MEDICAL SCIENCE MONITOR

EDITORIAL

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 1102-1104
DOI: 10.12659/MSM.914340

Received: 2018.11.29
Accepted: 2018.12.04
Published: 2019.02.09

Anti-Diabetogenic Properties of Mineralocorticoid Receptor Antagonists: Implications for Enhanced Safety and Efficacy of Post-Transplantation Pharmacotherapies

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Yingzi Ming
ABCDEF George B. Stefano
ABCDEF Richard M. Kream
ABCDEF Quan Zhuang

Transplantation Center, Third Xiangya Hospital of Central South University, Engineering and Technology Research Center for Transplantation Medicine of National Ministry of Health, Changsha, Hunan, P.R. China

Corresponding Author: Yingzi Ming, e-mail: myz_china@aliyun.com
Source of support: Self financing

Widespread usage of the calcineurin inhibitors tacrolimus and cyclosporine A as post-transplantation immunosuppressive agents is fraught with severe nephrotoxic and diabetogenic side effects. More recently, tapering of calcineurin inhibitor-based immunotherapies with concurrent administration of the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus has been employed within pharmacological regimens designed to achieve better safety and efficacy for preservation of allograft kidney function. Collected preclinical data and recent clinical study, however, indicate that usage of calcineurin inhibitors and/or mTOR blockers as immunosuppressive agents promotes equivalent diabetogenic side effects. Based on a wealth of validating preclinical studies, we contend that the favorable metabolic effects of mineralocorticoid receptor antagonists, such as spironolactone, support their inclusion in novel immunosuppressive strategies to inhibit new onset type II diabetic symptoms in post-transplantation patient populations.

MeSH Keywords: Calcineurin • Diabetes • Metabolic • Mineralocorticoid Receptor • Mineralocorticoid Receptor Antagonists • Transplantation

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914340

969 — — 25

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Nephrotoxic and diabetogenic effects of the immunosuppressive calcineurin inhibitors (CNIs) tacrolimus and cyclosporine A following kidney transplantation has been well documented [1]. The diabetogenic effects of CNIs are compounded by maintenance steroid usage with resultant increases in insulin resistance and deposition of visceral adipose tissue [2,3]. Furthermore, post-transplantation usage of CNIs is functionally associated with reduction of insulin secretion by pancreatic β-cells [4]. Pharmacological tapering of CNI-based immunotherapies with concurrent administration of the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus has been evaluated within a variety of pharmacological regimens for preservation of allograft kidney function [5]. Consistent with previous clinical observations [6], a recent clinical study demonstrated that conversion of a cyclosporine A-based therapeutic regimen to employment of everolimus as the major immunosuppressive agent had little or no effect on post-transplantation development of new onset type 2 diabetes (T2D), or on the progression of pre-existing diabetic symptoms [5]. Additional studies have demonstrated toxic effects of mTOR inhibitors on pancreatic β-cell function with resultant decreases in insulin secretion [7]. Accordingly, there is a compelling need for further development of efficacious therapeutic strategies to inhibit new onset T2D in post-transplantation patient populations.

Mechanistic validation of clinical observations is provided by preclinical studies that demonstrate widespread constitutive expression of calcineurin linked to diverse pharmacological effects of CNIs in different tissues involved in regulation of glucose homeostasis, including pancreas, liver, skeletal muscle, adipocytes, brain, and gut [8]. Adipose tissue has been established as a focal point for development and persistence of T2D in humans. Severely impaired triglyceride assembly and storage within metabolically compromised adipocytes with resultant fatty acid efflux from adipose tissues is functionally linked to elevated concentrations of free fatty acid concentrations in the plasma [9–12]. Elevated plasma free fatty acids have been empirically shown to markedly diminish insulin sensitivity in several animal models. Accordingly, this clinical parameter has been established as a prime risk factor associated with the development and maintenance of T2D in human populations [13,14], and the therapeutic efficacy of major anti-T2D drugs is assessed by a co-ordinate reduction of both glucose and free fatty acids in the plasma [9,10]. A recent clinical study found that insulin resistance with resultant T2D symptomatology represents the major diabetogenic effect of tacrolimus administration in kidney transplant recipients [15]. Complementary preclinical studies have shown that tacrolimus and cyclosporin A functionally inhibit glucose uptake in cultured human adipocytes by reducing cell surface expression of insulin receptor-mediated glucose transporter type 4 (GLUT4) [16]. These data indicate that calcineurin is an important regulator of glucose transport in adipose tissues via trafficking and endocytosis of GLUT4 via insulin-mediated cellular processes and support clinical observations indicating diabetogenic effects of administered CNIs. It is also inferred that chronic usage of CNIs will engender spiraling periods of severe insulin resistance via free fatty acid release from metabolically compromised adipocytes.

In vivo studies employing genetically engineered knockout mice have demonstrated that functional upregulation of mTOR expression in adipose tissues is associated with favorable metabolic parameters including increased lean body mass, enhanced insulin sensitivity, and glucose tolerance [17]. Furthermore, upregulation of mTOR expression is associated with increased leptin production leading to reduction of food intake and upregulation of key regulatory genes PPARα and glycerol kinase (GK) in adipose tissues [17]. Preclinical studies utilizing cultured human adipocytes from diabetic patients have observed significant downregulation of the key regulatory transcription factor forkhead box protein O1 (FOXO1) that is functionally associated with impaired insulin signaling via significant reductions in insulin receptor and GLUT4 expression [18]. Importantly, downregulation of FOXO1 is associated with significant reductions in mTOR activity in insulin resistant human adipocytes, indicating that functionally linked FOXO1 and mTOR regulatory activities are critical for maintaining normal insulin responsiveness of human adipocytes. Importantly, these preclinical data indicate potential adverse metabolic effects of clinically administered mTOR inhibitors employed as immunosuppressive agents and support clinical observations that everolimus is ineffective in blocking post-transplantation development of new onset T2D [5,19].

Preclinical studies have demonstrated that aldosterone-mediated activation of the mineralocorticoid receptor (MR) is associated with nephrotoxic events via convergent enhancement of mTOR signaling pathways [20]. Accordingly, these data sets validate the clinical utility and efficacy of MR antagonists, notably spironolactone, as key pharmacological components of post-transplantation therapeutic regimens employing CNIs in combination with mTOR blockers. In contrast to mTOR blockers, however, MR receptor blockade promotes favorable cellular bioenergetics and metabolic integrity via enhanced brown adipose tissue (BAT) thermogenesis [21]. The authors contend that the observed shift in energy usage from lipogenesis to thermogenic heat dissipation indicates the potentially high therapeutic potential for MR antagonists for treatment of obesity-related pathophysiological conditions that include T2D and metabolic syndrome. Additionally, it has been demonstrated that MR negatively regulates brown remodeling of white adipose tissue through a modulation of autophagy, thereby providing a clinically compelling rationale for the use of MR antagonists to prevent the adverse metabolic consequences of adipocyte dysfunction [22]. Thus, it appears that

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

dysregulation of MRs in adipose tissue may represent a key mechanism in the development of obesity-related metabolic syndromes such as T2D, via induction of oxidative stress and mitochondrial dysfunction [23].

Conclusions

In conclusion, a recent clinical study indicated positive restorative effects of the MR antagonist spironolactone on impaired glomerular filtration rate and fibrosis in kidney transplantation patients previously treated with CNIs [24]. Unfortunately, the study did not include quantification of clinical parameters indicative of glucose homeostasis, but represents a starting point for further clinical studies designed to evaluate the therapeutic potential of traditionally employed as well as newer non-steroidal MR antagonists [25] as metabolically favorable immunosuppressive agents in combination with traditionally employed CNIs and/or mTOR blockers. We further contend that key diagnostic/prognostic measures of efficacious immunosuppressive regimens employing MR antagonists may include normative indices of adipocyte function, such as quantification of circulating and free fatty acids, and secreted adipokines such as leptin and adiponectin.

References:

1. Wissing KM, Abramowicz D, Weekers L et al: Prospective randomized study of conversion from tacrolimus to cyclosporine A to improve glucose metabolism in patients with posttransplant diabetes mellitus after renal transplantation. Am J Transplant, 2018; 18(7): 1726–34
2. Dong M, Parsaik AK, Eberhardt NL et al: Cellular and physiological mechanisms of new-onset diabetes mellitus after solid organ transplantation. Diabet Med, 2012; 29(7): e1–12
3. Yates CJ, Fourlanos S, Hjelmesaeth J et al: New-onset diabetes after kidney transplantation-changes and challenges. Am J Transplant, 2012; 12(4): 820–28
4. Rakel A, Karelis AD: New-onset diabetes after transplantation: Risk factors and clinical impact. Diabetes Metab, 2011; 37(1): 1–14
5. Sommerer C, Witzke O, Lehner F et al: Onset and progression of diabetes in kidney transplant patients receiving everolimus or cyclosporine therapy: An analysis of two randomized, multicenter trials. BMC Nephrol, 2018; 19(1): 237
6. Montero N, Pascual J: Immunosuppression and post-transplant hyperglycemia. Curr Diabetes Rev, 2015; 11(3): 144–54
7. Barlow AD, Nicholson ML, Herbert TP: Evidence for rapamycin toxicity in pancreatic beta-cells and a review of the underlying molecular mechanisms. Diabetes, 2013; 62(8): 2674–82
8. Chakkera HA, Kudva Y, Kaplan B: Calcineurin inhibitors: pharmacologic mechanisms impacting both insulin resistance and insulin secretion leading to glucose dysregulation and diabetes mellitus. Clin Pharmacol Ther, 2017; 101(1): 114–20
9. Cadoudal T, Blouin JM, Collinet M et al: Acute and selective regulation of glyceroneogenesis and cytosolic phosphoenolpyruvate carboxykinase in adipose tissue by thiazolidinediones in type 2 diabetes. Diabetologia, 2007; 50(3): 666–75
10. Cadoudal T, Leroyer S, Reis AF et al: Proposed involvement of adipocyte glyceroneogenesis and phosphoenolpyruvate carboxykinase in the metabolic syndrome. Biochimie, 2005; 87(1): 27–32
11. Beale EG, Hammer RE, Antoine B, Forest C: Disregulated glyceroneogenesis: PCK1 as a candidate diabetes and obesity gene. Trends Endocrinol Metab, 2004; 15(3): 129–35
12. Beale EG, Harvey BJ, Forest C: PCK1 and PCK2 as candidate diabetes and obesity genes. Cell Biochem Biophys, 2007; 48(2–3): 89–95
13. Bajaj M, Suraamornkul S, Kashyap S et al: Sustained reduction in plasma free fatty acid concentration improves insulin action without altering plasma adipocytokine levels in subjects with strong family history of type 2 diabetes. J Clin Endocrinol Metab, 2004; 89(9): 4649–55
14. Bajaj M, Suraamornkul S, Romanelli A et al: Effect of a sustained reduction in plasma free fatty acid concentration on intramuscular long-chain fatty Acyl-CoAs and insulin action in type 2 diabetic patients. Diabetes, 2005; 54(11): 3148–53
15. Chen QJ, Li J, Zuo SR et al: Tacrolimus decreases insulin sensitivity without reducing fasting insulin concentration: A 2-year follow-up study in kidney transplant recipients. Ren Fail, 2015; 37(4): 601–6
16. Fonseca A, Carvalho E, Eriksson JW, Pereira MJ: Calcineurin is an important factor involved in glucose uptake in human adipocytes. Mol Cell Biochem, 2018; 445(1–2): 157–68
17. Kang M, Liu X, Fu Y, Garvey TW: Improved systemic metabolism and adipocyte biology in miR-150 knockout mice. Metabolism, 2018; 83: 139–48
18. Rajan MR, Nyman E, Brannmark C et al: Inhibition of FOXO1 transcription factor in primary human adipocytes mimics the insulin-resistant state of type 2 diabetes. Biochem J, 2018; 475(10): 1807–20
19. Johnston O, Rose CL, Webster AC, Gill JS: Sirolimus is associated with new-onset diabetes in kidney transplant recipients. J Am Soc Nephrol, 2008; 19(7): 1411–18
20. Whaley-Connell AT, Habibi J, Nistala R et al: Mineralocorticoid receptor-dependent proximal tubule injury is mediated by a redox-sensitive mTOR/S6K1 pathway. Am J Nephrol, 2012; 35(1): 90–100
21. Thuzar M, Law WP, Dimeski G et al: Mineralocorticoid antagonism enhances brown adipose tissue function in humans: A randomized placebo-controlled cross-over study. Diabetes Obes Metab, 2018 [Epub ahead of print]
22. Armani A, Cinti F, Marzolla V et al: Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. FASEB J, 2014; 28(8): 3745–57
23. Lefranc C, Friederich-Persson M, Palacios-Ramirez R, Nguyen Dinh Cat A: Mitochondrial oxidative stress in obesity: Role of the mineralocorticoid receptor. J Endocrinol, 2018; 238(3): R143–59
24. Mortensen LA, Thiesson HC, Tougaard B et al: The effect of spironolactone on calcineurin inhibitor induced nephrotoxicity: A multicenter randomized, double-blind, clinical trial (the SPIREN trial). BMC Nephrol, 2018; 19: 105
25. Kolkhof P, Barfacker L: 30 years of the mineralocorticoid receptor: Mineralocorticoid receptor antagonists: 60 years of research and development. J Endocrinol, 2017; 234(1): T125–T40

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]