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NEUROPATHOLOGY OF STREPTOZOTOCIN-INDUCED RODENT MODELS OF ALZHEIMER'S DISEASE: A REVIEW ON BEHAVIORAL AND HISTOLOGICAL EVIDENCE

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Abstract

Alzheimer's disease (AD) is an incurable neurodegenerative disease with significant research efforts focused on developing effective treatments. Various rodent models, including transgenic and non-transgenic models, have been established to investigate AD and potential therapeutic interventions. Streptozotocin (STZ), a naturally alkylating antineoplastic agent with a diabetogenic effect on mammals is the widely used sporadic rodent AD model due to its ability to mimic certain aspects of sporadic AD observed in humans. Recent evidence has highlighted a correlation between STZ administration and AD-like neuropathology, characterized by exacerbated neuroinflammation and the manifestation of AD hallmarks in animals. However, certain key characteristics of STZ-induced AD pathology remain poorly described. Therefore, this review aims to summarize the neuropathological hallmarks of AD in rodents following STZ administration. STZ injection chronically produces multiple effects resembling AD's behavioral and pathological aspects. Rodents that received injection of STZ developed long-term progressive deficit of memory, learning and cognitive behaviour. Histologically, STZ affects neurons and synapses in the brain, accompanied by the presence of amyloid-beta (Aβ) plaques, tau hyperphosphorylation, white matter atrophy, and myelin damage. Understanding the connection between behavioral and neuropathological alterations following STZ administration and their relevance to AD pathology in rodents would significantly contribute to the field of AD animal models.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive behavioral, mental, and learning loss [1]. The major pathological hallmarks of AD include senile plaques and intracellular neurofibrillary tangles (NFT) [2]. Although study on AD has been conducted for decades, there is still no cure for the disease. The available drugs only reduce the progression and relief of the symptoms but fail to cure the disease [2].

Many AD rodent models, including transgenic and non-transgenic, have been developed and used for preclinical testing of pharmacological therapies. Unfortunately, none was translated into a successful treatment of human patients. Several factors were proposed as possible root causes of this failure. One of the most important factors is the inability of these models to mimic the clinical features of AD in humans [3].

The transgenic model shows many limitations in AD study, including limited plaque pathology, no development

of NFT, limited mutated amyloid-beta (Aβ) production, while others fail to demonstrate aspects of neuronal loss and dysfunction, including synaptic and axonal function [4-6]. The significant limitations of transgenic rodent models are that they primarily model familial/gene-based early-onset form of AD (fAD), which involves mutations in presenilin genes, despite the fact that the late-onset form accounts for more than 99% of diagnosed AD cases. More common late-onset AD is considered sporadic, which is thought to result mainly from environmental and lifestyle-related factors. However, genetic risk factors have also been identified, most notably apolipoprotein E gene (APOE). Furthermore, the pathology development observed in these transgenic models is typically non-physiological [7-9].

Compared to the transgenic models, a non-transgenic model, such as naturally occurring and chemically induced, is more favorable for AD research. Most non-transgenic models exhibit at least one hallmark of AD pathologies, such as Aβ plaques and NFT [8]. Moreover, the natural process of AD development can be observed when using non-transgenic models [8]. Some of them can also mimic the sAD pathology and clinical symptoms of AD that appear in humans [10]. The non-transgenic model can also exhibit a faster response and low-cost consumption [8-9].

The model employing the diabetogenic toxin streptozotocin injection has recently gained considerable popularity. Streptozotocin (STZ) is a glucosamine-nitrosourea compound widely used to induce diabetes in experimental animals [11]. Growing evidence suggests that STZ may aggravate the development of AD-like pathology in rodents. This model of sporadic AD has been reported to cause cognitive dysfunction and histological changes in rodents. STZ has been reported to cause significant impairment in rats' anxiety, spatial memory, and recognition memory without affecting motor function [10,12-14].

Meanwhile, the practical use of STZ has been found to enhance AD pathologies, such as the development of Aβ plaque, neurofilament protein, and tau phosphorylation [13-15]. The lack of this behavioral and histological evidence in other non-transgenic AD models led to a widened use of STZ-induced AD model. As it has gained massive interest among researchers recently, much evidence is needed to justify the reliability of this STZ-induced AD model. Therefore, the present review aims to summarize the behavioral and histological evidence of STZ-induced AD pathology in animal models.

STZ-BASED MODEL OF AD

Streptozotocin (STZ), C8H15N3O7, is a glucosamine-nitrosourea compound commonly used in the systematic induction of diabetes due to its ability to damage the pancreatic β cells and induce insulin resistance [16]. It is an antibiotic produced by the bacterium Streptomyces achromogens and exhibits a broad spectrum of antibacterial properties [17]. STZ also shows sufficient evidence of carcinogenicity in animals [17]. STZ contains a glucose molecule linked to a highly reactive methyl nitrosourea moiety (Figure 1). Methylnitrosourea moiety is thought to exert cytotoxic effects of STZ. The glucose moiety directs the chemical to the pancreatic β cells [18].

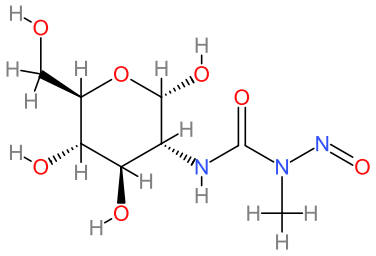

Figure 1. Chemical structures of STZ.

Administration of STZ via different routes causes brain insulin resistance. It leads to AD pathology, including accumulation of Aβ, hyperphosphorylation of tau, generation of free radicals, and impairment of cognitive function. A previous study suggested that STZ causes toxicity by producing reactive oxygen species or reactive nitrogen species [19]. STZ was also absorbed by insulin-secreting β-cells and caused cytotoxicity. In addition, STZ also leads to the alteration of glutathione homeostasis and inhibits the activity of respiratory enzymes, leading to ATP synthesis inhibition [20]. Injection of STZ via intracerebroventricular (ICV) is the most common model inducing AD [21].

BEHAVIORAL CHANGES IN STZ-INDUCED AD MODEL

Locomotor Activity & Anxiety Disorder

The development of several Alzheimer-like indices of brain metabolic and behavioral disturbances in rats subjected to STZ injection(s) is considered to be a dynamic process. Most experimental evidence has demonstrated that STZ injection(s) did not cause any obvious sign of motor dysfunction in rats (Table 1). The rearing, crossing, and distance travel activity covered by animals that received STZ (3 mg/kg) in the open field did not differ from that of the controls, indicating that the locomotor activity remained intact [10,22-25]. Furthermore, no apparent motor dysfunction was observed in rats treated with STZ at 0.5 – 2 mg/kg intracerebroventricularly [23,26-29]. Commonly, the animals exhibited lower locomotor activity after the craniotomy procedure. However, the reduction in movement might be balanced by restless behavior during the weight gain period [22]. This might explain the fact that locomotor activity is less affected.

Another study reported that injection of STZ affects the distance travel and exploratory activity of the rats as measured in the open-field test [22]. An increase in

locomotor activity was observed in rats when administered with a single ICV injection of 3 mg/kg STZ [14,30]. It is marked by the increase in total distance and duration of walks. The study of STZ doses higher than 3 mg/kg is uncommon in locomotor activity studies. However, a previous study suggested that doses of ≥3 mg/kg promote increased locomotor activity [31].

In contrast, a decrease in locomotor activity also has been reported in ICV-STZ (3 mg/kg) treated rats [32]. It is believed that the impairment is caused by CNS depression, and STZ causes CNS depression by impairing oxidative stress and eventually causing the impairment in locomotor activity [32]. From these results, a different effect on locomotor activity has been observed even with the same dose of STZ used. Thus, other experimental factors may affect locomotor activity in STZ-induced rats. For instance, a recent study shows that the rats exhibit decreased locomotor activity due to high-light exposure compared to low-light exposure during the test [33].

Anxiety is a neuropsychiatric disorder. STZ causes insulin resistance and is involved in anxiety behavior [34-36]. In the most recent studies, anxiety behavior has been measured by elevated plus maze (EPM) and Open-field tests (Table 1). STZ injection (0.1 mg/site) was reported to increase anxiety-like behavior in mice. Lacking cholinergic transmission induced by STZ can postulate anxiety-like behaviors [10]. Another study reported an increase in anxiety-like behaviors in rats 3-weeks after ICV administration of STZ at 1 and 3mg/kg. In a long-term study, a low dose (0.5 mg/kg) of STZ could also increase rat anxiety-related behaviors [23]. The findings suggest that STZ can induce anxiety-like behavior in rodents, depending on the doses and time.

Spatial Memory and Working Memory

The role of STZ in inducing spatial memory impairment has gained much attention. Spatial performance deficit generally is followed by the occurrence of the hippocampal lesion (bilateral dorsal) at 30-50% of the total hippocampal area [39]. The previous study suggested that spatial memory is correlated to the myelinated axon, and this is because STZ was able to impair oxidative stress and result in myelin damage. Thus, the communication of myelinated axons may be disrupted and lead to spatial memory impairment [40].

Morris Water Maze (MWM) task has been widely utilized to assess the effect of STZ on spatial memory [13,14,23,32,41]. Other than that, the Barnes maze and Y-maze test are frequently used to measure the spatial learning capacity in STZ-induced rats [27,42]. In these learning paradigms, substantial evidence has been compiled in support of learning being impaired by STZ.

An increasing number of studies have demonstrated that rats treated with ICV-STZ (0.5 - 3 mg/kg) cover longer swim paths or display longer escape latencies in the MWM task than the sham-operated control [23,41]. Besides, in the Barnes maze test, the STZ-treated rats have higher latency and strategy scores compared to the control group [12,42]. Other than that, the less time spent in the new arm in Y-maze also indicates a spatial memory deficit in the rats after 30 days of STZ administration [24]. Thus, it has been firmly established that STZ administration compromises spatial learning in rats. The impairment was reported to occur as early as 14 days after STZ administration [41].

It is interesting to establish whether the learning impairment was affected by the STZ concentration or duration of the STZ treatment. Hence, the learning performance has been compared between different STZ doses at various time points in rats [23,30,43,44]. In the Y-maze test, ICV-STZ (0.5 mg/kg) after 3 and 9 weeks of administration revealed no difference in working memory as compared to the sham group, but after 14 weeks, the STZ group committed significantly more errors which indicates memory impairment [23]. In contrast, the higher concentration of STZ (1 and 3 mg/kg) is able to cause impairment in working memory as early as three weeks [23]. These results convincingly support that the effects of STZ on cognitive function are dose- and time-dependent.

Recognition Memory

On the other hand, recognition memory is dependent on the hippocampus and the adjacent perirhinal cortex [45]. As compared to spatial memory, the recognition memory was found to be impaired only after the hippocampal lesion was nearly complete (75-100%) [39].

In a previous study, STZ was reported to cause a decrease in adult neurogenesis [24]. A positive correlation between adult neurogenesis and recognition memory was found in a recent study. A decrease of adult neurogenesis in the subventricular zone (SVZ) and dentate gyrus (DG) area was found to cause cognitive deficit [24]. In a non-spatial learning paradigm, the object recognition test, rats administered with a low dose of STZ (0.5 mg/kg) performed as well as the controls after three weeks of treatment, but a delayed learning impairment had developed by six weeks, which was further enhanced afterward [23]. Meanwhile, the deficit in recognition memory has been observed in rats as early as 14 days when administered with a higher concentration of STZ (3 mg/kg) [14]. Some studies reported that cognitive impairment is related to spatial learning and memory [24], and it is maybe explained by the fact that both memories are associated with hippocampal.

Table 1. Locomotor activity and anxiety changes in STZ-induced models

Type of Changes	Dose of STZ	Rodent's strain	Time of Test	Test	Results	Ref.
Locomotor activity	3 mg/kg	Male Wistar rat	Day 9, Week 3, 9, 10, 13	Open-field test, Y-maze test	No significant changes in rearing and crossing activities No significant changes in velocity and distance travel	[10,22-24]
		C57BL/6 mice	Week 2, 3	Open-field test	Significant increase in distance travel and time spent at the center Significant increase in total duration of high walk	[14,37]
		Male Wistar rat	Week 3	Closed-field test	Decrease in total activity counts	[32]
	2.25 mg/kg	Male Wistar rat	Week 2	Open-field test	No significant changes in the total duration of walking	[37]
	2 mg/kg	Male Wistar rat	Day 30	Elevated plus maze, open-field test	No significant changes in velocity and distance travel	[27,31]
	1.5 mg/kg	Male Wistar rat	Day 11	Close-field test	Increases in total activity counts	[38]
		Male Wistar rat	Week 2	Open-field test	No significant changes in the total duration of walking	[37]
	1 mg/kg	Male Wistar rat	Week 3, 9, 13	Open-field test, Y-maze test	No significant changes in the number of arm entries No significant changes in the total duration of walking	[23,37]
	0.5 mg/kg	Male Wistar rat	Week 3, 9, 13	Y-maze test	No significant changes in the number of arm entries	[23]
	0.1 mg/site	Swiss male adult mice	Day 9, 23	Open-field test	No significant changes in rearing and crossing activities	[10]
Anxiety	3 mg/kg	C57BL/6 mice	Day 22, Week 3, 9, 13	Open-field test, Elevated plus maze	Less time spent in open arms Less time in center Less time spent in open arms	[14,23,26]
	1 mg/kg	Male Wistar	Week 3, 9, 13	Open-field test	Less time spent in the center	[23]
	0.5 mg/kg	Male Wistar	Week 13	Open-field test	Less time spent in the center	[23]
		Male Wistar	Week 3, 9	Open-field test	No changes in time spent in the center	[23]
	0.1 mg/site	Male Wistar rat	Day 7, 21	Elevated plus-maze	Less time spent in open arms	[10]

Table 2. Time needed for STZ rodent model to exhibit memory deficit in different doses

Dose of STZ	Rodent's strain	Route of administration	Type of memory			References
			Spatial memory	Working memory	Recognition memory	
3 mg/kg	SD rat	Single ICV	2 weeks	-	3 weeks	[12]
	C57BL/6 mice	Double ICV (1.5 mg/kg each))	-	-	2 and 3 weeks	[13]
	C57BL/6 mice	Single ICV	3 weeks	-	3 weeks	[14]
	SD rat	Bilateral IHC	12 weeks	-	-	[21]
	Male Wistar rat	Single ICV	4 weeks	4 weeks	3 weeks	[23]
	Male Wistar rat	Single ICV	4 weeks	-	4 weeks	[24]
	Male Wistar rat	Double ICV	1 week	-	-	[37]
2.25 mg/kg	Male Wistar rat	Double ICV	1 week	-	-	[37]
2 mg/kg	Male Wistar rat	Single ICV	-	-	4 weeks	[38]
1 mg/kg	Male Wistar rat	Single ICV	10 weeks	4 weeks	9 weeks	[23]
0.5 mg/kg	Male Wistar rat	Single ICV	14 weeks	13 weeks	13 weeks	[23]

Table 2 summarizes the onset of memory deficit following the administration of STZ at various concentrations. Animals develop cognitive deficits at variable time points after the induction with STZ. Impairment to the spatial, working, and recognition memory was observed after 2-3 weeks of exposure to the high dose of STZ (3 mg/kg) [12,13,23,24]. However, in contrast to the high dose, rats had no significant impairment to the spatial, working, and recognition memory three weeks after a low-dose (0.5 or 1 mg/kg) of STZ induction [12]. Instead, a low dose of STZ injection (0.5 mg/kg) induced a delayed deficit in spatial and working memories, which was observed at 14 weeks post-lesion, and also in recognition memory which was observed only after six weeks of STZ administration. Overall, 3 mg/kg is found to be the most effective dose to cause impairment in rats' spatial, working, and recognition memory in the shortest time.

HISTOLOGICAL CHANGES IN STZ-INDUCED AD MODEL

Amyloid-beta Pathology

AD is mainly associated with increased production or aggregation of Aβ [46]. The increase in glycogen synthase kinase-3 (GSK3β) may involve in Aβ regulation (47). β and γ-secretase are the enzymes that involve in APP cleavage. They are able to yield Aβ peptide aggregation and form senile plaque. γ-secretase is one of the enzymes involved in APP cleavage at the C-terminal Aβ domain [48].

It has been previously demonstrated that ICV injection of STZ induces Aβ40 and Aβ42 in rats [49]. Intracellular accumulation of Aβ has been observed in rats three months following STZ (3 mg/kg) injections [44]. Meanwhile, intracellular and extracellular Aβ plaques were detected at 6 and 9 months following the STZ (3 mg/kg) induction [44]. In addition, deposition of Aβ peptide was also found in the hippocampus after 6 and 9 months of STZ (3 mg/kg) injection [50]. Another study detected the immunoreactive signal of Aβ within blood vessel walls in hippocampal stratum pyramidale nine months after STZ administration, indicating the deposition of Aβ [43]. It has been suggested that the accumulation of Aβ plaques in the hippocampus might be related to the reduction of memory performance over time. Deposition of Aβ peptide in the brain tissue was also observed three months after the lesion, even lower doses of STZ (1 mg/kg) were used [51].

In contrast, there are no significant changes in the expression of Aβ in the hippocampus one month after the STZ (3 mg/kg) administration compared to the control [43]. Hence, the Aβ pathology appears to be time-dependent, although the underlying mechanism of Aβ deposition is still unclear [52].

Tau Protein Pathology

The hyperphosphorylation of tau decreases tau's binding to the microtubules [53]. GSK3β is known as a key to the hyperphosphorylation of tau protein. The underlying mechanism of GSK3β in tau protein is the ability of GSK3β to phosphorylate tau protein that is abnormally attached to the microtubule. Hence, detachment of tau protein from the microtubule occurs [54]. Due to the detachment, tau protein tends to aggregate, forming NFT.

STZ has been demonstrated to induce tau phosphorylation. Using immunohistochemical analysis, a significant increase in tau protein expression was observed in rats' CA1 and cerebral cortex following STZ (3 mg/kg) administration as compared to the control group [55]. Prominent brown staining (DAB) around the blue-stained nucleus (hematoxylin) was found after 21 days of STZ (3 mg/kg) administration, indicating an increase in tau phosphorylation compared to the control group [41]. STZ also causes the tau protein to self-aggregate, demonstrated by paired helical filaments (PHFs) structure observed under transmission electron microscopy (TEM) [41]. PHF is known as an early sign of NFT formation. The AT8 immunohistochemical experiment detected the moderate positive AT8 signal as early as one month after STZ (3 mg/kg) administration compared to the control group [44].

Another study reported a significant increase in phosphorylated tau protein level 14 days following STZ injection, although the total tau protein remained unchanged [12]. However, total tau protein and phosphorylated tau levels were markedly increased three months after STZ treatment [12]. In rats, it has been demonstrated that STZ induces tau phosphorylation, specifically at Ser396, Ser404, Ser199, and Thr212 [14,56] (Figure 2). Meanwhile, tau phosphorylation in mice at Thr205 and Ser199/202 has been demonstrated 21 days after STZ injections [14]. The species of rodents used in the experiment seem to play a role in the hyperphosphorylation site at tau protein.

Neuronal Loss

A neuron is highly susceptible to apoptosis-related cell death. Apoptosis can be caused by various factors, including oxidative damage. The discovery of DNA damage, nuclear apoptotic bodies, and chromatin condensation are consistent with the theory [57]. All these findings become evidence of apoptosis events in the AD brain. STZ causes deprived glucose uptake, and thus, it triggers the cells to self-damage, which is apoptosis. This cascade of mechanisms seems to be agreed in STZ-induced AD.

A recent study reported an elevated number of apoptotic neurons after 35 days of STZ injection [58]. In another study, the apoptotic neuron cells were found to increase in the STZ-

treated group as early as 14 days. It is evaluated by the increased number of TUNEL-positive cells in the brain [59]. The previous experiment also observed the cytoplasm shrinkage and the existence of dark pyknotic nuclei in neurons after 14 days of STZ administration, indicating severe neurodegenerative damage [59]. The atrophied degenerated neurons were also observed in STZ-treated rats compared to the normal group [55].

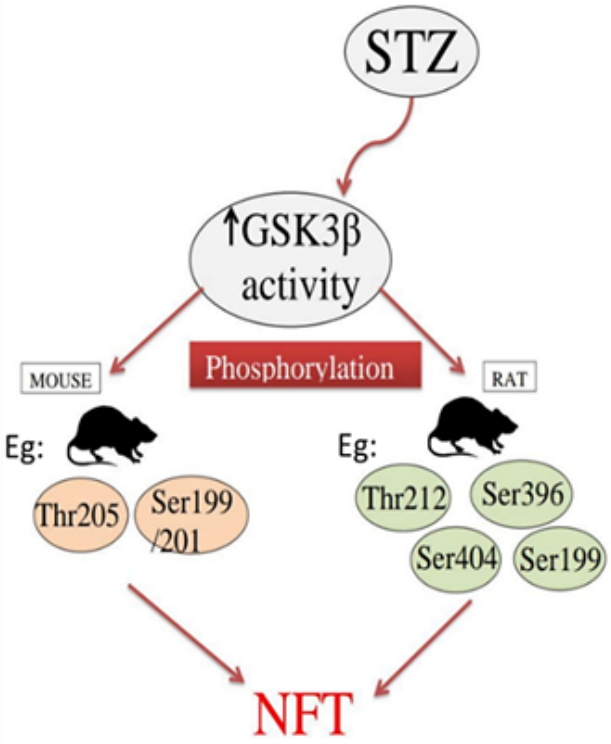

Figure 2. Phosphorylation of tau protein by STZ. GSK3β: glycogen synthase kinase- 3β; NFT: neurofibrillary tangles; Ser: serine; Thr: threonine; STZ: streptozotocin.

White Matter Damage

White matter is the part of the brain that consists of axons (nerve fibers) and neurons (extensive nerve cells). These nerve fibers are surrounded and covered by the myelin sheath that demonstrates white color. Thus, white matter damage in AD is strongly related to myelin, axonal loss, and oligodendrocytes damage [60]. However, the report on white matter damage following STZ administration is still limited.

White matter is primarily composed of the corpus callosum (61). A high dose of STZ (3 mg/kg) causes changes in the corpus callosum area [62]. One week after administration of STZ (3 mg/kg), the corpus callosum thickness reduction in the brain was found, indicating white matter atrophy. After three months, white matter atrophy was seen to be worse. Meanwhile, in low-dose STZ (1 mg/kg), it took a long time to demonstrate the damage, which is three months [62]. Other studies also reported white matter damage at the fornix area accompanied by reactive microglia [40].

Synaptic Loss

Synaptic loss in AD is correlated with Aβ. Aβ can impair synaptic plasticity, which is the ability of the synapse to undergo changes, whether strengthened or weaken [13]. It is suggested that a soluble Aβ disrupts the synaptic and eventually causes synapse loss [63]. The suggestion is supported by the recent finding demonstrating that synapsin level reduction parallels a high Aβ level after STZ administration [13]. This may prove that STZ causes the overproduction of Aβ, which leads to synapse problems, as explained above.

Synapsin 1 and synaptophysin protein have been reported to decrease after 35 days of STZ administration [14,64]. Both proteins are involved in organizing vesicles at presynaptic terminals [65]. In another study, the researchers found the synapsin level decreased as early as 14 days after STZ treatment [13]. STZ also causes a reduction in post-synaptic proteins, including post-synaptic density-95 (PSD-95) [66]. PSD-95 is a signaling protein that helps the transmission of synapse protein in the post-synaptic terminal. Meanwhile, STZ has been found to increase the NR2B expression and suppress the NR2A expression [67]. Alteration in these synaptic proteins may lead to synaptic loss and disrupt the synaptic function (Figure 3).

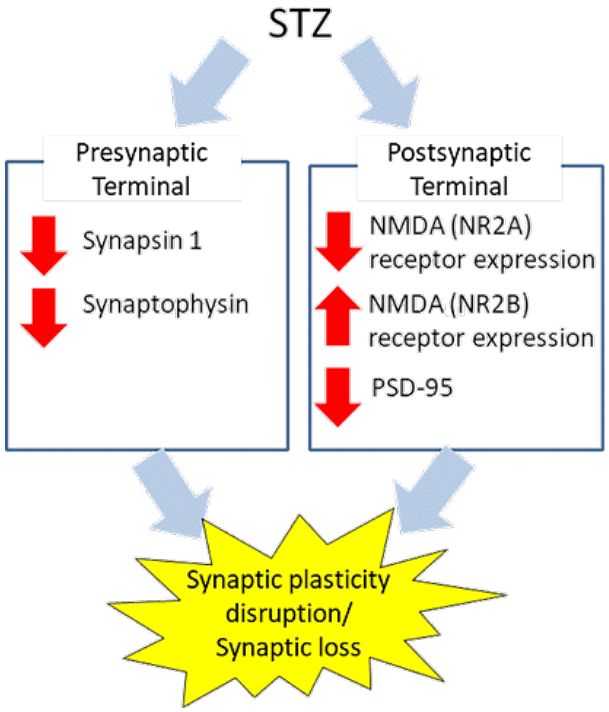

Figure 3. STZ induces synaptic loss and disrupts synaptic plasticity. STZ: streptozotocin; NMDA: N-methyl-D-aspartate; PSD-95: postsynaptic density protein 95.

Myelin and Axonal Loss

STZ can cause damage to myelinated neurons [68]. The formation of cluster myelinated axons in the dentate gyrus (DG) area was observed in STZ-treated rats [40]. STZ disrupts nerve growth factor (NGF) transport via fornical axonal fiber and causes accumulation of NFG in the hippocampus. This is the first study that reported STZ-induced damage in axons and myelin in the fornix, anterior hippocampus, and periventricular structure [40]. ICV-STZ was found to cause a morphology distortion in myelinated axons that also contributes to white matter damage [40].

Compared to AD, many pieces of evidence on the effects of STZ on myelin impairment have been reported in the diabetic model. One of them reported the thickness of the axon and myelin increased after five weeks of treatment [69]. Even though intraperitoneal-STZ (IP-STZ) is not directly induced AD, the underlying mechanism of STZ action may be quite similar. However, the mechanism of STZ in causing myelin impairment is still unclear. Since STZ is known to induce oxidative stress, this may be the underlying mechanism of STZ affecting myelin (Figure 4). Increased oxidative stress was found to disrupt the protein and lipid of the myelin membrane [70]. Meanwhile, oligodendrocytes were also found to be reduced after STZ administration via the IP route [71]. Oligodendrocytes are the cells that involve in myelin production and stabilizing neuronal connectivity. From this, we can conclude that STZ not only disrupts the myelin but can also prevent the production of myelin by causing the loss of oligodendrocytes.

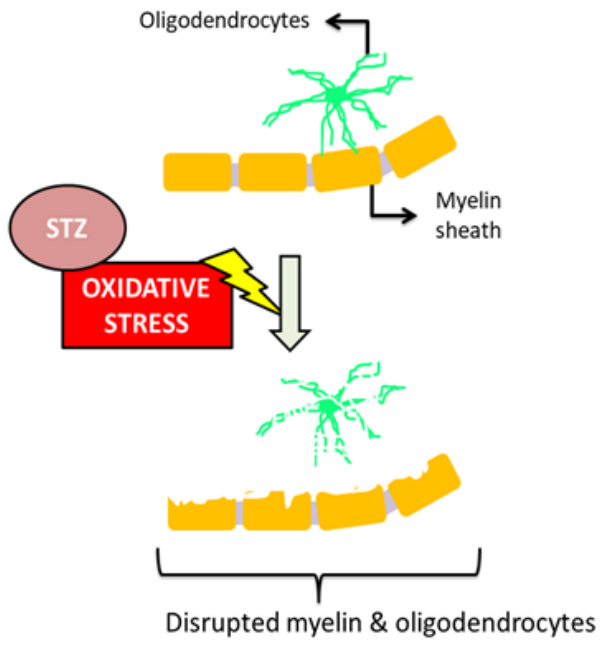

Figure 4. Streptozotocin (STZ) causes disruption of myelin.

CONCLUSION AND FUTURE RESEARCH PERSPECTIVE

The majority of AD cases are sporadic in nature. However, few rodent models develop the extensive pathological hallmarks observed in sAD patients and do not present all abnormalities in human AD. Nevertheless, many aspects of AD were observed following the administration of STZ. Behavioral outcomes have routinely been the primary outcome measure in determining the appropriate model for AD since changes in these are related to the cognitive failure associated with AD [72]. Rodent model that received injections of STZ developed a progressive deficit of learning, memory, and cognitive behavior. The administration of STZ has also induced the important hallmarks of AD: Aβ plaques and tau phosphorylation similar to human pathology. STZ also disrupts the chemical balance in the brain, especially in glucose metabolism. This leads to many structural changes in the brain that could mimic AD patients, such as synaptic loss, myelin damage, white matter damage, and neuronal loss. Therefore, based on the comprehensive evaluation, STZ successfully exhibits many features of sAD as seen in humans. Hence, it is proven that STZ is a reliable non-transgenic AD model for rodents.

This STZ-induced rodent model represents a reliable and useful model in AD research. However, further investigation is warranted to elucidate the underlying mechanisms through which STZ induces AD-like neuropathology in rodents, especially for better understanding disease complexity and developing new therapeutics for AD. This could involve exploring the specific pathways involved in neuroinflammation, Aβ plaque formation, tau hyperphosphorylation, and white matter atrophy in response to STZ. In addition, investigating the relationship between behavioral deficits and specific neuropathological alterations induced by STZ can provide valuable insights into the causal links between these aspects. Future studies can employ longitudinal assessments, molecular imaging techniques, and advanced behavioral paradigms to establish more precise correlations between behavioral changes and underlying neuropathological processes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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