Side Effects Of CNIs

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The Many Faces of Calcineurin Inhibitor Toxicity – What the FK?

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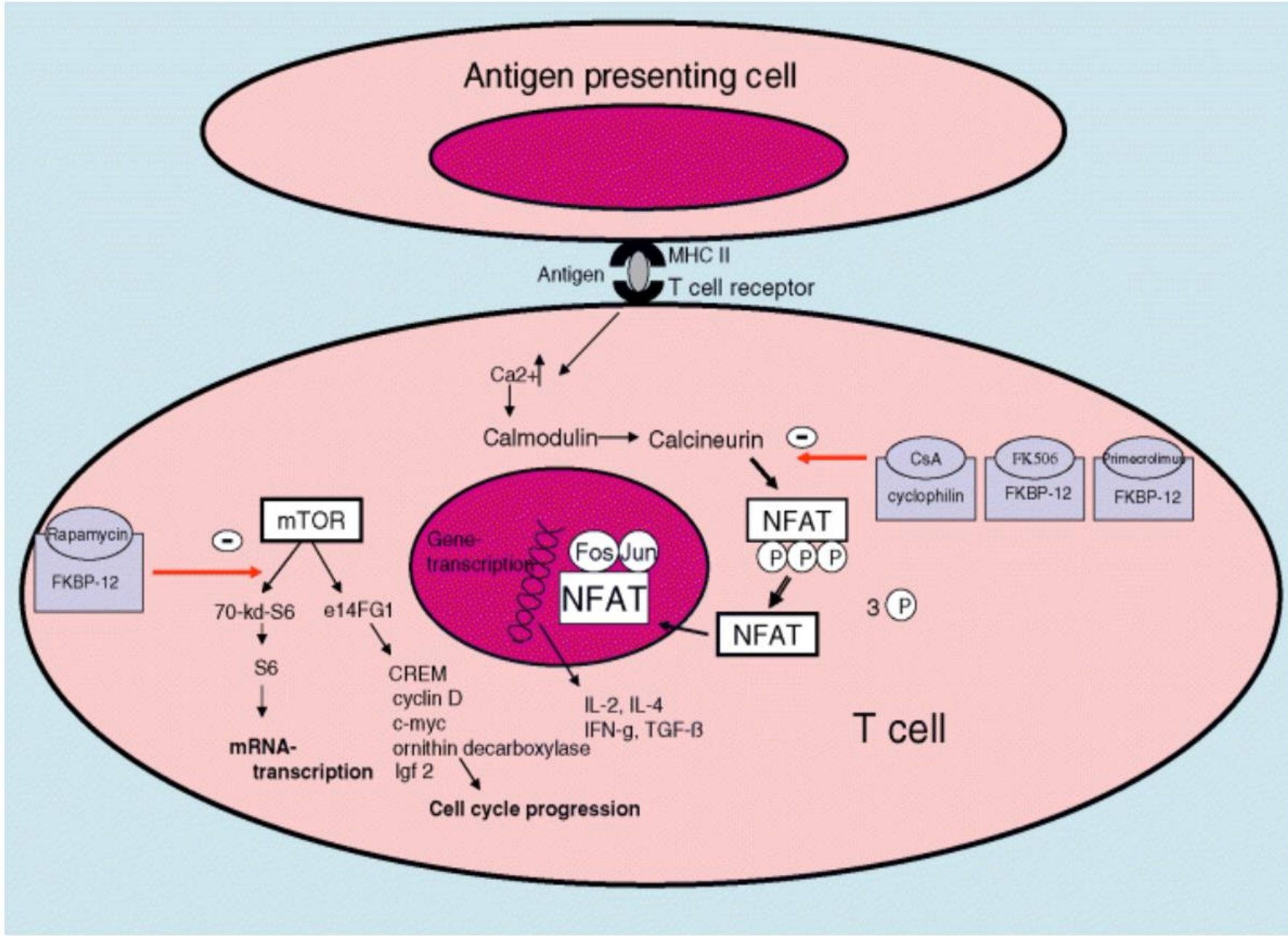
Adv Chronic Kidney Dis. 2020 January ; 27(1): 56–66. doi:10.1053/j.ackd.2019.08.006

- ✓Calcineurin inhibitors (CNIs) have been the **backbone of solid organ transplant immunosuppression** for several decades, with over 90% of kidney transplant recipients maintained on CNI containing immunosuppression regimens in 2017 .
- ✓
- ✓Their use has been described as a significant contributing factor in **acute** and **chronic allograft injury** and ultimately allograft loss .

- ✓Virtually **universal presence of CNI nephrotoxicity** on allograft biopsy by **10 years** after kidney transplant.


Antigen presenting cell
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FKBP-12
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Rapamycin
FKBP-12
mTOR
70-kd-S6
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Fos
Jun
NFAT
NFAT
P P P
3 P
CREM
cyclin D
c-myc
ornithin decarboxylase
Igf 2
Cell cycle progression
IL-2, IL-4
IFN-g, TGF-ß
T cell

Pharmacokinetics

- ✓CsA and FK can be administered orally (PO), sublingually (SL), or intravenously (IV)
- ✓PO CNIs have **variable intrapatient oral bioavailability**, with **area-under-the-curves** fluctuating **up to 50%** based on **formulation**, **timing**, and **concomitant administration with food.**
- ✓CNIs are **highly plasma protein bound**, **lipophilic drugs with a large volume of distribution**.

- ✓Metabolism is predominantly **hepatically** mediated via the cytochrome **P450 enzyme system (CYP3A).**

- metabolites are then **excreted in the bile** with an elimination half-life ranging from **10–48 hours**.

- The **therapeutic effects of FK are prolonged** relative to CsA owing to a **highly active metabolite with equal immunosuppressive potency** to the parent drug.

- **CsA metabolites have only 10–20% of parent drug activity.**

- **Polymorphisms resulting in CYP3A5 loss of function** may also significantly influence drug metabolism and exposure, and lead to **higher incidence of CNI-related nephrotoxicity**.1

- **Polymorphisms in ABCB1** which encodes the **efflux transporter P-glycoprotein present in enterocytes, hepatocytes, and kidney cells** may influence oral bioavailability and drug clearance as well as CNI concentrations in kidney tubular epithelial cells.

- ✓Though the **current mainstay of pharmacokinetic monitoring is 12** hour trough level measurement **(C0) of CsA and FK**, studies have shown poor **correlation with the 0 – 12 hour area-under-the-curve (AUC).**

Nephrotoxicity

- ✓**Acute Nephrotoxicity**
- ✓Acute nephrotoxicity can occur **at any time post-transplantation** and **at any level of drug exposure**,
- ✓**most commonly** observed in patients with **supratherapeutic trough** levels

- ✓Acute toxicity is of particular concern **immediately after transplantation** as **CNI-induced vasoconstriction** can cause delayed-graft function (**DGF)** post kidney transplant or **primary nonfunction** and c**an impair recovery from AKI of other etiologies.**

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- ✓Acute CNI toxicity often presents with **an increase in plasma creatinine** concentration due to **acute afferent arteriole vasoconstriction**.
- ✓**Vasoconstriction and increased allograft vascular resistance** may occur **prior to clinically** evident nephrotoxicity.

- ✓The mechanism is likely due to significant **impairment of endothelial cell** function resulting from **decreased production of vasodilating prostaglandin E2** and **nitric oxide .**

- ✓and **increased production of thromboxane and endothelin** in the afferent arterioles.
- ✓This leads to an acute reduction in renal blood flow (RBF), which is **reversible** after CNI dose reduction or drug cessation.

- ✓CNIs are also associated with the acute development of de novo thrombotic microangiopathy **(TMA).**

- ✓The mechanism ,likely involves **CNI-induced vascular endothelial cell injury,** and the risk increases with **concomitant use of mTOR** inhibitors.

- ✓**CNI toxicity** may be more pronounced in the setting of
- ✓**volume depletion** and
- ✓ **diuretic use**,
- ✓**older donor** age,
- ✓**high doses of CSA or FK**
- ✓**concomitant use of nephrotoxic** drugs especially NSAIDs
- ✓concomitant use of **CYP3A4/5 or P-glycoprotein inhibitors**,
- ✓ patients with **genetic polymorphisms** leading to altered CYP3A4/5 and P-glycoprotein function.

- ✓**genetic testing** for polymorphisms in the **CYP3A4/5** or **ABCB1 genes** may **aid in CNI dosing** and prognostication for patients likely to have high CNI peak exposures.
- ✓There is some evidence in animals and in vitro that **decreased P-glycoprotein expression may contribute to increased renal CsA levels**, leading to nephrotoxicity.

Clin Pharmacol Ther. 2003 Sep;74(3):245-54. doi: 10.1016/S0009-9236(03)00168-1.

Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus

Dennis A Hesselink [1], Ron H N van Schaik, Ilse P van der Heiden, Marloes van der Werf, Peter J H Smak Gregoor, Jan Lindemans, Willem Weimar, Teun van Gelder

Affiliations + expand

PMID: 12966368 DOI: 10.1016/S0009-9236(03)00168-1

Abstract

Background: therapeutic in
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enzymes cyto
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Ktx Recipients receiving Cyclospoeine =110
Tacrolimus=64
Genotyped for CYP3A4*B, *3, MDR-1C345T

Objective: Our objective was to determine the role of genetic polymorphisms in CYP3A4, CYP3A5, and MDR-1 with respect to interindividual variability in cyclosporine and tacrolimus pharmacokinetics.

Methods: Kidney transplant recipients receiving cyclosporine (n = 110) or tacrolimus (n = 64) were genotyped for CYP3A4*1B and *3, CYP3A5*3 and *6, and MDR-1 C3435T. Dose-adjusted trough levels

Background: The calcineurin inhibitors cyclosporine (INN, cyclosporin) and tacrolimus have a narrow therapeutic index and show considerable interindividual variability in their pharmacokinetics. The low oral bioavailability of calcineurin inhibitors is thought to result from the actions of the metabolizing enzymes cytochrome P450 (CYP) 3A4 and CYP3A5 and the multidrug efflux pump P-glycoprotein, encoded by MDR-1.

Objective: Our objective was to determine the role of genetic polymorphisms in CYP3A4, CYP3A5, and MDR-1 with respect to interindividual variability in cyclosporine and tacrolimus pharmacokinetics.

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C3435T polymorphism in tacrolimus dose requirement. None of the polymorphisms studied correlated with cyclosporine dose-adjusted predose concentrations.

Conclusion : CYP 3A5*3/*3require less Tacrolimus compared with CYP3A5*1

CYP3A4*1B requires more tacrolimus compared with CYP3A4*1 homozygotes.

Conclusion: As a group, patients with the CYP3A5*3/*3 genotype require less tacrolimus to reach target predose concentrations compared with CYP3A5*1 allele carriers, whereas CYP3A4*1B carriers require more tacrolimus to reach target trough concentrations compared with CYP3A4*1 homozygotes.

- **Diarrhea** can produce **variable effects** on CNI levels depending on the **etiology.**

- **Infectious diarrhea** can **increase CNI levels** due to **impaired activity** of **intestinal CYP3A** and **decreased drug efflux by intestinal P-glycoprotein**.

- **Osmotic diarrhea** can **decrease intestinal CNI absorption** resulting in reduced drug levels.

- ✓Symptoms of **PO CNI overdose** are generally **mild** and may include **confusion, hypertension, somnolence, nausea, and headache**

- ✓**IV overdose** is associated with **increased morbidity** and led to one death
- ✓due to **cerebral edema** in a retrospective analysis of CNI overdoses reported to a Swiss poison center.

- ✓The management of acute nephrotoxicity in the setting of CNI overdose is generally **supportive** and resolves with a **reduction in CNI dose**.

- ✓**Highly protein bound** CNIs are **not effectively** cleared with **extracorporeal treatment** modalities.

- ✓**Inducers of the p450 system** have been occasionally used to **lower toxic CNI levels.**
- ✓However, **evidence is limited to several case reports** that describe the use of **phenytoin or phenobarbital**, while use of rifampin or carbamazepine have not been reported.

- ✓Additionally, **enzyme induction is not immediate** and is typically **delayed until at least 48–72 hours** after initiation of the medication inducer raising concerns for timing and the potential efficacy of this strategy.

- ✓With increasing use of **recreational and medicinal cannabis** worldwide, including **cannabidiol (CBD)**, potential interactions with CNI metabolism are of interest as **CBD inhibits CYP3A4**.

- ✓A case report of a woman taking **FK for interstitial nephritis** while enrolled in a **high dose purified CBD** clinical trial of up to almost 3 grams daily, demonstrated a **3-fold increase in dose normalized FK serum concentration.**

Chronic Nephrotoxicity

- ✓CKD and ESRD can result from chronic CNI exposure in many solid organ transplant recipients.
- ✓Chronic CNI nephrotoxicity commonly presents as an **irreversible**, **progressive decline in allograft function**

- ✓from a combination of **chronic hemodynamic effects**
- ✓ **direct tubular effects**.

- It is **difficult to clinically and histologically distinguish** CNI-induced nephrotoxicity from chronic allograft nephropathy
- **Key kidney biopsy findings** in chronic CNI toxicity include
- **obliterative arteriolopathy**
- **hyalinization of the afferent arteriole**,
- **ischemic collapse or glomerular scarring**,
- **tubule vacuolization**,
- **focal and global segmental glomerulosclerosis**,
- **focal interstitial fibrosis associated with macrophage influx**,
- and **tubular atrophy often referred to as striped fibrosis**.

- ✓Several potential therapies have been considered in an attempt to prevent or reverse the cascade of effects resulting from CNI-induced arteriolar vasoconstriction
- ✓**Calcium channel blockers** (CCBs) are generally considered first-line antihypertensives **immediately following kidney transplantation** and may be beneficial in **combating the vasoconstrictive effects** of CNIs.

- ✓ Clinical studies have **not shown superiority in blood pressure lowering or preservation of kidney function** over other anti-hypertensive agents.

- ✓**RAAS blockade attenuates CSA induced interstitial fibrosis** and **arteriolopathy** in rats.
- ✓ Among kidney transplant recipients, **ARBs decrease circulating plasma levels of TGFβ**, a cytokine which plays a central role in causing CNI-induced interstitial fibrosis
- ✓However, a recent meta-analysis has shown inadequate evidence to determine if RAAS blockade improves clinical outcomes in kidney transplant recipients.

Urinary Biomarkers of CNI Toxicity

- ✓**Urinary biomarkers** show promise in **detecting CNI-induced nephrotoxicity** although their use remains in pre-clinical stages.

- ✓In rats treated with **CSA for 3 weeks**, increased **urinary KIM-1, TNF-α, fibronectin**, and **microalbuminuria** indicated **acute CsA nephrotoxicity**.

- ✓ A **delayed increase** in **urinary osteopontin and TGF-β** indicated **chronic CsA nephrotoxicity.**

- Though treatment options for now are limited to minimizing CNI exposure at the risk of suboptimal immunosuppression, **conversion to belatacept** has been shown to stabilize eGFR in patients with **chronic CNI nephrotoxicity**.

Calcineurin Inhibitors: A Double-Edge Sword

Adaku Ume[1], Tara-Yesomi Wenegieme[1], Clintoria R. Williams[1]

[1]Wright State University, Department of Neuroscience Cell Biology and Physiology, Boonshoft School of Medicine, College of Science and Mathematics

- ✓calcineurin (CnA) activity has identified distinct actions of two main ubiquitously expressed isoforms: **CnAα** and **CnAβ**.
- ✓In the kidney, **CnAα is required for development.**
- ✓ **CnAβ predominantly modulates the immune response** and glomerular hypertrophic signaling powered by activation
- ✓ of the transcription factor, (NFAT).

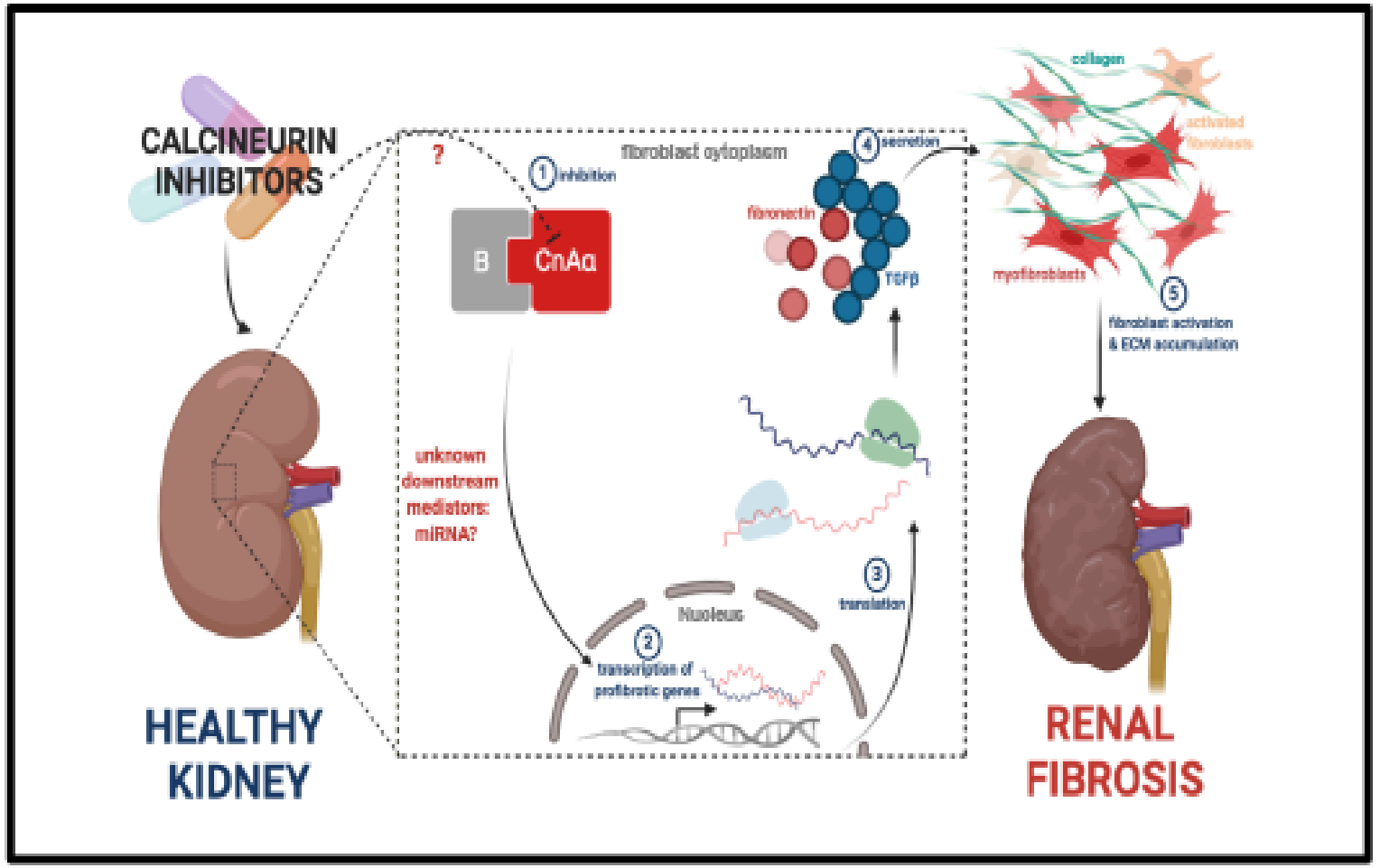
Am J Physiol renal Physiol.2021 Mar 1; 320(3): F336–F341..

- ✓data has shown that a **loss of CnAα activity** contributes to the
- ✓expression of **profibrotic proteins** in the kidney.

- ✓Transforming Growth factor-β **(TGF-β**) is known to be a major contributor to this fibroproliferative disease.

- ✓CNIs have also been reported to increase in vitro and in vivo **TGF-β**
- ✓**expression** and **receptor activity** in experimental models.

Calcineurin inhibitor (CNI)-induced nephropathy may be isoform-specific



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J Am Soc Nephrol. 2016 Jan; 27(1): 107–119.
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PMCID: PMC4696563
PMID: 25967121

Calcineurin and Sorting-Related Receptor with A-Type Repeats Interact to Regulate the Renal Na^+-K^+-$2Cl^-$ Cotransporter

Aljona Borschewski,[*] Nina Himmerkus,[†] Christin Boldt,[*] Katharina I. Blankenstein,[*] James A. McCormick,[‡] Rebecca Lazelle,[‡] Thomas E. Willnow,[§] Vera Jankowski,[‖] Allein Plain,[†] Markus Bleich,[†] David H. Ellison,[‡] Sebastian Bachmann,[*] and Kerim Mutig[*]

- ✓ Borschewski and colleagues demonstrated that loss of CnAβ activity increases the **abundance and activity** of the (**NKCC2**) in rats.

  NKCC2 overactivity is known to promote electrolyte (and water) retention, leading to hypertension.

Electrolyte disorders

- **Hyperkalemia**
- **Hypertension may be more common with CsA**,
- **Hyperkalemia may be more common with FK**.
- Hyperkalemia is **common early post-transplant** due to **DGF,**
- **trimethoprim**
- **higher serum CNI levels**

- Reported **incidence** ranging from **25 to 44%** in kidney transplant recipients on calcineurin inhibitors[CNIs].[1]

- Simultaneous **kidney-pancreas transplant recipients with bladder**
- **drainage** are reported to have more frequent hyperkalemia, with
- one study reporting an incidence of **73%**.[2]

1. Int J Organ Transplant Med. (2012) 3:166–75.
2. Transplantation (1996) 62:1174–5.

Electrolyte disorders

- **Hyperkalemia**
- CNI-induced hyperkalemia has been attributed to **volume expansion** induced **pseudohypoaldosteronism**, with suppression of the renin-angiotensin-aldosterone system.

- In **distal convoluted tubular epithelial cells**, **calcineurin** functions to **activate kelch-like 3 (KLHL3**), a component of the E3 ubiquitin ligase complex, which **targets WNK1 and WNK4 for degradation**.

- In mice, **FK prevented KLHL3 activation** and therefore **unregulated WNK1 and WNK4-**SPS1-related proline/alanine-rick kinase **(SPAK**) mediated **activation of NCC**, contributing to **salt-sensitive hypertension**.

- **Loss of KLHL3** in the collecting duct **increases paracellular chloride** conductance through interactions with claudin-8 to recapitulate Gordon's syndrome.

- CNI-induced hyperkalemia is commonly associated with **hypertension, hyperchloremic metabolic acidosis, and hypercalciuria,** a similar **phenotype to Gordon's syndrome** or familial hyperkalemia and hypertension (**FHHt**).
- **Case series** have reported a **prevalence of CNI-induced Gordon's** phenotype in between **10–33%** of kidney transplant recipients treated with CNIs.

- Although **clinical evidence is lacking**, mechanistic studies suggest that CNI-induced hyperkalemia should be **treated with alkali salts** and **thiazide diuretics.**

- In a **small retrospective** study of OLT recipients**, fludrocortisone** decreased serum potassium **without effect** on serum **creatinine, systolic blood pressure, or diastolic blood pressure over 14 days**

Electrolyte and Acid-Base Disorders in the Renal Transplant Recipient

*Vaishnavi Pochineni and Helbert Rondon-Berrios**

Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States

- ✓ Inhibition of calcineurin allows for the phosphorylation of these kinases which **activate NCC** increasing sodium chloride reabsorption in the distal convoluted tubule.

Tacrolimus and cyclosporine, by inhibiting calcineurin, **decrease the expression of the mineralocorticoid receptor.**

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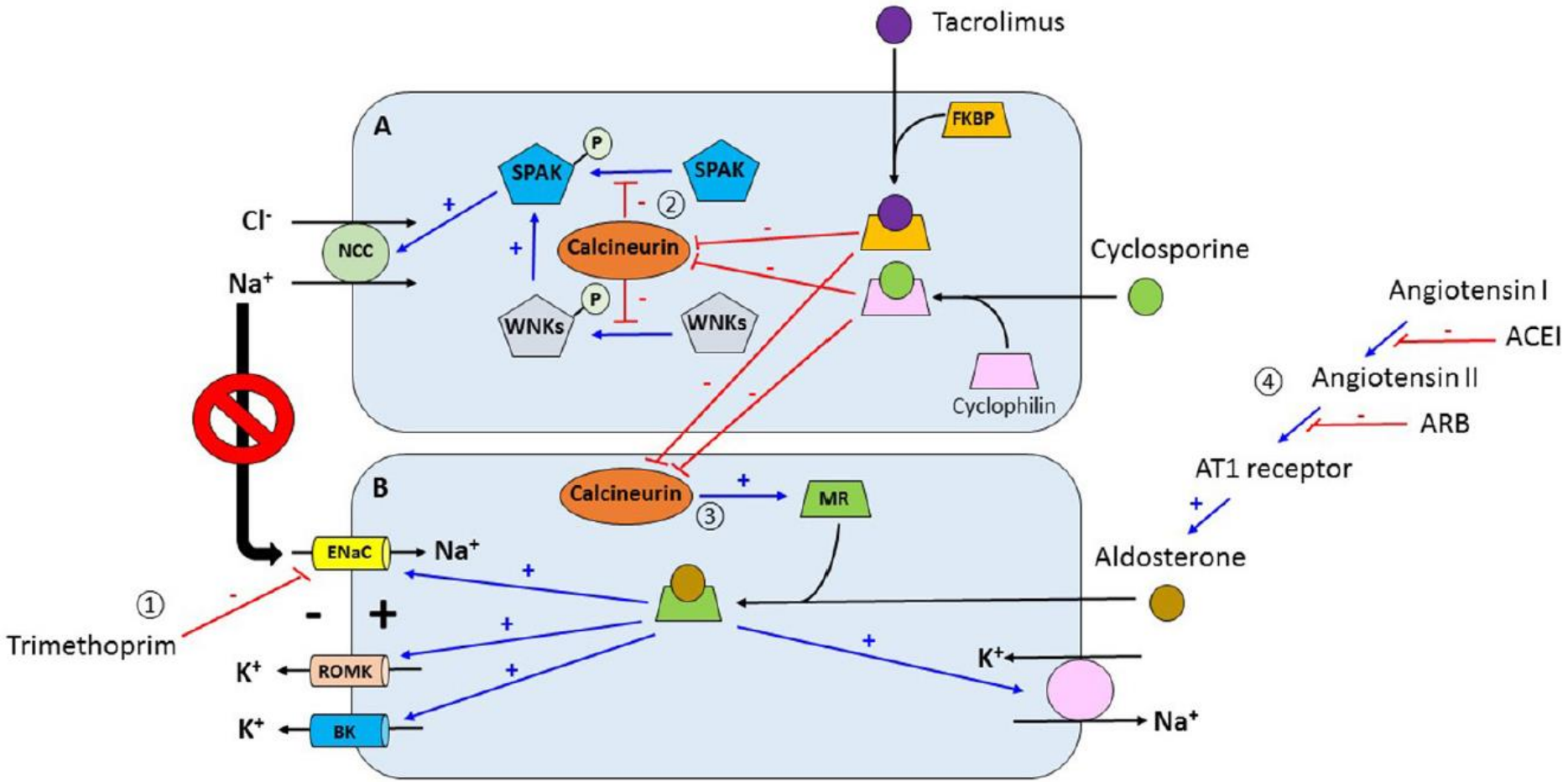


Front. Med. 5:261. doi: 10.3389/fmed.2018.00261

Metabolic Acidosis

- **Chronic metabolic acidosis** is associated with **increased risk of**
- **graft loss**,
- **death-censored graft failure**,
- **mortality**
- Among kidney transplant recipients and this may potentially be exacerbated by concomitant CNI therapy.
- Acidosis may be due **to impaired tubular acid secretion** from either a direct effect of **hyperkalemia** , **CNI-induced effects**, or **low aldosterone levels**.

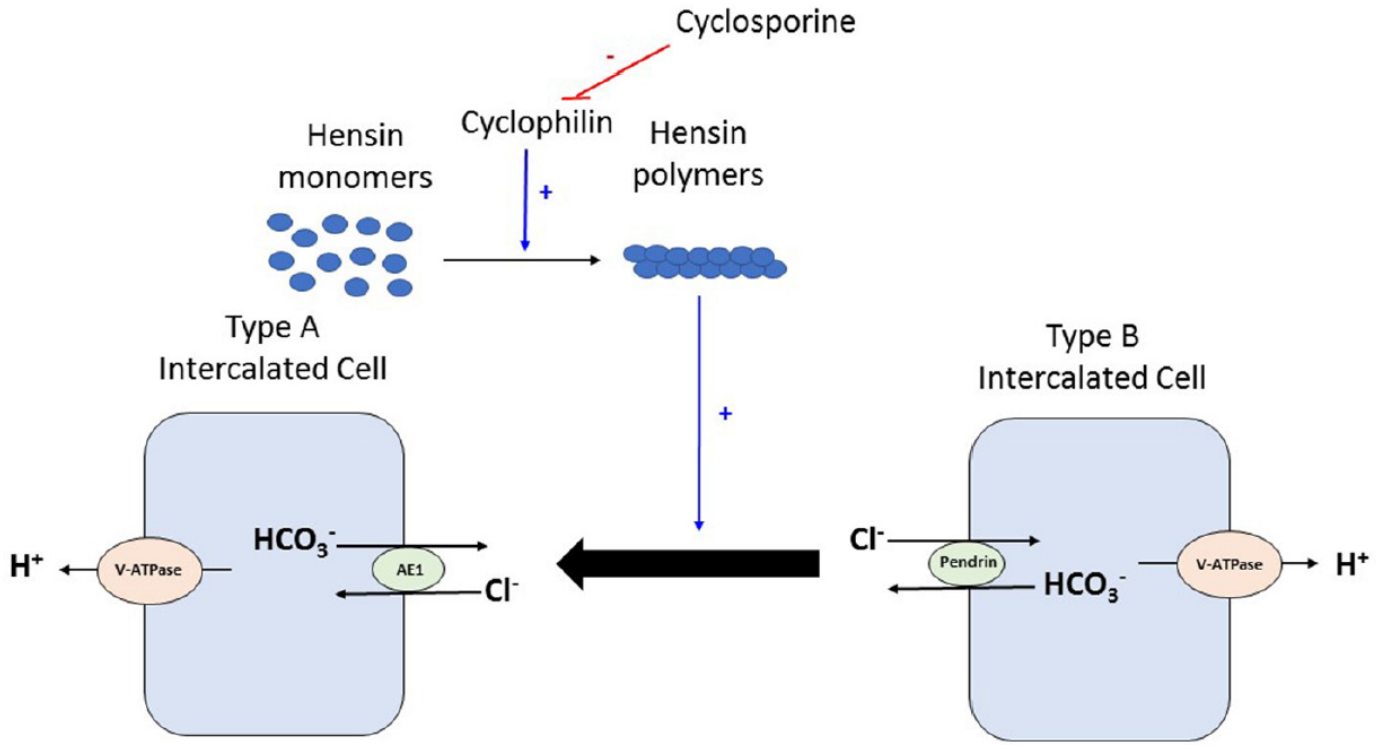


FIGURE 2 | During times of acid load, type B intercalated cell converts to type Aintercalated cell to facilitate proton excretion. This process requires deposition of polymers of a protein called Hensin in the extracellular matrix. Cyclophilins are enzymes that assist in protein folding/oligomerization and are needed for polymerisation and deposition of Hensin. Cyclosporine by binding to and inhibiting the enzymatic activity of cyclophilin, prevents this adaptation of the intercalated cell from the bicarbonate secreting beta form to the acid secreting alpha form. V-ATPase, vacuolar type proton ATPase; AE, Anion exchanger 1.

Watanabe S, et al. Cyclosporin A produces distal renal tubular acidosis by blocking peptidyl prolyl cis-trans isomerase activity of cyclophilin. Am J Physiol Renal Physiol. (2005) 288:F40–7.

- ✓**Alkali therapy prolongs survival and kidney outcomes among patients with CKD.**

- ✓However, the **benefits of sodium bicarbonate among kidney transplant recipients remains unknown**.

- ✓An **ongoing multi-center, randomized placebo-controlled trial** aims to test if sodium bicarbonate treatment will preserve kidney graft function and decrease kidney function decline following transplantation.

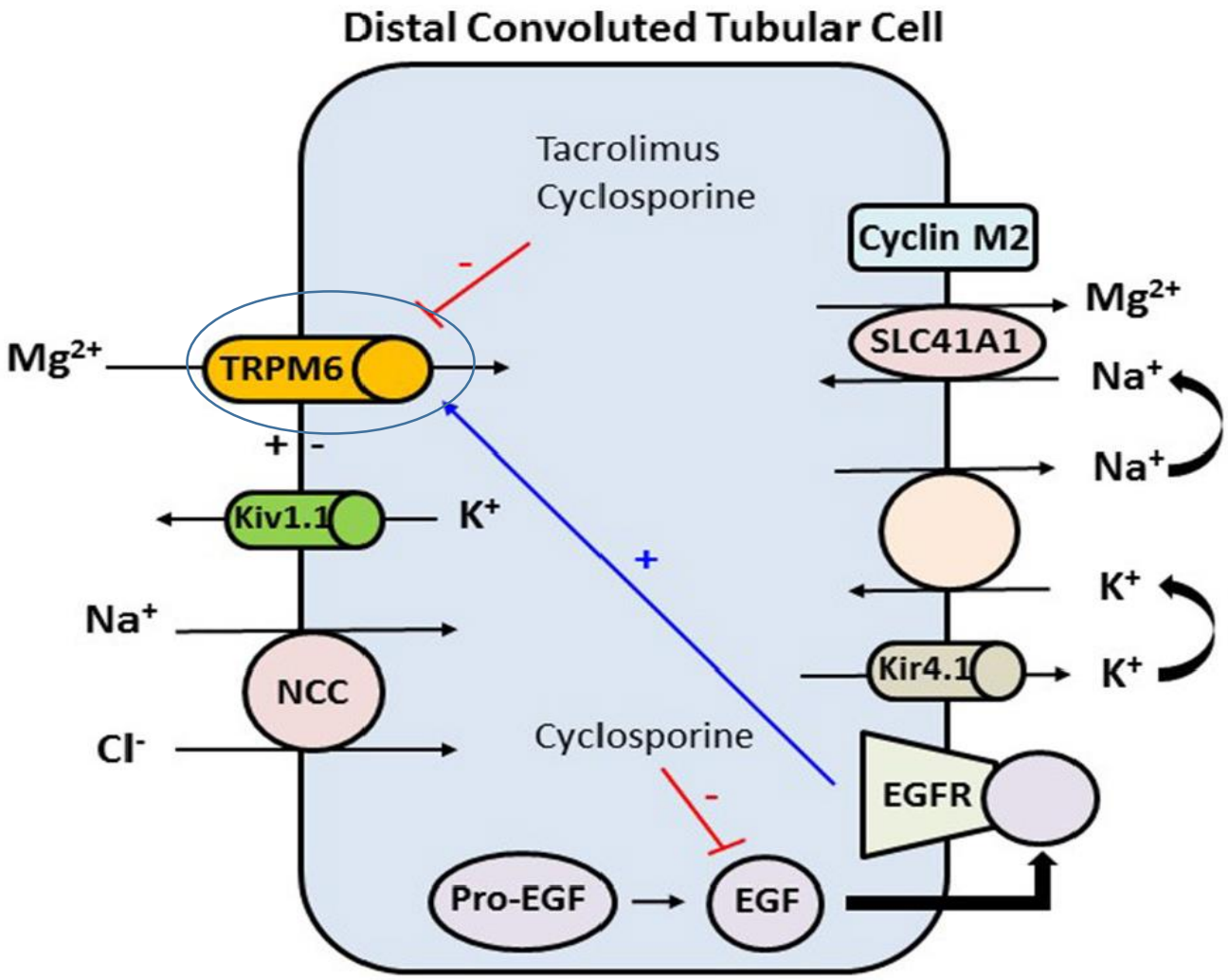
Hypercalciuria

- **Hypercalciuria is common** among kidney transplant recipients treated with **CNIs**, and CNIs have in turn been shown to cause hypercalciuria in animal models.
- CNIs also cause **hypocitraturia**, **increasing the risk of developing urolithiasis or nephrocalcinosis.**
- CsA has been shown to **impair kidney calcium reabsorption** through **reduced TRPV5 expression** in mice,and induce **high turnover bone disease.**

- **Thiazides reverse CNI-induced Gordon's phenotype** and are also commonly used to **reduce hypercalciuria** and prevent recurrent calcium nephrolithiasis in native kidneys.
- However, **no studies** have directly studied the **efficacy of alkali** therapy or **thiazides** to reduce the risk of calcium stone formation in kidney transplant recipients.

Hypomagnesemia

- **Hypomagnesemia is also common** among kidney transplant recipients treated with **CNIs** .
- **Hypomagnesemia** is associated with an increased risk of new onset diabetes after transplantation **(NODAT**) ,**cardiovascular morbidity.**
- CNIs cause renal magnesium wasting due to **impaired tubular reabsorption through TRPM6**.
- Clinical management of CNI-induced hypomagnesemia generally consists of **exogenous supplementation** to replete deficits and raise the serum magnesium level
- Magnesium supplementation was even demonstrated to **attenuate CsA-induced kidney interstitial fibrosis and tubular atrophy** in a rat model.



J Am Soc Nephrol. (2004) 15:549–57
Nephrol DialTransplant. (2014) 29:1097–102

✓In renal transplant recipients, **hypomagnesemia** is reported with **high prevalence** with the lowest serum magnesium concentration noticed around **second month** post transplantation.[1]

✓The incidence of **hypomagnesemia** and that of post-transplant diabetes (previously referred as NODAT)is reported to be **higher** among patients **using tacrolimus** than those on cyclosporine.[2]

1. Transplant Rev. (2015) 29:154–60.
2. Transplant Proc. (2010) 42:2910–3.

Hyperuricemia

- CNIs are nephrotoxic agents, and HUA is a common complication of CNI therapy .

- Cyclosporine induced HUA has been associated with the reduction of urinary
- clearance of UA due to :
- **increased proximal tubular reabsorption**,
- **decreased tubular secretion**,
- **decreased GFR.**

- **Tacrolimus** has also been found to be associated with HUA , but
- at a **less frequency**.

medicina

MDPI

Article

Predictors of Hyperuricemia after Kidney Transplantation: Association with Graft Function

Inese Folkmane [1,2,*], Lilian Tzivian [1,3], Elizabete Folkmane [1,4], Elina Valdmane [1,2], Viktorija Kuzema [2,5] and Aivars Petersons [2,5]

There were **144 patients** (mean age 46.6 ± 13.9), with **42.4%** of them having HU. Predictors of HU in KTR were the presence of **cystic diseases** (OR = 9.68 (3.13; 29.9)), the **use of diuretics** (OR = 4.23 (1.51; 11.9)), and the **male gender** (OR = 2.45 (1.07; 5.56))

Medicina 2020, 56, 95; doi:10.3390/medicina56030095

Risk factors and management of hyperuricemia after renal transplantation

Xiaoyu Zi[1†], Xi Zhang[2†], Chuan Hao[2*] and Zhenxing Wang[2*]

[1]Department of Rheumatology, The Second Hospital of Shanxi Medical University, Taiyuan, China,
[2]Department of Urology, The Second Hospital of Shanxi Medical University, Taiyuan, China

There are a number of risk factors associated with post transplant HUA including, **older age**, **male** gender, **calcineurin inhibitors**, **diuretic**s, **hypercalcemia, lower(eGFR)**, **long-term pre transplantation dialysis** and the presence of **pre transplant hyperuricemia**.

Front. Surg., 06 January 2023

Hypertension

- Hypertension is associated with **adverse short-term** and **long-term allograft outcomes** and can lead to **increased morbidity** and **mortality** post-transplant.
- Hypertension is **common** after kidney transplant due to a number factors including **allograft dysfunction**,
- **volume overload**,
- **corticosteroid use**,
- **acute rejection**,
- **transplant renal artery stenosis**,
- **recurrent disease**,
- **post-transplant proteinuria**.

- Recent Cochrane review established that
- **CsA increases blood pressure** in a **dose-dependent** manner compared to placebo
- **risk of stroke**,
- **myocardial infarction**,
- **heart failure**,
- **other hypertension related adverse cardiovascular events.**

- **CNIs** raise blood pressure and cause hypertension through multiple mechanisms including
- **tubular salt reabsorption**,
- **peripheral vasoconstriction**,
- **sympathetic nervous system.**
- .

- ✓The **WNK kinase pathway** is involved in mediating CNI-induced hypertension.

- ✓Kidney biopsies from patients treated with a CNI had pronounced **increase in kidney cortex NCC** and **phospho-NCC expression** compared with the azathioprine (AZA) treated and healthy control groups.

- ✓Animal studies have revealed kidney specific **deletion of FK binding protein** in mice to **attenuate FK induced hypertension and hyperkalemia** and **hydrochlorothiazide to reverse FK induced hypertension**, which was dependent on **WNK4-SPAK pathway** activation of NCC.

- ✓Another study of rats treated with **CsA revealed increased abundance** of **WNK4 in kidney tissue**, which was further demonstrated in **distal convoluted tubule cell culture.**

- ✓**CsA and FK increased renin content** of mouse **collecting duct principal cells** associated **with increased vascular endothelial growth factor** production and **worsening of local hypoxia and fibrosis.**

- ✓Suggesting **a role for NKCC2 activity** in mediating **salt reabsorption**, CsA treated rats demonstrated **increased NKCC2** and **phosphorylated NKCC2 kidney abundance**, which was dependent on the presence of vasopressin.

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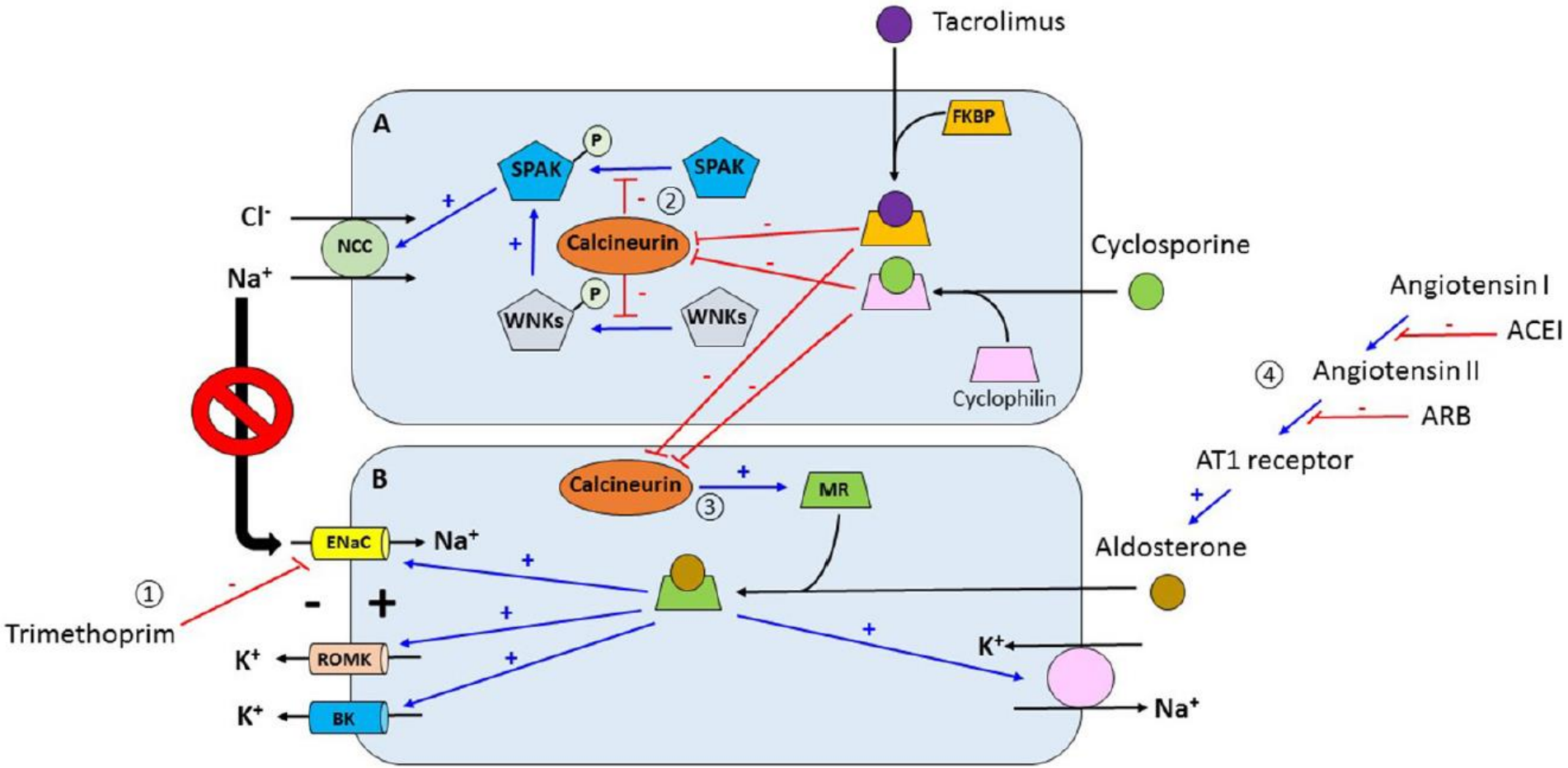

Front. Med. 5:261. doi: 10.3389/fmed.2018.00261

Circulation Research

ORIGINAL RESEARCH

Calcineurin Controls Hypothalamic NMDA Receptor Activity and Sympathetic Outflow

Jing-Jing Zhou, Jian-Ying Shao, Shao-Rui Chen, Hui-Lin Pan

- ✓ Calcineurin (proteinphosphatase-2B) is **broadly expressed in the brain**, including the paraventricular nuclear (PVN) of the hypothalamus, which is critically involved in **regulating sympathetic vasomotor tone.**

Systemic administration of FK506 (3 mg/kg per day) for 14 days caused a gradual and profound increase in arterial blood pressure in **rats**, which lasted at least 7 days after discontinuing FK506 treatment.

Normal calcineurin activity in the PVN constitutively **restricts sympathetic** vasomotor tone via suppressing NMDA receptor activity, which may be targeted for treating calcineurin inhibitor–induced hypertension.

Circulation Research. 2022;131:345–360

Dyslipidemia

- **Both CsA and FK** are associated with **impaired lipid metabolism**, with **CsA having a more profound impact.**
- Abnormalities of the lipid profile include increased **total cholesterol**, low density lipoprotein cholesterol (**LDL-C**), non-high density lipoprotein cholesterol (**non-HDL-C**), **triglycerides**, **apolipoprotein B** and **apoO-III**.
- In vitro studies have shown that CsA **inhibits sterol 27-hydroxylase** (OYP27A1), which is **required for 27-hydroxycholesterol formation** and **cholesterol metabolism.**

- As **27-hydroxycholesterol inhibits** 3-hydroxy-2-metyhylglutaryl coenzyme A (**HMG-CoA**), the rate-limiting **enzyme involved in cholesterol biosynthesis**.
- **CsA leads to an increase in HMG-CoA activity and a subsequent increase in cholesterol levels.**
- CsA also **inhibits the 26-hydroxylase**, leading to a **decrease in bile acid synthesis from cholesterol and increased serum levels**.
- Lastly, CsA may contribute to **reduced triglyceride breakdown** via **inhibition of lipoprotein lipase activity.**

- **Statins** are recommended for all patients with kidney transplants and is considered **first-line** pharmacotherapeutic options and remain the backbone of dyslipidemia management post-transplant for their proven benefits in reducing major adverse cardiovascular events.
- Care should still be taken when **selecting a statin agent** and **dose** due to the **potential for CYP3A/P-glycoprotein mediated drug interactions**.
- **Fluvastatin, pravastatin, rosuvastatin and pitavastatin** may be easiest to manage due to their non-CYP3A mediated metabolism
- **Simvastatin should be avoided** whenever possible due to significant potential for drug interactions and increased rates of myopathy and rhabdomyolysis

New Onset Diabetes After Transplantation (NODAT)

- **FK has been associated with a higher incidence of NODAT**
- In addition to CNI use, risk factors for the development of NODAT include
- **increased body mass index (BMI**)
- , **maintenance corticosteroid use**
- **hepatitis C virus infection**, and
- **cytomegalovirus (CMV) infection**
- Interestingly, CNI-induced **hypomagnesemia**, which is more common with FK than CsA, was shown to be an independent risk factor for the development of NODAT.
- CNIs interfere with **NFAT signaling in pancreatic b-cells**, as they do in T-cells, and **decrease insulin secretion**

- The **high levels of FK-binding protein 12** in **pancreatic β-cells** relative to **cyclophilin** may explain the **higher risk of NODAT with FK** use.

- In addition to **lifestyle modifications**, **early insulin initiation** to manage hyperglycemia post-transplant has been proposed to **decrease oxidative stress** on the pancreas caused by an absolute insulin deficiency and **reduce the odds of developing NODAT** in the future.

Neurotoxicity

- Neurotoxicity is a frequent treatment-limiting concern among patients treated with CNIs
- Mild symptoms are more common with FK150 and include **tremor**, **neuralgia**, and **peripheral neuropathy**
- **Severe symptoms** affect **up to 5 %** of patients and include **psychoses**, **hallucinations, dysarthria, vision loss, seizures**, **cerebellar ataxia**, **paresis**, and **leukoencephalopathy**
- Severe neurologic toxicity is more commonly **associated with spikes** in CNI exposure and typically demonstrates little correlation with trough levels,

- **Intravenous CNI** administration and rapid titration post-transplant **may be risk factors**
- The exact mechanism of CNI associated neurotoxicity is not completely understood as CNIs are **highly lipophilic** medications and **do not readily cross the blood brain barrier**
- However, proposed mechanisms include **altered CNS permeability** due to **increased endothelin** production as well as increased production of **toxic free radicals** resulting from CNI-induced mitochondrial dysfunction.

PRES

- CNIs have been associated with **hypertensive encephalopathy** and posterior reversible encephalopathy syndrome (**PRES)**
- Patients can develop **severe headache**, **visual disturbances**, altered **consciousness**, and **seizures**.
- Most cases of PRES **resolve over days to weeks** without complications, however, **death and permanent neurologic disability** can occur from **cerebral edema** either from intracranial hemorrhage or the disease itself.
- In a study published by Bartynski et al., PRES developed in around **0.5%** (27) of 4222 patients who underwent solid organ transplantation within the study period.

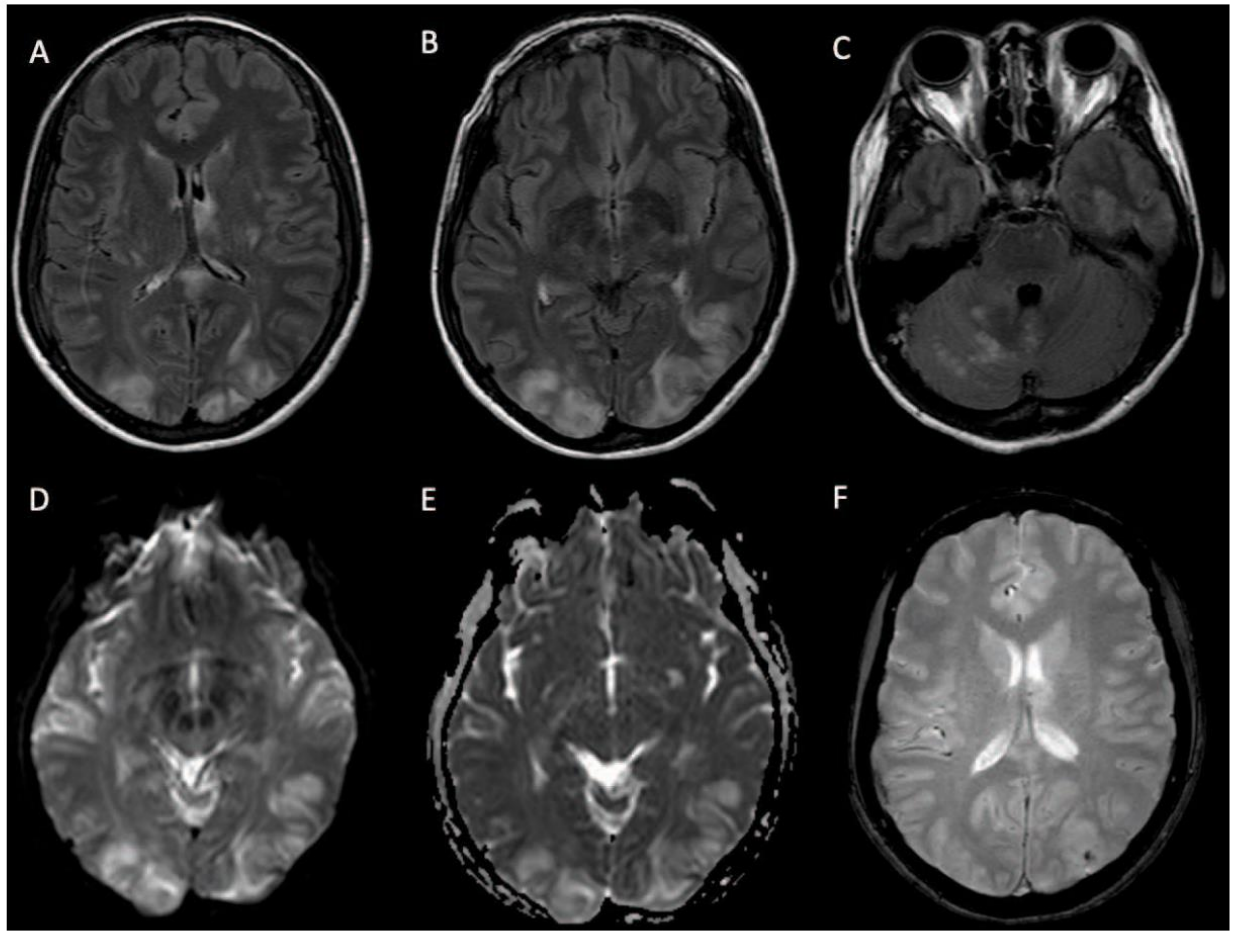

Figure 1 Imaging findings in typical PRES. MR scan of the brain of a 39-year-old woman with PRES who presented with visual disturbance, seizure and fever. (A–C) Prominent cortical and subcortical white matter signal hyperintensity on T2 FLAIR involving bilateral occipital and left anterior parietal lobe, left frontal lobe, and the splenium of the corpus callosum with additional foci involving both the anterior left thalamus and posterior left putamen. There are also patchy hyperintense T2 FLAIR signal foci within the right cerebellar hemisphere. (D,E) Areas of diffusion-weighted imaging hyperintensity and hyperintense apparent diffusion coefficient signal involving the occipital cortex bilaterally consistent with vasogenic oedema, which corresponds to regions of high T2 signal on the FLAIR images. (F) There is a small focus of blooming within the left occipital lobe, in keeping with petechial haemorrhage. FLAIR, fluid-attenuated inversion recovery; PRES, posterior reversible encephalopathy syndrome.

- **Gradual blood pressure lowering** and s**witchin**g to an alternative **immunosuppressant** are often associated with clinical improvement.

- **Risk of PRES** is increased among patients with significant **fluid overload**, **elevated blood pressure**, or **impaired kidney function**.

Gingival Overgrowth & Hair Growth

- The underlying pathophysiology of gingival overgrowth (GO) is related to **inhibition of intracellular calcium influx**, with possible additional roles for **fibroblasts**, **cytokines**, and **matrix metalloproteinases**.

- GO, **more commonly** linked to **CsA use**, is associated with impaired **oral hygiene**, **mastication**, **pain**, and **disfiguration**
- a **synergistic relationship** has been shown between CsA and **dihydropyridine CCB**s in the development of GO.

- CsA and FK have opposing effects on hair growth
- **Hypertrichosis associated with CsA** may be related to **inhibition of** NFAT in follicular keratinocytes.
- PO CsA has even been reported for the **treatment of alopecia areata**
- Conversely, **FK is associated with the development of alopecia**, though the mechanism is unknown.
- In females it is thought to potentially be related to an imbalance in **sex hormones** and generally responds favorably to **topical minoxidil** therapy.

Tacrolimus vs Cyclosporine

- More prominent neurologic side effects with FK such as **tremor and headache**
- ●More frequent incidence of **NODAT**
- ●More frequent **diarrhea, dyspepsia, and vomiting**
- ●More frequent **alopecia**
- ●Less frequent hirsutism, gingival hyperplasia, and hypertension
- In addition, **tacrolimus** but not cyclosporine has **rarely** been reported to induce a **hypertrophic cardiomyopathy** and **severe neutropenia**.

ORIGINAL ARTICLE

Diagnosis and Treatment of Calcineurin Inhibitor-Induced Pain Syndrome in Chronic Kidney Disease Stage 5 Transplantation

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Of 12 patients, 7 (58.3%) patients were male and 5 (41.6%) were female. At this study, bone magnetic resonance imaging (MRI) was diagnostic modality of choice.

- The isolated and combined articular manifestations contain **bilateral** knee pains (n=4, 33.3%); bilateral symmetrical pain in feet (n=3, 25%); bilateral knee and feet pain (n=2, 16%); bilateral knee and ankle pain (n=1, 8.3%); bilateral wrist, elbow, hand, and knee joints pain(n=1, 8.3%); hand, knees, ankle and feet joints involvement (n=1, 8.3%)
- Bone scintigraphy shows an **increased tracer uptake** by the foot bones indicating hyperperfusion, hypervascularity, and hypermetabolism.
- **MRI demonstrates a bone marrow edema** that is **limited at the epiphysis of the distal tibia and in the border of different vascular supply terrorities**.
- High or normal cyclosporine or TAC levels are helpful in diagnosis of CIPS.

- ✓The most effective treatment of CIPS is **reduction dose of calcineurin** inhibitors and other treatment modalities include **switching** of immunosuppressants, calcium channel blockers, GABA analogs, IV pamidronate and conservative therapies.

- ✓Resolving of bone pain occurred from 1 week until 3 months after reduction or withdrawal of drug and disappearance of bone marrow edema revealed after 6 months on MRI.