Free Radicals and Antioxidants., 2024; 14(1):32-33.
https://www.antiox.org

Correspondence

Rodent Models of Streptozotocin-Induced Diabetes as Suitable Paradigms for Studying Diabetic Kidney Disease

Haoxin Liu[1], Yucheng Wang[2], Ying Wang[2,*], Liang-Jun Yan[1,*]

[1]Department of Pharmaceutical Sciences, UNT System College of Pharmacy, University of North Texas Health Science Center, Fort Worth, Texas, USA.
[2]Institute of Medicinal Biotechnology, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, CHINA.

The purpose of this correspondence is to highlight the usefulness of Streptozotocin (STZ)-induced type 1 diabetes for studying Diabetic Kidney Disease (DKD) which is also known as diabetic nephropathy.[1] DKD is a major microvascular complication of diabetes regardless of type 1 or type 2 diabetes.[1] DKD is also a leading cause for the development of end stage renal failure.[1] The main features of DKD is thickening of the glomerular basement membrane caused by accumulation of matric glycoproteins and collagens, resulting in increased albumin secretion and a decreased glomerular filtration rate.[2,3] Abnormal structural changes such as mesangial expansion, podocyte cell death, and tubular interstitial fibrosis also contribute to glomerular hyperfiltration and proteinurea in DKD,[2,3] leading to decline in kidney function. Despite advanced knowledge garnered over the years on DKD pathogenesis and anti-DKD strategies, no effective treatments for DKD are presently available. Therefore, this unmet medical need will continue to drive intensive and vigorous researches to understand the underlying pathological mechanisms of DKD, in hopes to discover potential targets for DKD therapeutic purpose.

Animal models of DKD are indispensable tools for our understanding of DKD pathology and for testing the efficacy of numerous therapeutic approaches.[3] There are many rodent models of DKD, including genetically manipulated, diet-induced , chemical induced, or combination of each induction method such as High Fat Diet (HFD) feeding followed by intraperitoneal injection of Streptozotocin (STZ).[3] The creation of HFD-STZ rodent model is often time consuming for both studying DKD and evaluating the effectiveness of anti-DKD agents or compounds. Likewise, the use of genetically created animal models may also be a time consuming process if starting from scratch, and its use is usually not cost friendly and often incurs a large amount of spending for a given study period that necessitates long term testing. In terms of time saving and low cost spending, we think STZ induction of diabetes via intraperitoneal injection is a very suitable approach for studying DKD pathology and testing anti-DKD designs and strategies.[4]

STZ causes β cell death in the pancreas.[5] It enters into β cells via Glucose Transporter 2 (GLUT-2) and causes DNA damage,[6,7] leading to β cell death and decreased insulin secretion[5]. As such, blood glucose is elevated due to β cell dysfunction, leading to development of overt diabetes. It should be noted that STZ is a short-lived chemical once inside the body as it would be completely eliminated via the urinary system within 24 hr of injection.[5] Nonetheless, it has been established that STZ can also enter into nephrons via GLUT2 that is much less abundant in the kidney than in the pancreas.[8] This uptake of STZ by nephrons can cause acute kidney toxicity,[9] which can be either recovered quickly due to rapid elimination of STZ by the kidneys[10] or prevented by drugs such as p53 inhibitors or Sodium-Glucose Transporter 2 (SGLT2) inhibitors.[11] Thus it is often a good idea to conduct DKD-related experiments 21 days after STZ injection.[10] By this time no toxic effect of STZ on the kidney should remain and any dysfunctional changes in the nephrons can be attributed to diabetic hyperglycemia. Likewise, any beneficial effects of tested pharmaceutical drugs, compounds, antioxidants, or chemicals should be attributed to their anti-DKD properties instead of their possible anti-STZ toxicity capacities.

It should be pointed out that when STZ injection alone is used to create a DKD model, such a model should be considered that of type 1 diabetes[12] instead of type 2 diabetes[10] as STZ induction does not involve the initiation of insulin resistance. In contrast, HFD-feeding preceding STZ injection creates type 2 diabetes whereby HFD feeding induces insulin resistance followed by partial destruction of β cells by STZ[5] and insulin insufficiency due to β cell exhaustion by persistent hyperglycemia.[5] Moreover, the STZ animal model of DKD can allow for enough time for progression of DKD and testing of various anti-DKD strategies given that many animals can live beyond two years after STZ injection.[5]

It should also be noted that there is no standard protocol for STZ induction of diabetes in rodents. For rats, it is often one injection of STZ,[13] but the dosage of STZ may vary from investigator to investigator. For mice, some investigators prefer one injection with

DOI: 10.5530/fra.2024.1.5

a high dose of STZ while others prefer five or more consecutive injections with a low dose of STZ.[14-16] Nonetheless, for a given investigator or a laboratory the method of STZ treatment should remain the same so that experimental results can be readily reproducible.

In conclusion, streptozotocin-induced diabetes in rodents provides a robust approach for the study of diabetic kidney disease.

ACKNOWLEDGEMENT

L.J. Yan was supported in part by a grant from Diabetes Action Research and Education Foundation and by a Bridge grant (Grant number 2400071) from the University of North Texas Health Science center.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DKD: Diabetic kidney disease; **STZ:** Streptozotocin; **HFD:** High fat diet; **GLUT-2:** Glucose transporter 2; **SGLT2:** Sodium glucose transporter 2.

REFERENCES

1. Yan LJ. NADH/NAD(+) Redox Imbalance and Diabetic Kidney Disease. *Biomolecules*. 2021; 11(5)doi:10.3390/biom11050730
2. Lee SR, Lee HE, Yoo JY, *et al.* Nox4-SH3YL1 complex is involved in diabetic nephropathy. *iScience*. 2024;27(2):108868. doi:10.1016/j.isci.2024.108868
3. Giralt-Lopez A, Molina-Van den Bosch M, Vergara A, *et al.* Revisiting Experimental Models of Diabetic Nephropathy. *Int J Mol Sci*. 2020; 21(10)doi:10.3390/ijms21103587
4. Tesch GH, Allen TJ. Rodent models of streptozotocin-induced diabetic nephropathy. *Nephrology (Carlton)*. 2007;12(3):261-6. doi:10.1111/j.1440-1797.2007.00796.x
5. Wu J, Yan LJ. Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic beta cell glucotoxicity. *Diabetes Metab Syndr Obes*. 2015;8:181-8. doi:10.2147/DMSO.S82272
6. LeDoux SP, Woodley SE, Patton NJ, Wilson GL. Mechanisms of nitrosourea-induced beta-cell damage. Alterations in DNA. *Diabetes*. 1986;35(8):866-72. doi:10.2337/diab.35.8.866
7. Szkudelski T. The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiol Res*. 2001;50(6):537-46.
8. Bouwens L, Rooman I. Regulation of pancreatic beta-cell mass. *Physiol Rev*. 2005;85(4):1255-70. doi:10.1152/physrev.00025.2004
9. Norgaard SA, Sondergaard H, Sorensen DB, Galsgaard ED, Hess C, Sand FW. Optimising streptozotocin dosing to minimise renal toxicity and impairment of stomach emptying in male 129/Sv mice. *Lab Anim*. 2020;54(4):341-52. doi:10.1177/0023677219872224
10. Al-Qabbaa SM, Qaboli SI, Alshammari TK, *et al.* Sitagliptin Mitigates Diabetic Nephropathy in a Rat Model of Streptozotocin-Induced Type 2 Diabetes: Possible Role of PTP1B/JAK-STAT Pathway. *Int J Mol Sci*. 2023; 24(7)doi:10.3390/ijms24076532
11. Nakai K, Umehara M, Minamida A, *et al.* Streptozotocin induces renal proximal tubular injury through p53 signaling activation. *Sci Rep*. 2023;13(1):8705. doi:10.1038/s41598-023-35850-w
12. Alomari G, Al-Trad B, Hamdan S, *et al.* Alleviation of diabetic nephropathy by zinc oxide nanoparticles in streptozotocin-induced type 1 diabetes in rats. *IET Nanobiotechnol*. 2021;15(5):473-83. doi:10.1049/nbt2.12026
13. Wu J, Luo X, Yan LJ. Two dimensional blue native/SDS-PAGE to identify mitochondrial complex I subunits modified by 4-hydroxynonenal (HNE). Methods. *Frontiers in Physiology*. 2015-March-26 2015; 6doi: 10.3389/fphys.2015.00098
14. Zhou Q, Guo W, Jia Y, Xu J. Effect of 4-Phenylbutyric Acid and Tauroursodeoxycholic Acid on Magnesium and Calcium Metabolism in Streptozocin-Induced Type 1 Diabetic Mice. *Biol Trace Elem Res*. 2019;189(2):501-10. doi:10.1007/s12011-018-1494-8
15. Song L, Feng S, Yu H, Shi S. Dexmedetomidine Protects Against Kidney Fibrosis in Diabetic Mice by Targeting miR-101-3p-Mediated EndMT. *Dose Response*. 2022;20(1):15593258221083486. doi:10.1177/15593258221083486
16. Qi XY, Peng GC, Han QT, *et al.* Phthalides from the rhizome of Ligusticum chuanxiong Hort. attenuate diabetic nephropathy in mice. *J Ethnopharmacol*. 2024; 319(Pt 2):117247. doi:10.1016/j.jep.2023.117247

Correspondence:
Dr. Ying Wang, Ph.D.
Institute of Medicinal Biotechnology, Chinese Academy of Medical Science and Peking Union Medical College, Beijing-100050, CHINA
Email: wangying@imb.pumc.edu.cn

Dr. Liang-Jun Yan, Ph.D.
Department of Pharmaceutical Sciences, UNT System College of Pharmacy, University of North Texas Health Science Center, Fort worth, TX 76107, USA.
Email: liang-jun.yan@unthsc.edu

Received: 04-03-2024;
Revised: 02-04-2024;
Accepted: 26-04-2024.

Cite this article: Liu H, Wang Y, Wang Y, Yan LJ. Rodent Models of Streptozotocin-Induced Diabetes as Suitable Paradigms for Studying Diabetic Kidney Disease. Free Radicals and Antioxidants. 2024;14(1):32-3.