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The mechanism underlying streptozotocin injection for the development of a nontransgenic Alzheimer's disease animal model

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ABSTRACT
Streptozotocin (STZ) is a widely used chemical agent in biomedical research. It is primarily known for its ability to induce high blood glucose levels in animal models by selectively destroying pancreatic beta cells. Nonetheless, many studies have also used STZ to generate animal models of diabetic complications, such as Alzheimer's disease (AD) animal models. STZ induction promotes hyperglycemia, which activates numerous mechanism pathways that result in the production of pathogenic AD characteristics, including beta-amyloid accumulation and neurofibrillary tangles. Numerous theories exist to elucidate the mechanisms underlying diabetes and AD; however, studies on the potential of an animal model of STZ-induced AD remain limited. Thus, this review summarizes the pathogenesis associated with STZ exposure, particularly in AD animal model studies related to diabetes. More specifically, this study will discuss the relationship between increased blood glucose levels after STZ injection and the process of beta-amyloid formation and insulin dysfunction in the brain.
Keywords: Beta-amyloid, Brain, Hyperglycemia, Neuron, Tau protein.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory loss, cognitive impairment, and behavioral changes. Neurofibrillary tangles (NFTs) made from hyperphosphorylated tau protein and senile plaques containing aggregated amyloid beta peptide (Aβ) are two main histopathological hallmarks of AD (Deture and Dickson, 2019). Furthermore, research into disease-modifying AD treatments is continuously ongoing. Currently, U.S Food and Drug Administration-approved AD treatments are limited to symptomatic therapies such as donepezil, galantamine, rivastigmine, and memantine (Yiannopoulou and Papageorgiou, 2020). For this purpose, experimental animal models that accurately replicate the developmental pathology of AD in humans are necessary.

Transgenic mouse AD models are frequently used to identify the molecular pathways leading to memory deterioration. Previous research has shown that AD-transgenic animals are more accessible to generate NFTs than nontransgenic animals (Chen *et al.*, 2013). Correspondingly, studies have shown that Aβ plaque development takes longer in regular animal models than in transgenic animals (Oliveira *et al.*, 2021). However, there are limitations in using transgenic animals. According to Salkovic-Petrisic *et al.* (2013), transgenic AD models are not appropriate for investigating the origin, onset, and progression of pathological deposition of Aβ production in the brain under challenging circumstances that are not associated with mutations in the Aβ precursor protein (APP) gene. Indeed, high glucose increased Aβ production by inhibiting APP protein degradation rather than increasing APP gene transcription (Yang *et al.*, 2013b). A new nontransgenic rat model has been proposed as a representative model of AD that uses streptozotocin (STZ) induction. STZ has a diabetogenic effect that induces irreversible pancreatic beta-cell damage through free radical generation and DNA damage (Ravelli *et al.*, 2017). It is well known that the toxic effects of STZ dosage and its physiochemical properties continue to present major challenges for researchers. Factors such as preparation technique, solution stability,

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delivery route, and suitable dosage must be considered before establishing a study (Radenković *et al.*, 2016). For instance, multiple low doses (MLDs) of STZ in rodents resulted in mild hyperglycemia similar to type 2 DM, whereas a single high dose of STZ resulted in severe hyperglycemia similar to type 1 DM (Ventura-Sobrevilla *et al.*, 2011).

Furthermore, studies have proven that STZ induction, either via intraperitoneal or intracerebroventricular induction, can induce neuroinflammation, leading to impaired brain insulin signaling and cognitive decline in experimental animals (Wang *et al.*, 2019). Indeed, injecting STZ directly into the lateral ventricles did not affect blood glucose levels (Zhang *et al.*, 2018), but it did alter the brain insulin signaling pathway, resulting in neuropathological and behavioral abnormalities (Grieb, 2016). Meanwhile, intraperitoneal injections of STZ may also compromise brain insulin signaling by attenuating phosphoinositide 3-kinase (PI3-K) signaling and increasing glycogen synthase kinase-3β (GSK-3β) activation, resulting in cognitive impairment in STZ-treated rats and possibly explaining early synaptic changes in sporadic AD (Ansari *et al.*, 2023). In conclusion, both techniques may result in loss of cognition and an increase in Aβ deposits, total tau protein, and aggregated amyloid fragments in the brain. Therefore, this review discusses the relevant mechanism of STZ in generating animal models of AD due to hyperglycemia. The two basic mechanisms underlying diabetes and AD that are the subjects of this review are brain insulin resistance and amyloidogenesis (H. J. Lee *et al.*, 2018).

Characteristics of streptozotocin and its diabetogenic mechanism

STZ or -deoxy-2-([(methylnitrosoamino)carbonyl] amino)-D-glucopyranose] is a naturally occurring compound isolated from the soil bacteria *Streptomyces achromogenes*. This glucosamine-nitrosourea compound was originally developed as an anticancer agent for treating certain cancers of the islets of Langerhans and as an antibiotic for gram-negative bacteria (Abdollahi and Hosseini, 2014). Since 1963, It has been used in medical research to induce diabetes in experimental animals. STZ has a glucose analog structure with the addition of N-acetyl glycosamine and is toxic to pancreatic beta cells (Grieb, 2016).

STZ penetrates the islet of Langerhans cells via glucose transporter 2 (GLUT2) in the plasma membrane and exerts pathological effects on the development of diabetes in animal models (Fig. 1). STZ spontaneously degrades upon entering cells to produce isocyanate and methyldiazohydroxide molecules. Isocyanate and methyldiazohydroxide compounds cause intramolecular carboxylation and alkylation of cellular components, respectively. The methyldiazohydroxide molecule disintegrates to form a highly reactive carbonium ion (CH3+) as the main key to deoxyribonucleic (DNA) alkylation (Goud *et al.*, 2015). Next, the poly ADP-ribose polymerase-1 (PARP-1) enzyme becomes active when there is damage to the DNA chain. Overstimulating the PARP-1 enzyme depletes nicotinamide adenine dinucleotide + (NAD+), thereby reducing the amount of adenosine triphosphate (ATP) produced (Pieper *et al.*, 1999). A lack of ATP impairs mitochondrial function, resulting in the inhibition of insulin synthesis and secretion. Ultimately, free radicals will develop, damaging pancreatic cells, and causing hyperglycemia (Eleazu *et al.*, 2013). In addition, like other nitrosourea, STZ acts as a potential nitric oxide (NO) radical donor under in vivo conditions, mediating the destruction of pancreatic beta cells through DNA damage (Goud *et al.*, 2015). Nitric oxide can increase guanyl silage activity and the formation of guanosine 3′,5′-cyclic monophosphate (cGMP), which produces reactive oxygen during cell damage. In conclusion, the release of NO, generation of reactive oxygen species (ROS), DNA alkylation, reduction in cell function, inhibition of glucosaminidase enzymes, reduction in insulin synthesis, and elevation of blood glucose levels are common effects of STZ (Šoltésová and Herichová, 2011).

Streptozotocin alters insulin signaling in the brain

Brain insulin resistance is defined as the incapability of brain cells to respond to insulin normally. According to a recent study, there is a direct link between brain insulin resistance and insulin deficiency in type 2 diabetes (De Sousa *et al.*, 2020). However, both type 1 and type 2 diabetes mellitus share the commonality of insulin dysregulation, which is likely to have an impact on the brain (Talbot *et al.*, 2012). Moreover, consuming a high-fat diet continuously can alter brain insulin signaling and cognitive dysfunction (Kothari *et al.*, 2017). In the normal brain, insulin signaling activates PI3-K through phosphorylation at threonine 308 (Thr308), leading to protein kinase B or Ak strain transforming (AKT) kinase pathway activation. The activation of the AKT pathway will phosphorylate GSK-3β at serine 9 (Ser9) and inactivate it (Kleinridders *et al.*, 2014). Meanwhile, it is well known that GSK-3β is a major tau kinase in the brain involved in the phosphorylation of tau at many hyperphosphorylation sites, including Ser199, Ser202, and Ser396 (Liu *et al.*, 2007). Therefore, if insulin dysfunction occurs in diabetic disorders, it will block the AKT pathway and activate GSK-3β which then promotes tau hyperphosphorylation and NFTs (Burillo *et al.*, 2021). Moreover, GSK-3β activation could potentially increase levels of Aβ and Aβ deposits in AD brains. Aβ accumulation can also induce tau protein phosphorylation and inactivate insulin receptor substrate-1 (IRS-1) substrate via c-Jun N-Terminal (JNT) Kinase signaling, disrupting insulin signaling (Ma *et al.*, 2009).

Intracerebroventricular injection of STZ causes central insulin resistance (IR) by disrupting IR signaling, decreasing expression of IR substrate type 1 (IRS-

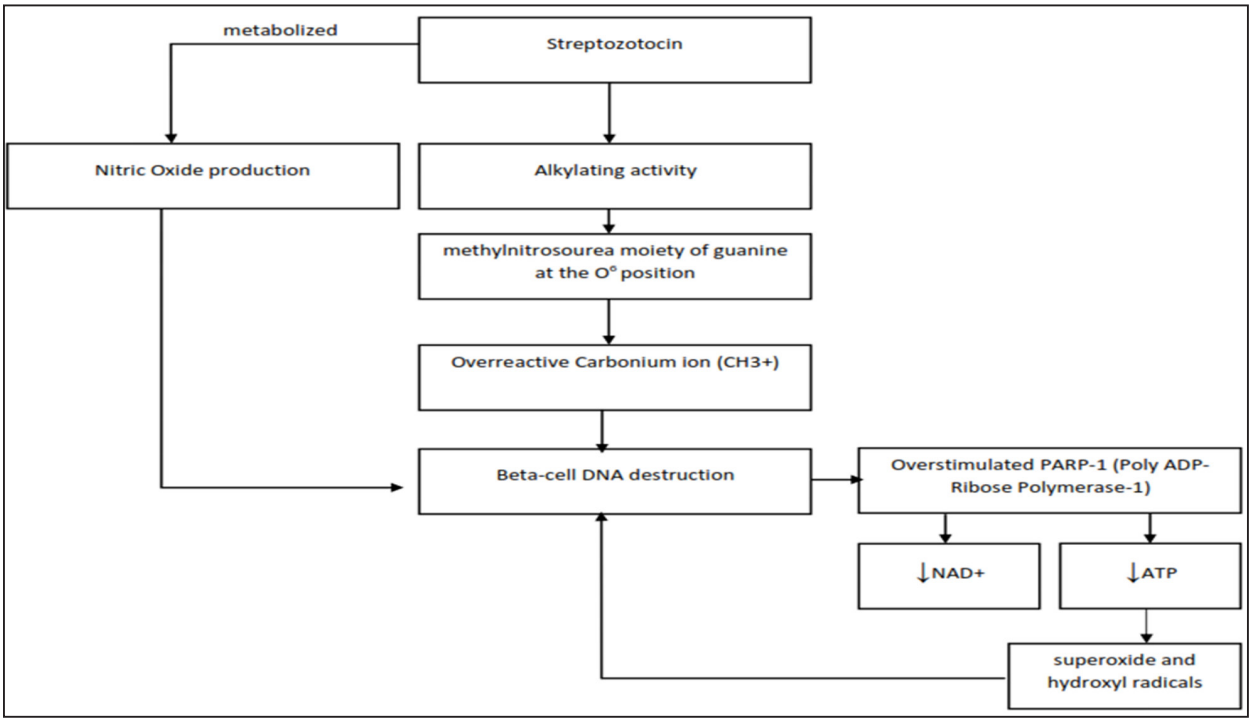

Figure 1. Streptozotocin pathomechanism in pancreatic beta cells. The DNA methylating activity of the methylnitrosourea moiety of STZ, particularly at the O6 position of guanine, causes DNA damage and necrosis in pancreatic beta cells. When the DNA of the cell is damaged, PARP-1 is activated, which causes a decrease in ATP and NAD+, resulting in the formation of free radicals and damaging pancreatic cells. NO, which is generated following the metabolism of STZ, is another potential pathway that has also been linked to cell death.

1), and increasing desensitization of IRs (Lester-Coll *et al.*, 2006). Furthermore, STZ injection via ICV, besides interfering with insulin signaling, can also increase GSK-3β activation and tau phosphorylation. Researchers have suspected that brain insulin resistance is closely related to decreased PI3K-AKT signaling activity and overactivation of GSK-3β (Deng *et al.*, 2009). On the other hand, IR using the intraperitoneal STZ injection method has also been widely reported by investigators (Yang *et al.*, 2013a). Grieb (2016) stated that peripheral administration of STZ does not directly harm IR signaling, but secondary causes, such as insulin deficiency leading to high blood glucose levels. Bathina *et al.* (2017) provided evidence to support this claim, stating that there was a correlation between elevated blood sugar levels and lower protein expression of pAKT/AKT, pmTOR/mTOR, pPI3K/PI3K, Foxo1 as a secondary messenger of insulin signaling and also GSK-3β in STZ intraperitoneal injection of male Wistar rats. The results indicate that STZ causes insulin signaling dysregulation via the PI3K pathway.

Streptozotocin-induced amyloid-β (Aβ) plaques and neurofibrillary tangles

It is well-established that STZ causes hyperglycemia and senile plaque formation. In a histological study, senile plaques, also known as Aβ plaque, consist of Aβ protein, degenerative neuronal processes, and reactive nonneuronal cells (Drummond and Wisniewski, 2017). In fact, Aβ plaques are extracellular structures consisting of a central core and a corona. The central core in the middle of the structure is composed of extracellular beta-pleated amyloid aggregation, which constructs the Aβ peptide. Meanwhile, the corona, which encircles the central core, comprises degenerating neurons (primarily axons) containing tau protein and ubiquitin (Serrano-Pozo *et al.*, 2011). Furthermore, Aβ peptide is a normal product of cellular metabolism generated from the proteolytic cleavage of a larger glycoprotein known as APP. Typically, APP is processed by enzymatic digestion α- and γ- secretase to form harmless peptide fragments in the non-amyloidogenic pathway, resulting in soluble Aβ (Chen *et al.*, 2017). This soluble protein can be transported from the brain to blood via the blood-brain barrier (BBB) via low-density lipoprotein receptor-related protein 1 (LRP1) to prevent Aβ peptide accumulation in the brain (Ramanathan *et al.*, 2015).

Moreover, hyperglycemia due to insulin deficiency can increase APP levels by reducing APP degradation and enhancing Aβ production (Yang *et al.*, 2013b). Moreover, APP can lead to mitochondrial dysfunction

and initiate stress signaling pathways (Reddy and Beal, 2008). In the diabetic brain, APP is processed via the amyloidogenic pathway. Amyloid plaques occur due to the accumulation of extracellular Aβ, derived from the enzymatic cleavage of APP through the β- and ɣ-secretase cleavage, which produces a 37–49 amino acid residue peptide. It then forms insoluble fibrous aggregates, causing amyloidosis and neurodegeneration (Murphy and Levine, 2010). In addition, two major isoforms of amyloid deposited in the AD brain are the 42-residue (Aβ42) as the main component and the 40-residue (Aβ40). Increased levels of Aβ42 or an increased ratio of Aβ42 induces Aβ fibril formations, and fibril accumulation develops into amyloid plaques, causing neurotoxicity through several mechanisms, such as the accumulation of free radicals, dysregulation of calcium homeostasis, inflammatory response, and activation of several signaling pathways pathway (Rajmohan and Reddy, 2017). Inflammatory cytokines such as interferon-γ (IFN-γ) induced microglial activation, which ultimately increases the production of inflammatory cytokines such as tumor necrosis factor-α (TNF-α). Furthermore, TNF-α will increase ROS levels and result in neuronal apoptosis. As brain-resident macrophages, microglia represent a therapeutic approach to coping with neuroinflammation (Sevenich, 2018).

Most amyloid hypothesis in AD studies postulates that overproduction of Aβ peptide, or failure to clear this peptide, causes amyloid deposition and accumulation, which is thought to be involved in the formation of NFTs leading to neuronal loss (Ma *et al.*, 2009). In 1963, previous research reported that the components of NFTs are two intertwined abnormal filaments called paired helical filaments (PHFs), between 15 and 32 mm in width, with a periodicity of around 80 nm. NFTs are formed by self-aggregates of hyperphosphorylated tau proteins. Tau protein was first discovered as a microtubule-associated protein (MAP) that stimulates tubulin assembly into microtubules, which localize primarily in the axon (Picone *et al.*, 2020). Under normal physiological conditions, tau protein stabilizes neuronal microtubules. However, in AD pathology, tau hyperphosphorylation causes microtubule disassembly, resulting in the generation of aberrant aggregates that are toxic to neurons, leading to synaptic dysfunction and cell death. This mechanism has been observed in several neurological conditions collectively referred to as tauopathies (Orr *et al.*, 2017).

Evidence from a previous animal study reveals that two weeks after ICV administration, STZ injection was potentially responsible for Aβ and neurofilament protein expression and NFTs. ICV-STZ injection promoted Aβ deposition in the brain, increasing the expression of p-tau protein and cleaved caspase-3, whereas

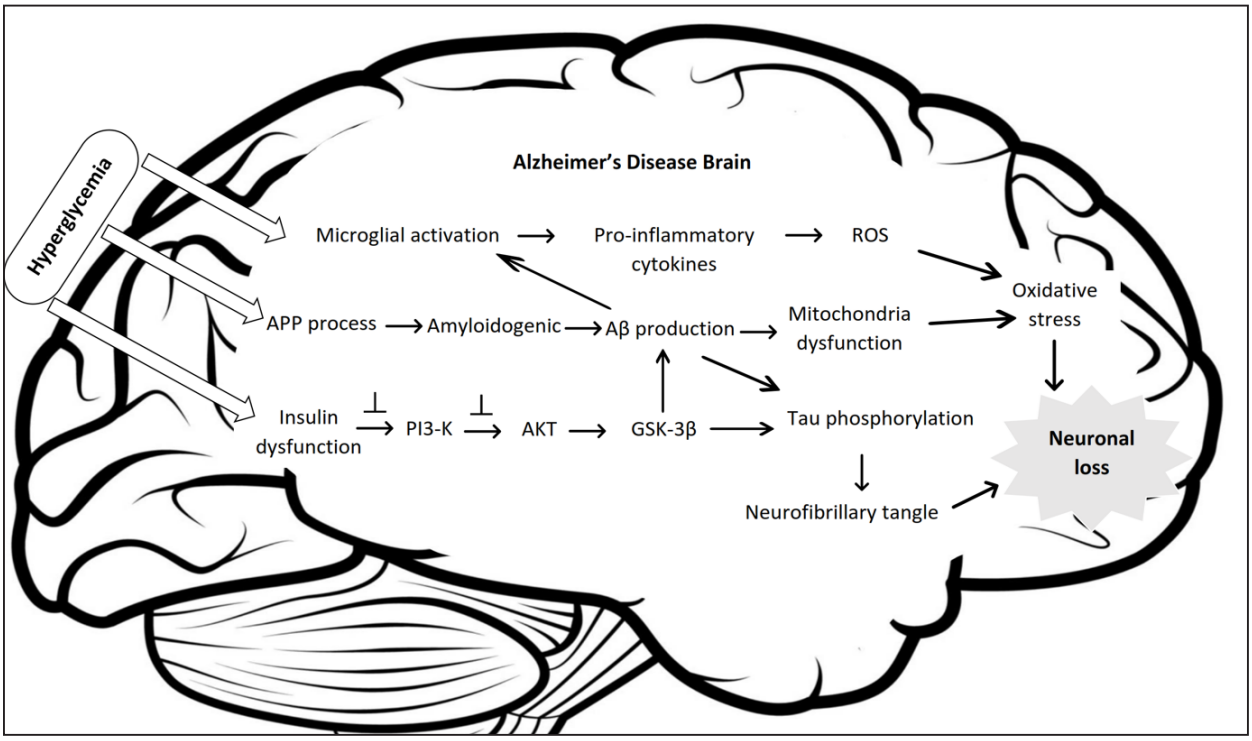

Figure 2. Summary of the impact of hyperglycemia after STZ injection in the animal brain. Hyperglycemia can affect macrophages and microglia as part of the innate immune system, increasing oxidative stress and inflammation, promoting amyloidogenic APP processing, and interrupting insulin receptors, causing insulin dysfunction.

p-PI3K, p-AKT, and p-GSK-3β protein expression was inhibited (Abdallah *et al.*, 2021). Another ICV STZ study revealed decreased IR mRNA expression and tau hyperphosphorylation at Ser396 predominantly in the hippocampus region (Gupta *et al.*, 2018). Previous studies have demonstrated that tau phosphorylation at Ser396 and Ser404 is crucial for impaired microtubule assembly, both of which are primarily responsible for tau-mediated tubulin polymerization functional loss (Evans *et al.*, 2000).

On the other hand, STZ injection via intraperitoneal elicited a different mechanism. Intraperitoneal injections of STZ significantly increase brain Aβ-42, β-secretase, and phosphorylated tau protein (Ali and Ali, 2022). Systemic injection of STZ cannot penetrate the BBB because of the lack of the STZ transporter GLUT2. Therefore, this method may influence brain metabolism indirectly because of high blood glucose levels, insulin deficiency, or other substances that may be toxic to the brain (Park, 2011). Systemic insulin deficiency in STZ-diabetic mice promotes reduced insulin-signaling pathway activity and increased GSK-3β activity in the brain (Jolivalt *et al.*, 2010). GSK-3β has been suggested to play a role in APP processing leading to Aβ formation (Lee *et al.*, 2003) and increased tau phosphorylation (Jope and Johnson, 2004).

Conclusion

Based on the presented discussion, Figure 2 shows the underlying mechanism of elevated blood glucose response following STZ injection. In addition, a few points that are worth noting in more detail are summarized below. First, STZ injection into the lateral ventricle of adult mice can impair glucose homeostasis and insulin signaling in the brain but not in the blood glucose body. Therefore, this method is not suitable for diabetes research to determine brain complications due to prolonged hyperglycemia. Second, the STZ effect discussed in this study is a general STZ effect, whereas different injection techniques exhibit distinct mechanisms. A single high dose directly damages pancreatic beta cells because of their cytotoxicity, causing extensive necrosis. In addition, MLDs induce limited apoptosis of pancreatic beta-cells, attracting mononuclear cells to eliminate the remaining cells (Cardinal *et al.*, 2001). According to Grieb (2016), a single high dose has been widely used as a short-term diabetic rodent model, while multiple low-dose models have been proposed as long-term diabetic rodent models. Meanwhile, long-term hyperglycemia is the primary physiopathology of diabetic encephalopathy (Tomás Díaz-Gerevini *et al.*, 2019). It is recommended to compare the mechanisms of each STZ approach in detail to construct an animal model of AD to aid investigators in conducting better investigations. Finally, the current study only examined two components contributing to hyperglycemia-induced AD. As a result, more research into other possible mechanisms should be undertaken to ensure comprehensive results.

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Conflict of interest

The authors declare that they have no conflicts of interest related to the publication of this manuscript.

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Authors' contributions

NT: conceptualization and writing of the original draft. HA: conceptualization, review, and editing. AF: review and editing. NS and ISAR: supervision. All authors have read, reviewed, and approved the final manuscript.

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