

REVIEW ARTICLE

Received 2017-02-05

Revised 2017-05-05

Accepted 2017-05-11

Drugs Induced Alzheimer's Disease in Animal Model

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Abstract

Alzheimer's disease (AD) can be described by characteristics like dementia, mental and cognitive dysfunctions, and memory impairment. Nowadays, with progresses of science, attempts to treat many diseases have increased. Laboratory animals help to discover new ways of treating disease. AD induced by chemical drugs in animal models can be useful in better understanding the mechanisms of disease and treatment of AD. In recent decades, many researchers have reported transgenic rat models of AD but this modeling has a great problem and does not contain all kinds of AD. There are two types of AD, including familial (5% of all AD) and sporadic, but the transgenic model does not show the complete model of AD, especially in sporadic form of AD, which is 95% of AD cases. We decided to describe another modeling of AD using chemical drugs such as colchicine, scopolamine, okadaic acid, streptozotocin, and trimethyltin.

[GMJ.2017;6(3):185-96] DOI:10.22086/gmj.v6i3.820

Keywords: Alzheimer's Disease; Hippocampus; Memory; Trimethyltin; Colchicine

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that can be characterized by cognitive dysfunctions and loss of memory, impairments of attention, and a progressive decline in language function [1]. Many factors might cause AD, including genetic defects, appearance of neurofibrillary tangles, altered amyloid precursor processing, mitochondrial defects, deficiency of neurotrophic factors, trace element neurotoxicity, energy metabolism deficit, and oxidative stress [1]. Researchers have shown that microtubule dysfunction is associated with AD and cog-

nitive dysfunction [2]. The hippocampus is a key region in neurological diseases, especially dementia and AD. Studies have shown that damage to the hippocampus region causes to cognitive dysfunction that leads to AD [3]. Treatment with inhibitors of cholinesterase caused cognitive dysfunction in patients with dementia and the animal model of AD [4]. The efficacy of drugs was shown in behavioral tasks, such as the Morris Water Maze (MWM), Radial Arm Maze (RAM), the spatial cone field task, the five choice serial reaction time, and the object recognition task. Animal models are essential tools in the etiology of disease like neurodegenerative disease.

GMJ

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One of the AD models is chemical drugs, which help AD researchers. In this review study, we discussed some chemical drugs (such as colchicine, okadaic acid [OKA], streptozotocin [STZ], trimethyltin [TMT], and scopolamine) for induction of AD-like modeling.

1. Neurogenesis and Memory

1.1. Neurogenesis in the Hippocampus

The hippocampus is a brain region that is responsible for learning, memory, and mood. One of the important reasons for memory and mood dysfunction is the reduction of the dentate gyrus (DG). The subventricular zone (SVZ) and the subgranular zone (SGZ) of neural progenitor cells generate neurons and glia in adulthood and during adulthood [5]. Neurogenesis also has a role in mood regulation; the dorsal hippocampus is an important region in memory formation and retrieval, whereas the ventral hippocampus is an important region in emotions [6]. The spatial learning and memory retrieval in the MWM test is associated with neurogenesis levels in MWM test of rats and mice [7]. In addition, studies have shown that learning tasks could increase neurogenesis in rats [8]. Altman and colleagues [9] were the first people who reported new neurons in the adult hippocampus are continually produced, which originate from adult neural stem cells of the SGZ. There are two types of neural stem cells (NSCs) that are distinguished with proliferative behaviors, morphologies, and molecular marker expression. Type 1 neural progenitor cells (NPCs) express specific molecular markers such as GFAP, Sox2, and Nestin [10]. Also, some morphogens play an important role during embryonic development of the nervous system such as, Notch, Shh, Wnts, and BMPs [11].

1.2. Neurogenesis in the Aging Hippocampus

DG cell death occurs at 2 months of age in mice and then decreases [12]. Studies showed that the number of cell divisions decrease in mice between the ages of 1 and 9 months life [13]. Studies have demonstrated that Notch signaling regulates adult neurogenesis and stops producing new neurons during aging [14].

The healthy neurons released CX3CL1 or Fractalkine (FKN) (as a neuro immune-regulatory protein) that caused microglia to stay inactive; during aging, FKN expression in the hippocampus is decreased. Blocking FKN in young animals caused a decreased the neurogenesis of the hippocampus that mediated with IL-1 β . There are some molecules that are released by neurons and increase with aging state, including CD47, CD55, and CD200 [15]. Another factor that caused the reduction of neurogenesis was the epigenetic changes in niche cells or NPCs [16]. The DNA methylation could change the potential fate in ageing NPCs from a neurogenic to a gliogenic fate.

2. Chemical Drugs for Induction of AD-Like Modeling

2.1. Colchicine

Colchicine is an alkaloid that is extracted from some plants of the lily family that was initially used to treat gouty arthritis. Then, colchicine was recognized as a prophylaxis of Mediterranean fever attacks; decades later, it was used for preventing amyloidosis. The distribution of colchicine in the brain is unequal and in the hippocampus (the area most affected in AD) it is three times higher than in other brain regions [17]. The drug selectively blocks acetylcholine transferase in the basal forebrain and hippocampus, which are regions responsible for memory [18]. When colchicine penetrates to subarachnoid space symptoms start to show, including jumpy and irritable behavior, aggression, and loss of body weight. Colchicine, used as a neurotoxin, is a microtubule-interrupting agent that leads to destruction of hippocampal granule cells. Colchicine causes degeneration of neurofibers through binding to tubulin (the microtubule structural protein), which is associated with a decrease in acetylcholine transferase and loss of cholinergic neurons, that cause impairment of learning and memory. Following the intracerebroventricular (ICV) administration of colchicine (15 μ g), cognitive dysfunction was caused and memory decreased in both MWM and elevated plus maze (EPM) tasks. Therefore, colchicine caused induction of cognitive dysfunction and dementia of Alzheimer's type [19].

Studies have demonstrated that 2–3 weeks colchicine ICV administration altered neurochemical levels and behavior dependent on dose and duration [20]. Furthermore, studies have reported that colchicine administration induced lipid peroxidation, decreased glutathione (GSH) and acetylcholine (ACH) levels in the brains of rats, and led to subsequent oxidative damage resulting in cognitive impairment [19]. One study showed that administration of vitamin D3 following the colchicine treatment improved the impaired cognition, restored the reduction of the brain derived neurotrophic factor (BDNF) level of hippocampus and antioxidants, and decreased the raising of the hippocampal A β peptide tissue level. In addition, the authors showed colchicine declines learning and memory and induces central neuronal damage and oxidative stress [21]. Researchers have shown impairment of memory and neurodegeneration characterized as a sporadic in the AD model after colchicine administration in rodents [22]. Another study showed that colchicine administration in AD model changed the anxiety-like behavior in EPM behavioral test [23]. Moreover, treatment with naproxen following the colchicine administration prevented the neurodegeneration and improved the cognitive dysfunction [19].

2.2. Scopolamine

Scopolamine is a muscarinic cholinergic receptor antagonist that is used for cognitive dysfunction in experimental animals. Injection of scopolamine (intraperitoneal) caused cholinergic dysfunction and impaired cognition in rats [24]. Also, studies have shown memory impairment induced with scopolamine, in consequence brain oxidative stress was altered [25]. Therefore, scopolamine-induced modeling is used for screening anti-dementia drugs in animal models. Previously, scopolamine used to induce twilight state and amnesia during childbirth in obstetrics. Then researches reported that scopolamine caused decreased activity of choline acetyltransferase (the enzyme responsible for acetylcholine [ACH] synthesis) in the cortex of AD patients [26]. The scopolamine model is used in cognitive research in AD

patients [27]. Scopolamine induced cerebral blood flow (CBF) and glucose metabolism changes, which have been studied with PET [28] and single photon emission-computed tomography (SPECT) [29]. Scopolamine increased blood flow in the left orbitofrontal and the lateral occipital cortex regions bilaterally and decreased rCBF in the region of the right thalamus, the precuneus and the right and left lateral premotor areas [28].

2.3. OKA

Studies have shown that OKA selectively inhibits the serine/threonine phosphatases 1 and 2 in rat brain [30]; on the other hand, in the brain of Alzheimer patients appeared a reduced activity of phosphatases [31]. In addition, OKA caused lack of memory and elevation of Ca²⁺ that had relationship with neurotoxicity [32]. The interference in calcium signaling caused alteration of the protein phosphorylation and dephosphorylation systems' balance, which involved in abnormal tau phosphorylation [33]. Studies have shown that increased intracellular Ca²⁺ resulted in the accumulation of amyloid beta, the hyper phosphorylation of tau, and neuronal death [34]. These characteristics also appeared in AD. Administration of OKA (200 ng, ICV) caused tau phosphorylation, memory impairment, and increased mRNA and protein expression of tau, CaMKII, Calpain, and GSK3 β in the hippocampus. Moreover, the result of water maze test confirmed the memory impairment in OKA treated rats [35]. Studies have shown that neuronal death following OKA administration is associated with the induction of Bax in rat brain [36]. It is worth noting that the Bax family and caspase cascade are key mediators of the apoptotic signaling transduction. The caspase-3 cleaved the abnormal tau protein that results in neuron death [37]. Studies have shown that treatment of OKA for 12 hours increased the Bax and caspase-3 activity in HT22 cells (hippocampal neuronal cell line) [38]. Nada *et al.* (2016) demonstrated that 100–500 nM OKA concentration induced the AD pathophysiology and formation of senile plaques that were observed with immunofluorescence labelling in the zebrafish brain

[39]. Kamat *et al.* (2013) showed that administration of OKA caused significant increase ($P < 0.05$) in PP2A, tau, CaMKII, and Calpain mRNA expression in cerebral cortex and hippocampus in rats [35]. Increased phosphorylation resulted in reduction of the normal tau stabilization of microtubules thereby leading to neuronal dysfunction [40]. In an animal study, it was shown that OKA administration caused deficit of memory in rats [32].

2.4. STZ

STZ is isolated from a strain of soil bacteria. Initially, it was used as an antibiotic and later used as an anticancer agent and drug therapy for neuroendocrine tumors. Studies have shown that injection of STZ (3 mg/kg) results in cognitive decline, decreased brain weight, increased A β of the hippocampus, and increased tau levels of the hippocampus [41]. Chen *et al.* (2014) showed that injection of STZ caused memory deficit and altered neurochemicals (Alzheimer-like) in brains of mice [42]. Studies have demonstrated that damage by STZ is restricted to special areas such as axons and myelin of the fornix, anterior hippocampus, and periventricular structures, which plays an important role in learning and spatial memory [43]. Also, another study has shown that the range and dynamics of brain neurodegeneration depends on the amount of STZ injection in rats [44]. In addition, studies have shown that injection of STZ into lateral ventricles performed a role as a non-selective neurotoxicant near the injection site.

2.5. TMT

TMT chloride (C₃H₉ClSn) has neurotoxic effects when used in neuronal degeneration research. Studies have shown that TMT treatment caused loss of pyramidal neurons in the hippocampus of rats [45]. After TMT drug injection, animals showed some behavioral changes such as seizures, aggressive behavior, self-biting, impairment of working memory, and hyperactivity. Studies showed that TMT intoxication caused cognitive and behavioral dysfunction in experimental animals and humans [46]. Studies have shown that TMT is a drug used in research of Alzheimer-like diseases in experi-

mental model [47]. The first target of TMT is the hippocampus, where it has toxic effects on pyramidal neurons. Structural damage begins 2–3 days after TMT injection (that appeared within 21 days), and continues during several weeks [48], although the time of onset and prolonged duration is a consequence of the relationship with hemoglobin of rat and TMT. The hemoglobin is associated with slowly and continuously releasing TMT into the plasma, and subsequently into the brain [49]. The TMT caused a cytotoxic effect on glial cells; studies have shown that following TMT administration, increased glial fibrillary acidic protein levels [50] and Na⁺-K⁺-ATPase activity changes due to swelling of primary cultures of astrocytes [51]. The mechanisms of cell death caused by TMT are not yet clear. Studies have shown that TMT administration with high concentrations caused necrotic death and low concentrations (0.01–0.1 μ mol/l) caused apoptotic cell death [52]. The apoptotic cell death is associated with duration and concentration of TMT on a hippocampus neuronal cell line (HT-22 cell), which is mediated by caspase [53]. Studies have shown that TMT induced memory impairment and lesions in the hippocampus in mice and rats [54]. One study showed that TMT exposure was associated with sigma 1 receptor stimulation in hippocampus [55]. Another study showed that TMT exposure caused significantly impaired olfactory learning, spatial memory, and learning in adult rats [56, 57]; also TMT caused hyperactivity in the pre-weaning stage and impaired the acoustic startle response in pre-weaning and adult rats that arose from pyramidal neuron loss in hippocampus [58–61]. TMT affected neurons, so TMT is used in neuronal degeneration studies [62] and studies of delayed neuronal cell death [63]. Although the mechanism of TMT-induced neurodegeneration is still not understood, some studies have shown neuronal apoptosis due to calcium overload [64]. Studies have shown that the TMT injection (12 mg/kg) caused spatial learning impairment [65]. In addition, another study showed that TMT increased anxiety, hyperactivity, and stress, and decreased BDNF level of the hippocampus in animal models [66]. Also, other studies

confirmed the neurotoxicity of TMT [95- 97]. TMT induces neuronal degeneration in both human and rodent central nervous systems [67]. Studies have shown that TMT administration caused neuronal loss in the dentate gyrus, frontal cerebral cortex, olfactory bulb, and anterior olfactory nucleus [68]. TMT toxicity has many manifestations such as disorientation, confabulation, amnesia, aggressiveness, hyperphagia, hearing loss, complex partial and tonic-clonic seizures, nystagmus, ataxia, and mild sensory neuropathy in humans. In limbic systems of humans and animals TMT causes neuronal death [69, 70]. The neural induction of TMT had a species-specific difference between rat and mouse [71]. In mice, TMT damaged dentate gyrus granule cells acutely in the first 3 days [72], although in rats induction of TMT developed over more than 3 weeks and CA1 and CA3 pyramidal neurons were most affected [73]. Other differences between mice and rats were related to LD50 dose; in mice, LD50 dose was about 1.7 mg/kg [74] and rats about 12.6 mg/kg [75]. TMT causes limbic system damage including the hippocampus, amygdala, pyriform cortex, and brain stem in mice [76] and rats [77]. Studies have shown that TMT caused lim-

bic-cerebellar syndrome that exhibits some signs including memory defects, confusion, seizures, tinnitus, insomnia, and depression. Studies have reported exposure of dimethyltin (DMT) damages the digestive tract and liver and causes stomach distention [82]. Studies have shown that TMT reduced dopaminergic marker expression in the hippocampus and impaired spatial memory in rats [83]. In addition, TMT induction reduced acetylcholine and glutamate concentrations of hippocampal [84].

Discussion

Today, with advances in science, researchers are looking for a way to treat AD. AD modeling opens new doors to treatment of AD. One of the AD modeling methods is AD transgenic rat modeling but this modeling does not include the entire symptoms of AD. Therefore, drug modeling of AD can be helpful in the AD research and may find better understanding of the mechanisms and treatment of AD. Previously, we examined TMT neurotoxicity in some research. Our findings and other knowledge has shown that TMT has neurotoxicity effects on the brain (Table-1). Also, some compounds and activity have a

Table 1. The Effect of TMT Neurotoxicity on Brain and Hippocampus

Authors	Year	Types of animal	The dose of TMT	Results
Ali <i>et al.</i> [88]	1987	Mice	0, 1.0 and 3.0 mg/kg oral	Low dose of TMT showed decrease in the ornithine decarboxylase (ODC) activity of hippocampus but the higher TMT dose caused an increase of ODC in the cerebellum, brain stem, and hippocampus.
Gunasekar <i>et al.</i> [89]	2001	Cell culture	0.01–0.1 μ M	Low-level exposure of TMT damages cerebellar granule cells through an apoptotic pathway.
Chen <i>et al.</i> [90]	2011	Embryonic Zebrafish	0–10 μ M	TMT caused secondary motorneuron-dependent tail bending.
Gasparova <i>et al.</i> [91]	2012	Rat	7 mg/kg, ip	TMT induced neurodegeneration.
Kim <i>et al.</i> [92]	2013	Mice	2.6 mg/kg, intraperitoneal [i.p.]	GSK-3/b-catenin signaling pathway in TMT-induced hippocampal cell degeneration.

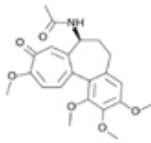
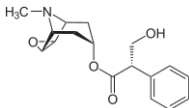
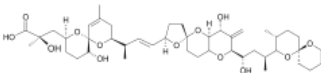
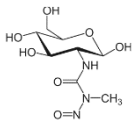
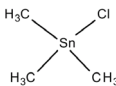
protective effect against TMT such as sodium valproate, lithium chloride, Gallic acid and endurance training, etc. (Table-2). Although no studies were found that compared this drug to others, we show some basic characteristic of these drugs in Table-3. There are two types of AD, including familial AD (FAD; early-onset) and sporadic AD (SAD; late-onset). FAD and SAD have common properties to each other, such as existence of A β plaques and neurofibrillary tangles (NFTs) of phosphorylated tau pro-

tein [85]. FAD is due to autosomal dominant mutations in the APP, PS1, and PS2 genes [86], but SAD is due to recessive mutations and a heritable component [87]. In addition, the transgenic model is suitable for better understanding of FAD (5% of all AD). Then we focused on drug induction of AD for understanding SAD (95% of all AD). There are some explanations of the mechanisms of TMT toxicity such as inhibition of ATP synthesis in mitochondria, increased intracellular Ca²⁺, decreased neurotransmitter

Table 2. The Neuroprotective Agents Against TMT

Authors	Year	Types of animal	The neuroprotective factor	Results
Jung <i>et al.</i> [93]	2013	Rat	Gugijihwang-Tang	Gugijihwang-Tang protected nervous system and improved the brain function.
Golestani <i>et al.</i> [65]	2014	Rat	Sodium Valproate	Valproic acid prevented TMT-induced memory deficits.
Yoneyama <i>et al.</i> [94]	2014	Mice	Lithium	Lithium had a beneficial effect on neuronal repair following neuronal loss in the dentate gyrus.
Moghadas <i>et al.</i> [66]	2015	Rat	Lithium Chloride	Lithium chloride is used as a solution to manage anxiety symptoms and cognition deficits after TMT intoxication.
Shams-Alam <i>et al.</i> [95]	2015	Rat	Lithium Chloride	Lithium chloride prevented neuronal apoptosis and preserved granular cells in the cerebellum.
Zare <i>et al.</i> [96]	2015	Rat	Chloride & endurance training	Chloride & endurance training increased BDNF level and improved the characteristics of Alzheimer disease.
Rafiei <i>et al.</i> [97]	2016	Rat	Gallic Acid & endurance training	Endurance training and Gallic acid increased the level of hippocampal BDNF in a model of TMT-intoxication.
Sakhaie <i>et al.</i> [98]	2016	Mice	Coenzyme Q10	Coenzyme Q10 diminished neuronal necrosis and improved learning & memory.
Kim <i>et al.</i> [99]	2016	Mice & cell culture	Magnolol	Magnolol administration prevented TMT-induced hippocampal neurodegeneration and glial activation.
Moghadas <i>et al.</i> [52]	2016	Rat	Gallic Acid	Gallic acid treatment against TMT-induced hippocampal degeneration.

Table 3. The Comparison Between Colchicine, Scopolamine, OKA, STZ, and TMT Drugs

Drugs	Molecular Formula	Structural Formula	Neurotoxicity effect
Colchicine	C ₂₂ H ₂₅ NO ₆		Impairment of learning and memory, cognitive dysfunction, etc.
Scopolamine	C ₁₇ H ₂₁ NO ₄		Impaired cognition, decreased activity of choline acetyltransferase, etc.
OKA	C ₄₄ H ₆₈ O ₁₃		Memory impairment, neuronal death, increased PP2A, tau, CaMKII, etc.
STZ	C ₈ H ₁₅ N ₃ O ₇		Cognitive decline, memory deficit, etc.
TMT	C ₃ H ₉ ClSn		Spatial learning impairment, cognitive and behavioral dysfunction, necrotic death, memory impairment, etc.

OKA: Okadaic acid; **STZ:** Streptozotocin; **TMT:** Trimethyltin

uptake, increased ROS, and glutamate excitotoxicity [78]. Also, TMT affected some cells and molecules like JNK (c-Jun N-terminal kinase) and PKC (protein kinase C) that caused the cytotoxic response [79]. Studies have shown that TMT increased the corticosterone level and learning impairment, and it damaged the neurons of the hippocampus in rats [80]. Secretion of corticosterone in a stress situation changed hippocampal morphology and prevented neurogenesis in the adult brain [81]. Some compounds have neuroprotective effects against neurotoxicity agents. One study showed that administration of lithium (100 mg/kg) generated neural stem/progenitor cells in the dentate gyrus in two to four days after treatment with intraperitoneal (ip) injection of TMT (2.9 mg/kg) [94]. Another study demonstrated that administration of magnolol (25mg/kg, ip), following the induction with TMT (2.6 mg/kg, ip), prevented necrotic/apoptotic cell death, BV-2 cell microglial activation, oxidative stress, and MAPK activation [99].

Conclusion

According to studies, chemical drugs such as colchicine, scopolamine, OKA, STZ, and TMT could induce AD by affecting the hippocampus. Previously, we examined TMT neurotoxicity in many studies [65, 66, 95- 97] and showed TMT caused neuronal destruction, anxiety, depression, memory deficit, and induced neuronal degeneration in hippocampus. Also, according to the research we suggested other compounds (like colchicine, scopolamine, OKA, and STZ) have characteristics of neural degeneration of the hippocampus that are used for induction of AD.

Acknowledgments

This study elicited from the PhD thesis of Ms. Samira Malekzadeh who studied in Islamic Azad University of Shiraz. The authors wish thanks the technical and equipment supports of the Stem Cell and

Transgenic Technology Research Center. Also, we especially thank Mr. Shahrokh Zare for technical support of this study.

Conflicts of Interest

The authors have no conflict of interest.

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