique to compose efficient and respective neurodegenerative disease models in cell lines such as COS-7, HC2S2, HEK-293, HeLa, Neuro-2a, NSC-34, PC-12, and SH-SY5Y. We indicated best medium formula to growth of neuronal cells as well as differentiation chemicals and time/dosages. In the review, it was aimed to summarize not only give information about cell lines, methodological procedures and molecular mechanisms of the diseases but also represent future perspective and offers to this field of neuroscience research.

Keywords: Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Cellular models

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List of Abbreviations;

6-OHDA, 6-hydroxy dopamine; **AD**, Alzheimer's disease; **ALS**, Amyotrophic lateral sclerosis; **APP**, Amyloid precursor protein; **CDK-5**, Cyclin-dependent-like kinase type 5; **GSK-3β**, Glycogen synthase kinase-3β; **HD**, Huntington's disease; **MPP+**, 1-methyl-4-phenylpyridinium; **MPTP**, 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine; **NGF**, Neuronal growth factor; **mHtt**, Mutant huntingtin protein; **PD**, Parkinson's disease; **poly-(CAG)n**, poly-glutamine repeats; **PMA**, Phorbol myristate acetate; **PP2A**, Protein phosphatase 2 subtype A; **SOD1**, Copper/zinc-binding superoxide dismutase; **TDP-43**, Transactive response DNA-binding ribonucleoprotein 43

Introduction

Neurological disorders (NDs) are generally characterized progressive neuronal damage and resulted with destruction of neuron structure or loss of function and finally apoptosis. Systemic indicators of NDs are going with low quality of life, personal care necessary, as age-related loss of mental and motor functions, life-threatening and death. NDs debouch with different

reasons including alcoholism, genetically factors, stroke, chemicals and toxins however sometimes couldn't root on a clear reason. The main separating difference them to other nervous system diseases is a phenomenon that neurodegeneration. Actually, it is basically as a consequence of degradation of protein architecture or a genetic defect in a chromosome. NDs can be divided into four main groups such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and Parkinson's disease (PD). However, prion diseases, spinal muscular atrophy (SMA) and spinocerebellar ataxia (SCA) can also be classified under NDs. According to the WHO 2016 data, AD is the fifth rank of ten common death causes. Because of many ND types have no cure, understanding to cellular and molecular basis of neurodegeneration is very important to develop new therapeutic strategies (https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death).

Cellular models are given basic, sustainable, economic and as much as possible optimized outputs of the systemic disorders under *in vitro* conditions. Moreover, *in vitro* model approaches are using for many pathologies including cardiovascular and respiratory disorders, various cancers, ischemia models, viral and bacterial diseases as well as neurological diseases and also provide indispensable solutions for molecular levels of cellular anomalies and reversals. Day by day researchers come up with new *in vitro* model approaches or therapeutic aspects for cellular mimics of NDs. They are not only contributed to animal and human phase studies for later but also put out novel data in itself. Hence, in this review, cell line models of four famous ND types are criticized and general features of *in vitro* models are tried to summarize.

In vitro approaches to cellular and molecular basis of NDs

Neurodegeneration used as an umbrella term, caused by the situations which are directly or indirectly affecting to neuronal functions, including age, chemicals, unprecedented protein expressions and genetic defects in the nervous system. Therefore, every pathophysiological condition in the nervous system such as multiple sclerosis, hypoxia and metabolic defects are not referred to as neurodegeneration. NDs come out from several parts of the brain and so they are grouped under cerebral cortex, basal ganglia and spinal cord originated causes. Although more than a hundred different NDs are diagnosed, researchers focus on treatments of four types that approved as more abundant. For example, the diseases affect cerebral cortex classified into dementing (AD) and non-dementing status. Basal ganglia related diseases affecting to substantia nigra, thalamic and brain stem nuclei characterized by movement anomalies and grouped as hypokinetic (PD) and hyperkinetic (HD) conditions. The diseases highly affecting to spinal cord is another separate subgroup including ALS and spinal muscular atrophy (Przedborski et al. 2003). Growing evidences proved that apoptosis, calcium signaling, oxidative stress and mitochondrial dysfunction are related with neurodegeneration. Even so, almost ten percent of NDs are assessed as relevant to hereditary factors. There are some protein factors under the mechanism of neurodegeneration (Soto 2003; Williams and Paulson 2008; Hettiarachchi et al. 2009). Extracellular amyloid-β deposition as inclusions and excessive phosphorylation of cytosolic tau protein underlie the molecular basis of AD therefore induce the neurodegeneration and cell death (Hasegawa 2016; Coskuner-Weber and Uversky 2018). Biochemical hallmarks of ALS are also modified and aggregated proteins that accumulate in cytosol of lower and upper motor neurons. The transactive response DNA-binding ribonucleoprotein 43 (TDP-43) and the copper/zinc-binding superoxide dismutase (SOD1) deposits are considered to be signs of ALS (Chong and Forman-Kay 2016; Hanspal et al. 2017). The HD is an autosomal dominant characterized neurodegenerative disease and trinucleotide codon repeats (CAG)n of exon 1 in HTT gene cause to synthesis of poly-glutamine chains in huntingtin protein mutant (mHtt) structure. Cytosolic aggregation of mHtt is the reason why impairment of protein degradation and folding metabolisms in cytosol, it induces mitochondrial dysfunction and disrupts synaptic signaling (Labbadia and Morimoto 2013). Presence of α-synuclein (Lewy bodies) triggers loss of dopaminergic neurons in substantia nigra, cause of PD (Smith et al. 2005; Dadakhujaev et al. 2010).

In cellular models, neurodegeneration can induce by chemicals (i.e. okadaic acid), neurotoxins (i.e. rotenone) or directly mutant protein metabolites (i.e. amyloid-β) of the diseases.

Cell line	Growth medium	Differentiation agent, dose and time	Target pathway of differentiation method	Observations
SH-SY5Y	DMEM:HAMS' F12 (1:1) including 10% FCS and 1% penicillin-streptomycin antibiotics solution (Oz and Celik 2016).	RA, 5 µM and 7 days incubation with normal growth medium (Um et al. 2007)	PKC activation	Enhanced neuronal morphology, neurite outgrowth and enzymatic activity. Mutant protein expressions or neurotransmitter secretion. Increased susceptibility to neurotoxins. Expressing various neuronal markers such as tau, NeuN, neurofilament 200 kDa, glutamic acid decarboxylase, and NMDA receptors and firing action potential, and responding to NMDA receptor agonists and antagonists (Evangelopoulos et al. 2005; Dong et al. 2011; Khwanraj et al. 2016).
		RA, 10 µM and 6 days incubation with 1% FCS containing growth medium (Jamsa et al. 2004; Lopes et al. 2017)		
		RA, 10 µM and 4-6 days incubation with normal growth medium (Sharma et al. 1999)		
		RA, 10 µM and 3-10 days incubation with normal growth medium (Dodurga et al. 2013)		
		Staurosporine, 1 µM and 15 days (Yuste et al. 2002); 30 nM and 3 days (Tieu et al. 1999); 25 nM and 3 days with normal growth medium (Jalava et al. 1992; Mollereau et al. 2007)	Non-selective PKC inhibition by prevention of ATP binding to the kinase	
		PMA (synonym TPA), 25 nM and 3 days (Kukkonen et al. 1997); 20 nM and 3 days (Tettamanti et al. 1996); 16 nM and 3 days (Koistinen et al. 2016); 15 nM and 7 days (Filograna et al. 2015) with normal growth medium	PKC inhibition	
PC-12	RPMI-1640 medium 10% FCS, 5% heat inactivated horse serum and 1% penicillin-streptomycin antibiotics solution (Yurekli et al. 2013).	NGF, 50 ng/ml for 2 days (Yurekli et al. 2013), for 4 days (Gallagher et al. 2000) or 6 days (Dupont et al. 2000)	PKC activation	
Neuro-2a	DMEM basal medium containing 10% FCS and 1% penicillin-streptomycin antibiotics solution (Lee ES et al. 2015).	Serum starvation, FCS free medium and 2 days (Tettamanti et al. 1996); RA, 20 µM and 2 days incubation with 2% FCS containing growth medium (Tettamanti et al. 1996); 1 mM dbcAMP incubation with normal growth medium for 3 days (Tremblay et al. 2010) or 5 mM for 3 days (Wang GH et al. 1999)	Serum withdrawal induced differentiation stimulates ERK1/2, Akt signaling and related pathways; dbcAMP enhances PKA and tyrosine hydroxylase enzyme activities	
NSC-34	DMEM medium including 10% FCS without antibiotics (Cookson et al. 1998).	Serum starvation, 1% FCS in DMEM:HAMS' F12 medium including 1% non-essential amino acids and 2-4 weeks incubation (Kanjilal et al. 2014) or 1-2 days incubation then in normal growth medium for weeks (Eggett et al. 2000; Madji Hounoum et al. 2016).	Serum starvation causes slowly proliferation, decreasing metabolic activity but induce differentiation	
HC2S2	DMEM:HAMS' F12 (1:1) containing 1% N2 supplement (Park EM et al. 2005).	Tetracycline; (1 µg/ml) addition to growth medium and 5 days incubation (Asahi et al. 1998; Ohtsuka et al. 1998). Doxycycline; (0.1 µg/ml) addition to growth medium and 5-10 days incubation (Berger et al. 1998).	HC2S2 cells under control of *tet* transactivator. Tetracycline and derivates suppress v-*myc* expression that stops proliferation and induces differentiation (Hoshimaru et al. 1996).	

Table 1. Effects of various differentiation agents to neuronal cell lines. Most of differentiators target to PKC pathway. PKC activation or inhibition may cause to increasing neuronal characterization and decreasing cellular proliferation and metabolic activity. (Reductions: dbcAMP: dibutyryl cAMP sodium salt, EGFR: epidermal growth factor receptor, ERK1/2: Extracellular signal-regulated protein kinases 1 and 2, FCS: fetal calf serum, NGF: neuronal growth factor, NMDA: N-methyl-D-aspartate, PKC: protein kinase C, PMA: Phorbol 12-myristate 13-acetate, (also known as TPA), RA: retinoic acid)

However, each neurodegenerative disease is affected to different metabolic pathways of the neuronal cells, and various functional regions of the brain tissues. Generally, degeneration of neurons is resulted to apoptosis, and in pathological regions of the brain, loss of its function. Degeneration can be spread in the similar functional group of the cells and tissues; thus, functional loss also invades by the time. Local or general shrinkage of the brain is also observed due to decrease of cell viability and increase of neuronal apoptosis.

There are a lot of restrictions understanding of molecular machinery in many disorders. Lack of *in vitro* models, studying difficulty of disease affected cells and tissues, official ethical commitments about reaching the patient's samples and physiological features of neuronal and cardiac systems are make the cellular models of diseases much necessary (Bahmad et al. 2017). Because of less staff, time and economical necessities and getting highly optimized results with cell culture studies, researchers are used *in vitro* mimicking of pathophysiological conditions in cellular models. Although, it's very difficult to make inferences about systemic pathologies and whole-body effects of diseases, the advantages of cell culture studies become a basement level going across to *in vivo* and phase studies and very suitable to understanding cellular machinery of the disease progression.

Cell line preference to neurodegeneration studies

Investigators have to choose proper cellular model systems and induction methods to establish a functional and reflective experimental model for diseases. There is limited number of cell line utilized as disease model to investigate neurodegeneration due to lack of neuronal originated cell line counts. However, sometimes, researchers focus on just toxic or mutant protein production pattern of neurodegeneration and they have been used non-neuronal originated cell lines such as African green monkey kidney COS-7 (ATCC, CRL-1651) and HEK-293 (ATCC, CRL-1573) and HeLa (ATCC, CCL-2). It will be taken the neuronal cell lines to the center of this paper and summarize five most common for the neurodegeneration studies such as HC2S2, Neuro-2a, NSC-34, PC-12 and SH-SY5Y cell lines.

The HC2S2 (RRID: CVCL_6A80) is neural progenitor cells firstly isolated by rats then used for HD model. Complete growth medium formula for HC2S2 cell line is that DMEM and HAM'S F12 basal medium mixture (1:1 volume ratio) containing 1% N2 supplement (100x) at a final concentration and additional antibiotics solutions needed (Park EM et al. 2005).

The Neuro-2a (N2a; ATCC, CCL-131) is a mouse brain neuroblastoma cell line widely used for neurodegeneration and toxicology studies. Complete growth medium formula for N2a cells is that DMEM basal medium including 10% FCS and 1% penicillin-streptomycin antibiotics solution at a final concentration (Lee ES et al. 2015).

The **n**euroblastoma x **s**pinal **c**ord clone-34 (NSC-34; Cedarlane, CLU140) is a spinal cord motor neuron and mouse neuroblastoma hybrid has motor neuron characteristics (acetyl choline synthesis, storage and release etc.) and highly proliferative features (Cashman et al. 1992; Eggett et al. 2000; Tovar et al. 2009). Complete growth medium formula for NSC-34 cells is that DMEM basal medium nutrient including 10% FCS at a final concentration without antibiotics solution (Cookson et al. 1998).

The PC-12 (ATCC, CRL-1721) rat adrenal pheochromocytoma is another cell line by using neurodegeneration model studies because of its inducible character for neuronal morphology. The cell line can be differentiated by neuronal growth factor (NGF) and it shows neurite outgrowth and gains neuronal morphology. Growth medium formula for PC-12 cells is that RPMI-1640 basal medium nutrient with L-glutamine including 10% FCS, 5% heat inactivated horse serum and 1% penicillin-streptomycin antibiotics solution at a final concentration (Yurekli et al. 2013).

The SH-SY5Y (ATCC, CRL-2266) neuroblastoma cell line is well-known and widely being used as cellular model for NDs. Because of its dopaminergic neuronal activity and enzymatic profile, the SH-SY5Y cells suitable for pharmacological studies. The cells can be differentiated by retinoic acid and other factors to show highly neuronal chemistry and morphology. Growth medium formula for SH-SY5Y cells is that DMEM and HAM'S F12 basal medium mixture (1:1 volume ratio) including 10% fetal bovine serum (FCS) and 1% penicillin-streptomycin antibiotics solution at a final concentration (Oz and Celik 2016).

Localization in the nervous system	ND type	Molecular basis of NDs	Mimic or target of cellular model
Hippocampus and cerebral cortex	AD	1- Amyloidogenic degradation of amyloid precursor protein (APP) by β-secretase and then γ-secretases forms amyloid beta 40 and 42 fragments. Assembly of extracellular presenilin-1 or presenilin-2 by fragments. 2- Tau proteins abnormally hyperphosphorylated by glycogen synthase kinase-3β (GSK-3β) and the cyclin-dependent-like kinase type 5 (CDK-5) enzymes. The main regulator of tau phosphorylation is the protein phosphatase 2 subtype A (PP2A), regulates the phosphorylation of tau both directly as well as by regulating the activities of phosphorylation enzymes, indirectly. Dysregulation of PPA2 caused intracellular deposition of hyperphosphorylated tau protein tangles.	Okadaic acid is a well-known inhibitor of PP2A enzyme activity. The enzyme inhibition causes neurodegeneration of cells by hyperphosphorylated tau proteins in PC-12 and SH-SY5Y cells.
Spinal cord	ALS	Cytosolic accumulation of post-transcriptionally modified TDP-43 ribonucleoprotein and misfolded SOD1 aggregations in motor neurons. Loss of upper and lower motor neurons in spinal cord.	In order to mimic endogenous accumulation of the mutant protein aggregates researchers using transfection methods to achieve cellular ALS model in Neuro-2a and NSC-34 cells.
Basal ganglia (substantia nigra, subthalamic nucleus, caudate nucleus, putamen and globus pallidus etc.)	If disease progression with involuntary movements (hyperkinetic or chorea) refers to HD; Unintentional movements (hypokinetic) refers to PD	Mutant huntingtin protein by expression of poly-(CAG)n repeats of HTT gene (HD); Loss of dopamine secretion and α-synuclein aggregates forms to Lewy bodies (PD).	Mutant huntingtin (mHtt) protein residues induce by plasmid transfection in HC2S2, Neuro-2a, PC-12 and SH-SY5Y cell lines. Furthermore, mHtt expression also perform by non-neuronal COS-7, HEK-293 and HeLa cell lines for HD researches. Investigation of PD is usually induced by different concentration and time dependent incubation of MPP+, 6-OHDA or Rotenone in mainly PC-12 and SH-SY5Y cell lines.

Table 2. Cellular and molecular pathophysiological mechanisms of NDs, cellular model systems and target pathways. Many of the researches about AD focus on okadaic acid usage and induction of tau hyperphosphorylation. TDP-43 and SOD1 mutations are target mechanism for cellular pathogenesis and transfection methods are preferred to mimic ALS. The poly-(CAG)n repeats are other genetic target for HD research. The mHtt protein expression studies are very common in the literature. In the PD researches, it can be found various chemical agents and processes to induction.

The cells express amyloid-β and α-synuclein and so it is very convenient cellular organization to evaluate AD and PD etiology (Kunzler et al. 2017).

Neurodegeneration inducers

It is necessary to criticize cellular metabolic processes in order to understand how neurodegeneration inducers work. There is different kind of factors reduce to neuronal activity and cell viability but increase apoptosis. Chemicals or toxicants, genetically modifications and exogenic mutant proteins are directly used in the experimental procedures.

It doesn't necessary but enhancing of neuronal characteristics and chemistry in neuronal cell lines by differentiation inducers have advantageous in NDs research. The PC-12 cell line expresses dopamine, epinephrine and other neuronal characteristic proteins, then it generally uses in neurodegenerative studies. In order to make differentiation of the PC-12 cells, neurotrophins frequently used in, and among them neuronal growth factor (NGF; N0513, Sigma) is very suitable since PC-12 cells naturally express NGF receptor. NGF induces signaling cascades including protein kinase-C (PKC) activation and causes to inhibition of cell proliferation but increases neurite outgrowth (Das et al. 2004).

Differentiated and un-differentiated SH-SY5Y cells are frequently used in neurological studies, especially differentiated SH-SY5Y cells are used in PD studies because they have excellent features differ from other cell lines such as showing human origin, tyrosine hydroxylase and dopamine-β-hydroxylase activities. SH-SY5Y cells respect their neuronal and dopaminergic characteristics especially in PD (Xie HR et al. 2010; Lazaro et al. 2017). Dose and time dependent retinoic acid incubation have been highly used to differentiation. Moreover, PKC activator phorbol myristate acetate (PMA; P8139 Sigma) and inhibitor staurosproine can also be used for differentiation methodology (Jalava et al. 1993; Tettamanti et al. 1996; Korecka et al. 2013; Filograna et al. 2015).

Although it is very well-known that differentiation enhances the neuronal character, genetically changings and morphology, many other studies also found in literature that used undifferentiated neuronal cell lines for neurodegeneration researches. Hence, differentiation preference seems to depend on the aim of experimental studies.

AD models

Although AD is most prevalent ND type and seventh most common death cause of the world, pathophysiology has not been clearly understood yet. There are two main hallmarks such as extracellular aggregations of amyloid-β fragments and intracellular deposition of neurofibrillary tangles which composed of mainly hyperphosphorylated tau proteins. Neuritic plaques occur sequential cleavage of APP by β- and γ-secretases to form 40 or 42 amino acid residues of amyloid-β. Abnormal hyperphosphorylation of microtubule associated tau protein and amyloid plaques formed by amyloid-β deposition are related to neurodegeneration, and AD inducers hit mainly target to them (Zhang S et al. 2013; Naziroglu et al. 2017).

The okadaic acid is a dinoflagellate toxin and well-known chemical inducer of AD model by inhibition of protein phosphatase type 1 and 2A (Gehringer 2004). Several studies have shown that neuronal cells to be used for AD model by different concentrations and time dependent okadaic acid incubation. Target metabolic pathway of okadaic acid stimulation is that protein phosphatase 1 and 2A inhibition in the neuronal cells, thus it increases intracellular tau phosphorylation and breaks glycogen metabolism (Aquilano et al. 2010; Li W et al. 2015).

The amyloid-β is a toxic mutant metabolite of amyloid precursor protein cut by β- and γ-secretase enzymes. It can directly use by induction of amyloid toxicity to mimic AD type cell death and other cellular pathologies. Extracellular amyloid-β incubation initiates caspase enzyme activity, mitochondrial dysfunction and induces apoptosis in neuronal cells. Hence, as a toxic metabolite of AD, different length of amyloid-β fragments (i.e. 25-35, 1-40 and 1-42) used to induce experimental AD models in PC-12 and SH-SY5Y cell lines.

ALS models

Neurodegeneration in ALS is triggered by different endogenous and exogenous factors including production of ROS, excitotoxicity by glutamate, mitochondrial dysfunction and most of ALS cases are described with deposition of insoluble proteins by genetically mutations in cytoplasm of lower or upper

motor neurons (Liscic and Breljak 2011; Wada et al. 2012). Incidence of ALS cases have been estimated 1-2.6 person for each 100,000 peopled population (Talbott et al. 2016).

Hence, researchers handle various methods for induction of NDs including genetically modifications. In some studies, genetic manipulation of diseases is more suitable and best way to induct an experimental model because mutant protein expression of cell lines is natively limited. Plasmid transfections are necessary to get cellular ALS model and so SOD1 and TDP-43 expressing cell lines to make useful in studies. The Neuro-2a neuroblastoma and NSC-34 motor neuron cell lines mostly using to induce ALS model by SOD1 and TDP-43 mutant protein transfections.

HD models

The HD has monogenic autosomal dominant inherited character and in epidemiological studies, it was found that HD affected to 1 person in each 7300 peopled western populations (Bates et al. 2015). Another example of mutant protein transfection is experimental HD model studies. Repeats of (CAG)n poly-nucleotide in exon 1 of HTT gene (lay in chromosome 4) directly uses to induce mHtt protein expression in neuronal cell lines. Researchers use most common cell lines rat PC-12 pheochromocytoma and SH-SY5Y human neuroblastoma as well as rarely found HC2S2 cells to have experimental HD model. However, in some studies, researchers can directly focus on mutant protein expression and they can only use non-neuronal cell lines (COS-7, HEK-293 and HeLa) to investigate expression of mHtt protein.

PD models

PD is the second most prevalent ND type after AD, characterized by decrement of dopamine levels and loss of dopaminergic neurons in basal ganglia, especially in substantia nigra pars compacta neurons. The PD is affected by 1% of population above 60 years old (Tysnes and Storstein 2017). Most of PD patients acquire the disease non-hereditary (idiopathic or sporadic) multifactorial causes such as Lewy bodies' formation, harmful effects of oxidative stress, and mitochondrial dysfunction, although small patients (approx. 5%) suffer from PD are classified under familial type. Some gene mutations are responsible from familial PD and neurodegeneration processes which encoding α-synuclein (SNCA), parkin (PARK2), Parkinson disease protein 7 (DJ-1), PTEN induced putative kinase 1 (PINK1), dardarin (LRRK2) and ATP13A2 (PARK9) (Yang YX et al. 2009; Korecka et al. 2013).

Almost like all neurodegenerative diseases, oxidative stress and mitochondrial dysfunction are thought to major neuronal death cause to neurodegeneration in PD. It is also confirmed that mitochondrial complex 1 deficiency in some PD patients (Schapira 2008). Hence, the 1-methyl-4-phenylpyridinium (MPP+), 6-hydroxydopamine (6-OHDA) and rotenone are used to induce inhibitor effect on mitochondrial complex 1, thus a number of studies to be found about differentiated or undifferentiated model systems in PD research (Xie HR et al. 2010).

The MPP+ is a toxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which produced by enzymatic activity of mono amine oxidase type B (MAO-B) and selectively kills to dopaminergic neurons in substantia nigra. MPP+ breaks mitochondrial electron complex chain 1 and ATP synthesis, induces ROS production and neuronal apoptosis (Dauer and Przedborski 2003). Divalent cationic influx and intracellular magnesium deposition was observed MPP+ induced neurodegeneration and it seems to be a result of protection mechanisms of cellular metabolic functions (Shindo et al. 2015). Hence, MPP+ toxicity well-studied on PC-12 and SH-SY5Y dopaminergic cell lines and also called as experimental MPTP model of PD.

The 6-OHDA is a neurotoxic catecholamine analogue (dopamine and norepinephrine) which targeted to catecholaminergic neurons, it is used *in vivo* PD models, however it can't across the blood-brain barrier to achieve directly injected into brain by stereotactic technique (Bove et al. 2005). It passes cell membrane through transporters of dopamine and epinephrine, 6-OHDA incubation with cell culture medium is very suitable to induct *in vitro* PD models, because of its similar chemical structure to dopamine and epinephrine, and accumulates intracellular fluid (Simola et al. 2007). Enzymatically degradation of 6-OHDA by mono amine oxidase type A (MAO-A) or self-oxidation trigger neuronal apoptosis by the generation of ROS and Quinones (Jagmag et al. 2015). The low concentrations of 6-OHDA (10 µM) is non-toxic to cells and have

positive effects on cellular viability, although higher levels (50-100 μM) may cause intracellular calcium influx and ERK1/2 over phosphorylation that induce cell death (Park HJ et al. 2013). It was shown that optimal concentration level is very important for representative model studies to each neurotoxin.

Rotenone is a tropical plant toxin and another mitochondrial electron transport chain complex 1 inhibitor used to mimic PD. It can easily across the cellular membranes because of its lipophilic structure and also generates ROS production, alters mitochondrial membrane potential and induces apoptosis (Perier et al. 2003).

It is well known that SH-SY5Y and PC-12 cells can naturally express α-synuclein, but it is necessary to investigate the effectiveness of toxin models of PD, other neurodegenerative pathologies or drug targets on alteration of α-synuclein expression levels (Gomez-Santos et al. 2002). Hence, transient or stable transfection methods not only restricted for HD and ALS research, but researchers also use to mimic *in vitro* PD models by α-synuclein overexpression. In SH-SY5Y cells mutant (A53T) or human wild type α-synuclein gene encoding plasmids widely using for PD and synucleinopathy models. There are some records about PC-12 cells which are suitable model system for PD studies by transfection of mutant A30T or A53T α-synuclein genes (Zhou et al. 2009; Ito et al. 2010).

Conclusion

It is concluded that there were two different ways to form neurodegenerative disease models; one is differentiated and the other is undifferentiated cell line usage. Different kind of cell lines and differentiation methods were presented in Table 1. All of the neurodegenerative disorders and their models formed in the cell culture of these disorders mentioned above vary according to the cell type, the applied agents and the model to be created. It is also known that the reduction of FCS concentration is as a reason of differentiation. Hence, it is also important to use proper medium components in the cell culture. It is well known that SH-SY5Y and PC-12 cell lines widely used for neurodegenerative disease models, PKC pathway is main target to induce differentiation of these neuronal cell lines. Analogues of differentiation inducers which target the same molecular pathways and players can also be assessed as candidate for the development of new differentiation strategies.

While the AD is performed only with PC-12 and SH-SY5Y cell lines, that is, when the number of the models is restricted, there is a considerable variation in dose range. In AD models inducing by okadaic acid, the application differs greatly in terms of dose and duration. It is seen that researchers generally follow two main ways; 1) low dose and longtime course and 2) high dose and short time course incubation. In future studies, in order to develop highly representative and effective disease models, cross combinations of okadaic acid and Aβ inductions may try to AD models in both PC-12 and SH-SY5Y cell lines.

The NSC-34 hybrid cell line is only comfortable model system for experimental ALS studies. Genetic complexity of the disease also reverberated to cellular models because of so many genes play role on the generation of ALS. Taken together, in ALS experiments, investigators mainly aim to mimic SOD1 and TDP-43 genes overexpression by using transfection procedures.

It is summarized that in Table 3, the HD has a wider range of models in terms of cellular diversity although other models are not so diverse. HD studies mostly focus on mutant HTT gene expression and based on transfection methodology as shown in Table 3. In HD researches, mutant protein expression levels can also be evaluated by non-neuronal originated cell lines such as COS-7, HEK-293 and HeLa.

Researchers mostly preferred SH-SY5Y cell line to perform PD models. However, the neurotoxin diversity has a wide range for induction of PD models. Likewise, 6-OHDA, MPP+ and rotenone analogue chemicals such as piericidin A and amytal may be assessed as potential molecules for PD induction. The piericidin A is a member of acetogenins and a complex 1 inhibitor of electron transport chain, act as rotenone, therefore, it has to be investigated that whether this antibiotic shows similar toxic effects on neurological cell lines to mimic PD model. Alike to piericidin A and amytal for novel PD researches other PP1 and PP2A inhibitors such as calyculin A, fostriecin and cytostatin acting like okadaic acid, may be tested for new candidate agents in the AD models by questioning whether they have similar effects or not.

Model	Cell line	Methodology and concentrations	Time and practice	References
AD	SH-SY5Y	Okadaic acid (30 nM)	16 h	(Del Barrio et al. 2011)
		Okadaic acid (15 nmol/L)	24 h	(Wang YP et al. 2004)
		Okadaic acid (100 nM)	2 h	(Alvarez-de-la-Rosa et al. 2005)
		Okadaic acid (80 nM)	24 h	(Uberti et al. 1997)
		Okadaic acid (30 nM)	24 h	(Romero et al. 2014)
		Amyloid-β peptide 25–35 (1 μM) and/or Okadaic acid (3 nM)	20 h	(Buendia et al. 2015)
		Okadaic acid (20 nmol/L)	24 h	(Wang F et al. 2017)
		Okadaic acid (40 nM)	6 h	(Yuan Z et al. 2017)
		Okadaic acid (50 nM)	2 h	(Montilla-Lopez et al. 2002)
		Okadaic acid (50-200 nM)	5 h	(Leuba et al. 2008)
	PC-12	Amyloid-β peptide	24 h	(Araya et al. 2014)
		Amyloid-β peptide 1-40 (10-50 μg/mL)		(Kumaran et al. 2018)
		Amyloid-β peptide 1-42 (5 μM)		(Li H et al. 2017; Wang H et al. 2018)
		Amyloid-β peptide 25–35 (10 μM)		(Yan X et al. 2017)
		Amyloid-β peptide 25–35 (10 mmol/L)		(Li GZ et al. 2017)
		Amyloid-β peptide 25–35 (5 μM)		(Ostrovskaya et al. 2014)
ALS	NSC-34	TDP-43^{Q331K} mutant plasmid transfection	Stably transfection and selection by G418 incubation for 2 weeks	(Moujalled et al. 2017)
	Neuro-2a	SOD1 plasmid transfection and 0.2 μM SOD1 mutant protein (SOD1^{H46R}) inoculation	Different time course	(Cacabelos et al. 2016)
		Wild type human TDP-43 DNA encoded plasmid transfection	Transiently transfection with Lipofectamine-2000 reagent for 24h	(Munch et al. 2011)
HD	COS-7	Transfection of N-terminus of huntingtin with 21, 41, 51, and 72 uninterrupted (CAG)n repeats	24-72 h	(Narain et al. 1999)
	HEK-293	Transfection with mHtt containing 94Q plasmid	Transiently transfection for 24 h	(Liu Y et al. 2014)
	HeLa	Transfection with 28Q, 55Q and 74Q containing plasmids transfection	Transiently transfection through 24 h for all poly-Q regions and stable transfection for only 74Q	(Wang H et al. 2006)
	HC2S2	HTT exon 1; 28Q and 74Q containing plasmids transfection	Stably transfection and puromycin selection up to ten passages	(Dong et al. 2011)
	Neuro-2a	HTT N-terminal 16Q, 60Q and 150Q plasmids transfection	Stably transfected clones were selected by using Zeocin and G418	(Wong et al. 2008)
	PC-12	HTT exon 1; 23Q (for control), 74Q (for HD model), 103Q transfection	In 103Q stably transfection, PC-12 cells were selected by using G418	(Wyttenbach et al. 2001; Aiken et al. 2004; van Hagen et al. 2017; Fatoba et al. 2018)
	SH-SY5Y	N-terminal HTT 21Q (wild-type), 113Q (for HD pathology), 150Q (N terminal mutant) and 171Q (N terminal control) plasmids transfection	Transiently transfection by using Lipofectamine 3000	(Vidoni et al. 2016; Vidoni et al. 2017)
PD	SH-SY5Y	6-OHDA (15 μM)	24 h	(Hegarty et al. 2016)
		6-OHDA (20 μM)	24 h	(Rajendra Kopalli et al. 2012)
		6-OHDA (50 μM)	24 h	(Solesio et al. 2012; Sever et al. 2016)
		6-OHDA (100 μM)	24 h	(Mu et al. 2009; Jing et al. 2015; Jing et al. 2016; La Cognata et al. 2018)
		MPP+ (50 μM)	48 h	(Duka et al. 2009)
		MPP+ (100 μM)	96 h	(Zhang D et al. 2007)
		MPP+ (200 μM)	48 h	(Lu M et al. 2016)
		MPP+ (300 μM)	48 h	(Choi JS et al. 2010)
		MPP+ (500 μM)	24 h	(Ramalingam and Kim 2016; Gong et al. 2017; Lu JYD et al. 2017; Wang S et al. 2017; Yan W et al. 2018)

PD	SH-SY5Y	MPP+ (1 mM)	48 h	(Kim IS et al. 2011; Xie H et al. 2016; La Cognata et al. 2018)
		MPP+ (1.5 mM)	48 h	(Lamine et al. 2016)
		MPP+ (3 mM)	18 h	(Lee KW et al. 2013)
		MPP+ (5 mM)	24 h	(Verhaar et al. 2011; Verhaar et al. 2012)
		Rotenone (200 nM)	24 h	(Kang et al. 2017)
		Rotenone (500 nM)	24 h	(Condello et al. 2012; Yong-Kee et al. 2012)
		Rotenone (2.5 μM)	12 h	(Ryu et al. 2013)
		Rotenone (3 μM)	24 h	(Zhang X et al. 2014)
		Rotenone (5 μM)	24 h	(Kim S et al. 2011; Sun H et al. 2017)
		Rotenone (10 μM)	24 h	(Choi BS et al. 2014)
		Rotenone (20 μM)	24 h	(Jiang M et al. 2016)
		Rotenone (60 μM)	24 h	(Zhang JY et al. 2016)
		Rotenone (100 μM)	24 h	(Qin et al. 2015)
		Wild type human α-synuclein gene encoding plasmid transfection	Transiently transfection with human α-synuclein gene for 24 h, stably transfections started to selection by G418 after 48 h	(Tofaris et al. 2001; Alberio et al. 2010; Pyszko and Strosznajder 2014)
		Mutant human A53T α-synuclein gene encoding plasmid transfection	Stably transfections started to selection by G418 after 7 h and completed at 14 d	(Zhao et al. 2007)
	PC-12	6-OHDA (75 μM)	24 h	(Jiang BP et al. 2014; Liu H et al. 2015)
		6-OHDA (100 μM)	24 h	(Blum et al. 2000; Gorman et al. 2005; Meng et al. 2007; Feng et al. 2008; Han et al. 2014; Mei and Niu 2015; Yan JQ et al. 2015; Chang et al. 2016; Olatunji et al. 2016; Yang CP et al. 2016)
		6-OHDA (200 μM)	18 h	(Fan et al. 2014)
		6-OHDA (200 μM)	24 h	(Hou et al. 2015; Zou XD et al. 2016)
		6-OHDA (300 μM)	24 h	(Lin et al. 2015)
		MPP+ (100 μM)	10 h	(Yurekli et al. 2013)
		MPP+ (400 μM)	24 h	(Jodeiri Farshbaf et al. 2016)
		MPP+ (500 μM)	24 h	(Li X et al. 2013; Ye et al. 2013; Cheng et al. 2014; Zou Y et al. 2015)
		MPP+ (500 μM)	48 h	(Chen et al. 2016; Sun HJ et al. 2016; Zheng et al. 2016)
		MPP+ (1 mM)	24 h	(Huang et al. 2010; Santos et al. 2015; Zhang GF et al. 2015)
		Rotenone (1 nM) through 3 d, 1 w and 3 w for long time incubation; 1 nM, 10 nM and 100 nM through 48 h for dose dependent manner		(Yuan YH et al. 2015)
		Rotenone (0.5 μM)	24 h	(Wu et al. 2013; Wu et al. 2015)
		Rotenone (0.5 μM)	48 h	(Van Laar et al. 2016)
		Rotenone (1 μM)	24 h	(Goldstein et al. 2015; Liu H et al. 2016)
		Rotenone (4 μM)	48 h	(Im et al. 2013)
		Wild type human α-synuclein gene encoding plasmid transfection	Stably transfected cells with human wild-type (WT) α-synuclein gene and pTK-hygromycin encoding a hygromycin resistant gene	(Ito et al. 2010)
		Wild type human α-synuclein, and two mutants (A30P and A53T) genes encoding plasmid transfection	Stably transfected cells selected by G418 and Geneticin containing media. Transiently transfection for 48 h	(Martin-Clemente et al. 2004; Qian et al. 2008; Zhou et al. 2009)

Table 3. Different kinds of neuronal cell lines, neurodegeneration inducers, methods of induction, and duration of processes.

Another aspect of neurodegenerative disease progression is that cells tend to transfer their accumulated mutant proteins to another cell such as amyloid peptides, SOD1 and TDP-43, poly-glutamine and α-synuclein and it explains the disease spreading by the time in the target region of nervous system (Westergard et al. 2016).

In conclusion, cellular model studies are still frequently used due to their ability to be easily modeled as they give similar results to *in vivo* and clinical findings related to neurodegeneration, spread and molecular mechanisms of diseases. This review includes informative explanations for neuroscience researches mostly interested in neurodegenerative disease models, cell lines, and molecular mechanism underlying disease and target pathways for model inducers.

Collectively, it is very important to acquire improvement in cell culture studies that development of new neurotoxins and/or novel cell lines which naturally express mutant genes for modeling of diseases especially for ALS and HD studies. From this perspective, discovering new strategies and techniques may pave the way for new investigations and inspire the neuroscientists to explore novel methods for the other neurological diseases.

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