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"A REVIEW ON: TRANSGENIC AND CHEMICALLY INDUCED ALZHEIMER'S DISEASE LIKE COGNITIVE IMPAIRMENT IN RODENTS"

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ABSTRACT The most common neurodegenerative disorder in the world is Alzheimer's disease (AD), which affectts about 24 million people worldwide. Common AD symptoms include the following: Memory loss, difficulties speaking or writing, difficulty carrying out daily tasks, difficulties planning or solving problems, confusion about time or place, difficulties understanding visual cues, changes in mood and personality and difficulties talking and understanding. In this review, we focus on many animal studies of memory impairments that have been found because dementia has multiple etiologies. In order to better understand the pathophysiology of dementia and other cognitive disorders as well as to manage them, chemically produced animal models of memory deficiencies have become more popular. Transgenic models, on the other hand, have clear advantages and are now more often used. Also, the evidence we reviewed suggested that additional drugs used to induce AD, including as colchicine, sodium nitrite, scopolamine, and STZ, exhibit properties that are similar to hippocampus-related neuronal degeneration. The goal of the current study is to review about Alzheimer's disease, symptoms , objectives of using animals in research with special emphasis on inducing methods of Alzheimer's disease-like of cognitive impairment in rodents.

KEYWORDS :

1. INTRODUCTION

The most common neurodegenerative disorder in the world is Alzheimer's disease (AD), which affects about 24 million people worldwide. By 2050, it is predicted that this number will have quadrupled. The impairment of memory and behaviour in adults over 65 is known as dementia. The creation of neurofibrillary tangles as a result of the intracellular accumulation of hyperphosphorylated Tau protein and the deposition of B-amyloid (A beta) peptides on the extracellular surface of neurons are its key characteristics. Acetylcholine (Ach) deficits and oxidative stress brought on by increased glutamatergic transmission are additional factors that contribute to AD [1–5].

The incidence of Alzheimer's disease doubles every five to 10 years as people age. Its ratio varies by age group and is 1% for people aged 65 to69, 3% for people aged 70 to74, 6% for people aged 75 to79, 12% for people aged 80 to84, and 25% for people aged 85 and over [6].

2. Symptoms Of Ad

The consequence of the breakdown and loss of neuronal channels in brain cells is the most prevalent early indication of Alzheimer's disease. Common AD symptoms include the following: Memory loss, difficulties speaking or writing, difficulty carrying out daily tasks, difficulties planning or solving problems, confusion about time or place, difficulties understanding visual cues, changes in mood and personality (anger, anxiety, and depression), and difficulties talking and understanding [7-8].

3. Objective Of Using Animals In Alzheimer's Research

The study on AD heavily relies on animal models. These animal models may not exactly replicate the molecular manifestations of the disease in the human brain, but they are quite close anatomically [9].In terms of memory and motor abilities, neuroanatomy, and the endocrine system, mouse models are thought to be much superior to invertebrate models. As one model cannot account for all the cognitive, biochemical, behavioural, and histopathological problems, it is incorrect to employ only one animal model [10].A good model is one that replicates the pathology of the disease, can match the complexity of human behaviour in rats, and helps to create safer and more effective treatments [11].The extracellular deposition of senile plaques, extensive development of neurofibrillary tangles, chronic neuroinflammation, and loss of cholinergic neurons are the main neuropathological markers of AD[12,13].

A. Animal Models

I. Transgenic Mouse Models

Transgenic mice are employed as the primary animal species in AD research. Sequence homology between human APP and wild-type Mouse APP (695 isoform) is 97%.Three amino acids from the A sequence—R5G, Y10F, and H13R—are among the sequence changes between mice and humans that are significant[14, 15].Due to these variations, amyloid plaques do not develop in wild-type mice and A aggregation is impaired. As a result, mice cannot develop amyloid plaques without human APP expression. Early transgenic models expressed wild-type human APP in mice; however, despite increased levels of A (and related neuropathology) in these transgenic mice, they failed to consistently display severe AD-associated neuropathology[16-20].Expression of human APP with FAD-related mutations, on the other hand, led to persistent plaque pathology and varied degrees of downstream clinical traits associated with AD.The exact phenotype of each transgenic strain is largely determined by the FAD mutation, the promoter employed, and the background mouse strain. There have been several transgenic strains produced. Given that the pathology of the vast majority of AD transgenic models is dependent on the expression of FAD mutations and that the majority of AD clinical trials are carried out in sAD patients, whose pathogenesis for AD differs significantly from that of FAD, this presents one barrier to the success of these models being translatable. The neuropathology and related cognitive deficits for the transgenic mouse strains most frequently utilised in AD research. It should be noted that each model's level of sensitivity to cognitive testing, amount of tau-related disease, and degree of synaptic pathology (shown by ultrastructural investigations and/or electrophysiological) substantially varies, making direct comparisons between models challenging.

II .Transgenic mice expressing human APP and PSEN1 with FAD mutations

The first transgenic mice models produced APP that had a single FAD mutation. The PDAPP mouse, which expressed human APP with the Indiana mutation (APPV717F) driven by the PDGF-promoter, was the first example of such a model[21]. This mouse overexpressed APP dramatically (>10-fold).As a result, there was pathology indicative of human AD, such as plaque formation in the cortex and hippocampus, CAA, gliosis, synaptic dysfunction, and cognitive dysfunction .The Tg2576 mouse model closely followed the generation. The PrP promoter-driven production of human APP by Tg2576 mice with the double Swedish mutation (APPK670N/M671L) likewise caused a significant overexpression of APP (>5-fold) [22].Plaques formed in the hippocampus, cerebellum, frontal, temporal, and entorhinal cortices of Tg2576 animals. Moreover, cognitive impairment, CAA, synaptic dysfunction, and gliosis were all observed. The expression of the APP751 isoform, which is directed by the Thy1 promoter, contrasts with that of the APP695 isoform, which is driven by the PrP promoter, expressed in Tg2576 mice, in APP23 animals, which also express APPK670N/M671L[23].When compared to Tg2576 mice, APP23 mice form compact plaques more quickly and exhibit localized neurodegeneration, which is not present in Tg2576 mice. Additionally, APP23 mice have more pronounced CAA [24]).These variations exist despite equal levels of APP transgene expression, demonstrating that the promoter and APP isoform have a significant impact on the nature and progression of AD-related neuropathology in transgenic models.

It was later found that transgenic mice with more severe disease that manifested at a younger age were produced when various FAD-associated mutations were expressed simultaneously. This was observed in animals that showed several APP FAD mutations, such as the J20 mouse that expressed the Swedish and Indiana mutations[25], or more frequently, in mice that expressed both the APP and PSEN1 FAD mutations (known as APP/PS1 transgenic mice).In AD research, a number of different APP/PS1 transgenic mouse models have been created and are often employed. Each model has a unique phenotype that differs depending on the precise FAD mutations and the promoter employed. Examples include the extremely early plaque formation caused by the expression of APPK670N/M671L and PS1L166P, which starts at around 6weeks[26], and the later plaque formation caused by the expression of APPK670N/M671L and PS1M146L, which starts at about 6 months[27].The 5xFAD mouse model is the most extreme APP/PS1 animal model that is frequently utilised; these mice express the Swedish (APPK670N/M671L), London (APPV717I), and Florida (APPI716V) APP mutations, as well as the PS1M146L and PS1L286V mutations [28].Plaque formation occurs at 2 months after the expression of five FAD mutations, which occurs extremely early intraneuronal A accumulation at 6 weeks. In general, transgenic mice expressing human APP exhibit substantial plaque development, especially in parts of the brain that are frequently rich in plaques in AD, such as hippocampus and cortex. All have plaque-associated gliosis, comparable to that in AD, and the majority have localized pathology linked to synaptic impairment, such as impaired long-term potentiation and decreased levels of synaptic markers such synaptophysin. They all exhibit cognitive dysfunction, especially while doing activities requiring spatial memory. Yet it's crucial to remember that cognitive impairment often appears considerably earlier than in AD; in transgenic mice, it typically occurs at the same time as plaque growth, as opposed to decades later in humans. The absence of the extensive neurodegeneration and localized brain atrophy that characterise AD in these transgenic mouse models is a significant drawback. Although there is some indication of mild neurodegeneration in the majority of these mouse models, it only happened in very elderly animals and was confined to a limited number of areas of the brain. The other significant drawback of these mice models was that none produced neurofibrillary tangles, despite some showing signs of localized hyperphosphylated tau that may constitute "pretangles"[28, 26, 23, 29].

III. Tau-expressing Transgenic Mice

Neurofibrillary tangles do not occur in wild-type mouse tau.This is most likely because mature mice exclusively express 4R isoforms, not the combination of 3R and 4R isoforms found in humans, and because mouse and human tau share only 88% sequence homology. It's significant because only mice lacking endogenous tau produce tangles when all 6 isoforms of human tau are expressed, demonstrating that endogenous mouse tau prevents the aggregation of human tau [30].NFTs, on the other hand, are easily formed in transgenic mice that express human tau with mutations linked to FTLD; the most often used models are those that express 4R tau with P301L or P301S mutations[31-35].NFTs ,neurodegeneration, atrophy, and motor impairments appear in these mice. The requirement of these mutations for NFT development is a clear drawback of these transgenic mouse models, as these mutations are not linked to AD in humans and the emergence of mutant tau may alter its toxicity or interaction with A in a manner that is not consistent with AD.Additionally, over-expression of mutant tau causes serious motor impairments that are not seen in AD and obstruct cognitive testing.

IV. Plaques and Tangles In Transgenic Mice

A small number of studies[36-37,32,38-39] have described the creation of animal models that show plaques and tangles alike. To induce plaque and tangle formation in the same model, these models rely on the concurrent expression of mutant versions of APP, MAPT, and occasionally PSEN1 or PSEN2.The development of plaques and tangles is often not seen until old age in these models, and the constant and abundant expression of both plaques and tangles has proven problematic. Only, the 3xTg mouse model, which is thought to be the most thorough transgenic mouse model of AD pathology currently available, has been extensively employed in AD investigations out of all the published models[40].Intraneuronal A initially appears in 3–4-month-old 3xTg mice, with plaque formation in the cortex and hippocampus following at around 6–8 months. NFTs start to form at around 12 months, first in the CA1 region and later in the cortex; however, they are far less severe than NFTs in AD tissue mice also show signs of synaptic dysfunction, localized neurodegeneration, and cognitive abnormalities at 6 months. The synthesis of mutant A and tau, which is substantially overexpressed in a non-physiological manner and is not indicative of that in sAD, continues to be a limitation for 3xTg mice. Furthermore, these mice often do not develop widespread plaques and tangles until they are old, and even then, the pathology is less severe than is typically the case in AD.

V. Novel Transgenic Mice Models Useful for AD research

There are several transgenic mice models that are particularly effective at simulating a particular pathogenic aspect of AD. An excellent CAA model, for instance, is the Tg-SwDI transgenic mouse [41].This model exhibits the APP FAD variants from Sweden (APPK670N/M671L), the Netherlands (APPE693Q), and Iowa (APPD694N).Hereditary cerebral haemorrhage with amyloidosis (HCHWA), which has extensive CAA but less severe plaque pathology, is linked to the Dutch and Iowa mutations[42]. Starting at 3 months of age, Tg-SwDI animals develop a significant accumulation of fibrillar vascular A and less noticeable diffuse parenchymal plaques [41].).Contrary to the substantial arteriolar CAA in AD, CAA is primarily found in capillaries. Moreover, cholinergic neuronal death and cognitive impairment are localized in Tg-SwDI mice.It is crucial to test if treatment methods can effectively reduce vascular amyloid deposits without causing complications. Vasogenic edoema (or encephalitis) with/or without haemorrhage, also known as amyloid-related imaging abnormalities with edoema (ARIA-E) or with haemorrhage (ARIA-H)[43-46,19], has been a serious consequence in the ongoing passive vaccination AD clinical studies. ARIAs are also a significant problem in the recently published aducanumab trial, affecting 55% of patients in the high-dose and APOE4 carriers arm and contributing to a 35% patient drop-out rate[47- 48,46].Hence, it is crucial to create a treatment for CAA that works without causing vasogenic edoema or encephalitis[43-45,47,49,19].Thus, it is crucial to demonstrate that therapeutic techniques do not cause micro haemorrhages in preclinical testing in models with extensive CAA (which almost all patients with AD and roughly a third of aged cognitively normal individuals have)[50-51].The Osaka (APPE693) mutation is expressed in the APP E693-Tg model, which leads to a distinct phenotype of markedly enhanced expression of A oligomers, synaptic dysfunction, and cognitive deficits starting at age 8 months, but no plaque or tau pathology formation [29].This gives researchers the chance to investigate the pathogenic effects of A oligomers and/or the impact of therapies exclusively on these molecules, as they are regarded to be the most hazardous A species[52].The main advantage of these two mice models is that they more faithfully than other models imitate particular pathogenic aspects of AD. These models have the drawback of not accurately simulating all aspects of AD, which prevents them from being utilised as a comprehensive model of AD.

VI. Knock-in Mouse Models

The knock-in mice are the most current generation of transgenic animals that recreate the pathophysiology associated with AD.By humanizing mouse A and introducing specific APP FAD mutations, these mice are thought to be a far more physiological model of AD than any other transgenic mouse models, which all exhibit the confounding effects of APP over-expression. Hence, knock-in animals exhibit the same levels of APP and AICD expression as wild-type mice, and APP expression takes place physiologically in the appropriate brain areas and cell types. The timing of disease is dependent on the mutations produced, just like in other transgenic mouse models. For instance, breeding onto a PS1M146V knock-in background is the only way to get plaques when the Swedish, London, and Dutch mutations are knocked in [53]. A knock-in of the Swedish and Iberian mutations, on the other hand, causes plaque development to start at 6 months and gliosis, synaptic changes, and memory impairment to start at 18 months [54].More knock-ins of the Arctic mutation cause these mice to develop pathologies more quickly, including plaques that start to form at 2 months and become more extensive throughout the brain as well as memory impairment at 6 months [54].Even though these transgenic mice mark a significant advancement in the creation of more physiological transgenic models, it is still important to recognize that they are FAD rather than sAD models and that pathology only appears after the knock-in of a combination of distinct multiple FAD mutations.

VII.Transgenic Rat Models

There have also been a few fewer transgenic rat models of AD created. Transgenic rats have a number of potential advantages over transgenic mice, including greater physiological, morphological, and genetic similarity to humans; easier CSF collection, electrophysiology, and imaging due to their larger brains; and more complex behavioural testing due to their richer behavioural phenotype [55].Three transgenic rat models have been thoroughly studied in the literature[56-58].The phenotypic and restrictions of transgenic rats are comparable to those of transgenic mice, and the expression of several FAD mutations speeds up the onset of disease. The promoter chosen affects how widely, where, and how locally APP expression is expressed. Intriguingly, TgF344-AD rats have NFTs[56] despite only expressing endogenous rat tau and not human tau, despite all models exhibiting substantial amyloid plaque formation (although at lower levels than in transgenic mice).There are also 6 isoforms of endogenous rat tau, which suggests that there are more parallels between rat and human tau than previously thought. Many rat models have some level of cognitive impairment, but only the McGill-R-Thy1-APP rats have had this impairment thoroughly defined [57].In conclusion, transgenic rats have potential for use in AD research and have distinct advantages than transgenic mice; nevertheless, due to their relatively low usage, further characterization is required to adequately assess their suitability as AD model organisms.

Hypoxia Induced Memory Deficit

Vascular dementia is a widespread neurodegenerative condition that is brought on by chronic hypoxia [59].Dementia caused by hypoxia lowers blood flow to the brain, resulting in memory loss. Memory and learning impairment occur in animals exposed to sodium nitrite, hydroxylamine, carbon dioxide, and carbon monoxide [60]. Recent research has shown that hypoxia contributes to A buildup by affecting tau hyperphosphorylation, A breakdown and clearance, and neuronal degeneration [61]. Hypoxia causes neuroinflammation and changes cerebral blood flow, which affects how blood crosses the blood-brain barrier and, in turn, increases the amount of A that accumulates [62].The main benefit of this model is that it may be used to screen for nootropics and free radical scavengers that have the potential to improve memory [60].

Chemically Induced Animal Models

I. Scopolamine-induced Amnesia [63]

Acetylcholine, a neurotransmitter linked to cholinergic neurons, is crucial in the control of neuronal activities like memory, learning, and blood flow to the brain [64]. Similar to how diazepam impairs memory, scopolamine (Levo duboisine and Hyoscine), a tropane alkaloid, is a muscarinic receptor antagonist [65].It has frequently been employed in experimental research using rats or mice to cause memory impairment. Because it has the ability to inhibit neurotransmission, which causes cholinergic dysfunction. The aetiology underlying alzheimer and other neurodegenerative illnesses is thought to be influenced by oxidative stress, which is caused by the use of scopolamine [67,68].Based on the aforementioned activities, scopolamine hydrobromide is utilised as a neurocognitive stimuli at a dose of 0.4 mg/kg twice weekly intraperitoneally (higher doses of 0.6 and 1 mg/kg have also been administered) for the loss in memory and learning in animal experiments (rats or mice)[69, 70].Scopolamine-induced alzheimer's is a common method for initial screening of anti-dementia medications in animals and is a type of behavioural model. One of the behavioural tests, like radial arm maze, Y-maze, active avoidance, Morris water maze, etc., can be used to determine whether the test drug is effective in reversing interoceptive stimulus (scopolamine) induced memory loss after the changes in cholinergic neuronal activity induced by the drug [71].

II. Sodium Nitrite Induced Amnesia [63]

This particular interoceptive unpleasant stimulus model relies on changes in brain metabolism to determine the advantageous effects of drugs that affect memory and learning [64].Brain effects of sodium nitrite (NaNO2) According to metabolism, oxidative metabolism and cholinergic activity are closely related. Deficiencies in brain metabolisms and impaired cholinergic transmission caused by sodium-nitrite have both been demonstrated [72].The most important component of the brain, the hippocampus, which is also more vulnerable to oxidative stress damage, is essential for memory modulation. Reactive nitrogen and oxygen species (RONS), which are to blame for altered lipid, protein, and DNA structures as well as neurodegeneration and memory impairment, are known to diminish oxygen partial pressure at high altitudes and produce oxidative stress [67].In order to test learning and memory, many exteroceptive behavioural models, including such step-down passive avoidance, are used, including the subcutaneous infusion of sodium nitrite (75 mg/kg) [72].

III. Colchicine-induced AD-like symptoms

Colchicines may be possible medications that cause dementia through malfunctioning cholinergic neurons by either suppressing cholinergic reversal or destroying cholinergic passage cascades, according to advances in chemicals used for modelling AD[73–74].Colchicine may be used as a potential for modelling AD since it causes hippocampal lesions that impair cognition and reduce ChAT. By blocking cholinergic pathways, colchicine has the ability to induce neurotoxicity and memory loss. This would decrease the number of cholinergic neurons and, in turn, decrease cholinergic renewal, especially in the hippocampal region of the brain[75].Colchicine may impair memory by lowering dopamine, serotonin, and norepinephrine levels in the nucleus accumbens, cerebral cortex, and hippocampus as a whole [76].Furthermore, colchicine was demonstrated to lead to the generation of protein carbonyls after lipid peroxidation[77].Moreover, COX-1 and COX-2 expression levels as well as ROS production have been reported to increase with the use of colchicine[78, 79].Colchicine increases the glutamate/GABA ratio in the cortex[80] and causes MDA receptors to be excited, which then causes a rapid increase in the amount of Ca2+ entering the cell, which in turn causes the activation of enzymes that depend on Ca2+, such as xanthine oxidase, phospholipases A2, cyclooxygenase, proteases and protein kinases [81]. Colchicine (7.5 g in 10 L) administered intracerebroventricularly (ICV) was reported to reproduce rat and mouse cognitive memory impairment. After administering colchicine to induce cognitive impairment, a substantial memory deficit was seen two weeks later [74].Moreover, colchicine 3 g/mice (ICV injection) causes impairment in spatial memory [83].The fundamental benefit of this model is that it reproduces some indications of sporadic Alzheimer's type of dementia, including time-variant alterations in onset, behavioural patterns, and biochemical patterns, which are observed in human subjects [77].

IV. STZ (Streptozotocin) Induced Cognitive Impairment

A type of soil microorganisms from which STZ was identified. It was first employed as an antibiotic and then as an antitumor agents and a medication to treat neuroendocrine tumours.Studies have demonstrated that injecting STZ (3 mg/kg) causes cognitive deterioration, a decrease in brain mass, an increase in hippocampal A-and tau levels. According to research by Chen et al.(2014), mice's brains had changed neurochemicals that were similar to Alzheimer's disease and produced memory deficits[85].Research has shown that damage Axons and myelin of the fornix, the anterior hippocampus, and periventricular structures are only a few of the specific regions that are affected by STZ, and these regions are crucial for learning and spatial memory [86].Also, another study has demonstrated that the volume of STZ injection in rats affects the extent and dynamics of brain neurodegeneration [87].Moreover, research has demonstrated that injecting STZ into the lateral ventricles has an effect as a non-selective neurotoxin close to the injection site.

V. Alcohol Induced Memory Deficit

According to studies, ethanol impairs the hippocampus and cholinergic neurons, affects the sensory-motor system, and interferes with memory and learning [88].Higher dosages of ethanol interact with glutamatergic system and increase GABAergic transmission in memory-related areas of the brain, but acute ethanol administration creates excessive amounts of NO, which affects the process of learning and memory. Moreover, it raises adenosine levels extracellularly, which impairs memory [88].Another study on the neonatal ethanol paradigm involved feeding pregnant animals an ethanol-mixed food in order to cause memory impairment. Although this model could not require surgery, it is exceedingly laborious and time-consuming [89].

4. CONCLUSION

The last ten years have seen significant advancements in our understanding of the neuropathological mechanisms underlying the biochemical and cellular abnormalities in AD. Parallel to this, a wide variety of transgenic and nontransgenic animal models of AD have been created. Despite the fact that the effective animal models generate amyloid accumulation and plaques along with cognitive decline, other neuropathological with the present animal models, alterations like NFT are seldom perceptible. The best animal models for evaluating the effects of medications that prevent a production, fibril development, and brain deposition. In this review, we focus on many animal studies of memory impairments that have been found because dementia has multiple etiologies. In order to better understand the pathophysiology of dementia and other cognitive disorders as well as to manage them, chemically produced animal models of memory deficiencies have become more popular. Transgenic models, on the other hand, have clear advantages and are now more often used. Also, the evidence we reviewed suggested that additional drugs used to induce AD, including as colchicine, Sodium nitrite, scopolamine, and STZ, exhibit properties that are similar to hippocampus-related neuronal degeneration.

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