How calcineurin inhibitors cause hypertension

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Calcineurin is a calcium-dependent serine–threonine protein phosphatase. Calcineurin activates the target kinase network regulates the activity of the major sodium and potassium transporters in the distal nephron, including thiazide-sensitive Na–Cl cotransporters (NCC) and the renal outer medullary potassium channel (ROMK). WNK kinases modulate ion transport through two distinct regulatory pathways involving trafficking and phosphorylation. A schematic adapted from recent reviews is given in Figure 1. Mice that lack a catalytically active SPAK are strikingly hypotensive with marked reduction in NCC phosphorylation in the kidney and exhibit reduced Na+/K+2Cl− cotransporter (NKCC1) phosphorylation in the vessel wall [2]. SPAK and OSR1 kinases regulate SCL12A transporters with important physiological effects for sodium homeostasis by the kidney, aortic contractility and neuronal excitability. In vivo, SPAK plays a major role in the regulation of blood pressure and represents a potential target for diuretic development.

Rare mutations in WNK kinases cause FHH. However, genetic variations in WNK kinases have been associated with salt-sensitive essential hypertension [1]. Furthermore, heterozygous inactivating mutations in this pathway may protect from hypertension. The pathway has also been implicated in the hypertension associated with Type 2 diabetes mellitus. Acquired syndromes exist that exhibited similar clinical characteristics as PHA-II. One such syndrome occurs in almost every patient undergoing renal transplantation. These patients are invariably treated with CNI. They generally develop hypertension that is commonly associated with non-anion gap (mild) metabolic acidosis and hyperkalaemia.

Recently, Hoorn et al. [3] reported novel findings that may serve to explain the connection. The group hypothesized that CNI induce hypertension by stimulating NCC. They first studied wild-type mice and found that tacrolimus caused salt-sensitive hypertension and increased the abundance of phosphorylated NCC, WNK3, WNK4 and SPAK compared to control mice. They then gave tacrolimus to mice with a gene-disrupted NCC. Tacrolimus could not increase blood pressure in these mice. However, the hypertensive response to tacrolimus was exaggerated in mice overexpressing NCC. The blood pressure increases to tacrolimus were reversed by hydrochlorothiazide treatment. The investigators also included human studies. They showed that kidney transplant...
recipients treated with tacrolimus had a greater fractional chloride excretion in response to bendroflumethiazide than individuals not treated with tacrolimus. Furthermore, the renal NCC expression was greater as well. The findings make an appealing story that CNIs cause hypertension by inducing a form of acquired PHA-II. Conceivably, hydrochlorothiazide could offer an effective and inexpensive anti-hypertensive treatment for these patients. Strange would be the fact that clinicians did not stumble onto the observations independent of this study. In Europe, physicians generally give these patients furosemide for reasons unclear to this old clinician. Perhaps, furosemide is considered to be a vitamin rather than a drug. Four randomized trials done >30 years ago showed that NCC inhibitors lower blood pressure better than NKCC inhibitors. However, clinicians are difficult to convince; it must be a marketing phenomenon.

Some burning questions remain. How does tacrolimus stimulate NCC activation? What is the relationship between calcineurin and NCC? Presumably, the inhibition of calcineurin is responsible for NCC activation rather than some secondary action of tacrolimus. Does the activation require the prevention of NFAT dephosphorylation? Or does calcineurin interact in some not yet defined way with NCC? To the last point, I consulted with one of the authors (Sebastian Bachmann), who works at the Charité in Berlin. He shared with me Figure 2. Shown in normal mouse kidney is a remarkable colocalization between calcineurin and NCC. Conceivably, the process is calcineurin dependent and therefore inhibited by tacrolimus.

Also relevant perhaps is a recent study of genomic-derived markers in a model of CNI nephrotoxicity [4]. Rats were given generous doses of cyclosporine. The authors identified a group of genes whose expression in rat kidney was correlated with CNI-induced kidney injury. Among the candidates were Slc12a3, which encodes NCC, and the gene encoding kidney-specific Wnk1 (KS-WNK1). The proteins are outlined in Figure 1 and could potentially be involved in the mechanism of CNI-induced nephrotoxicity.
The down-regulation of NCC in rat kidney following CNI treatment was confirmed by immunohistochemical staining, and the down-regulation of KS-WNK1 was confirmed by quantitative real-time polymerase chain reaction. However, the authors did not study the phosphorylated versions of NCC. Furthermore, they conducted a toxicity investigation rather than a blood pressure study.

Most interesting is the report of acquired chimaerism in which a kidney from a patient with Gitelman syndrome (NCC deficiency) was transplanted into a non-Gitelman hypertensive recipient [5]. After transplantation, postural hypotension resulted, necessitating discontinuation of all anti-hypertensive medications used for treatment of CNI-induced hypertension. The authors basically describe an acquired Gitelman syndrome after transplantation. These prescient scholars suggested that their findings supported the potential use of thiazide diuretics in the treatment of CNI-induced hypertension, thereby supporting the work of Hoorn et al. [3].

Conflict of interest statement. None declared.

References

Benefit of cyclophosphamide therapy in IgA nephritis may have been obscured by warfarin-related nephropathy in the randomized trials in which warfarin and dipyridamole were used in combination with cyclophosphamide

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Kamei et al. [1] have recently described favorable long-term outcomes in pediatric IgA nephritis patients treated with warfarin, dipyridamole, prednisone and azathioprine. Likely, this work will revive interest in ‘combination’ therapy in the management of progressive IgA nephritis. We suggest, however, that this interest needs to be interpreted in light of a recently recognized mechanism of acute kidney injury (AKI), which we have termed warfarin-related nephropathy (WRN) [2–5]. We suggest that WRN, which is relatively common in chronic kidney disease (CKD) patients [3, 4], likely confounds the interpretation of the original randomized trials of combination therapy in adults with progressive IgA nephritis [6–8]. In these studies, the immunosuppressant was oral cyclophosphamide given in the usual doses >6 months. These studies have been interpreted as showing little or no benefit by combination therapy in progressive IgA nephritis [9]. However, since then, Ballardie has reported a randomized trial showing that, compared to the usual supportive therapy, oral cyclophosphamide at 1.5 mg/kg for 3 months followed by azathioprine therapy for 1–3 years was strongly beneficial in preventing end-stage renal disease in adults with progressive IgA nephritis [10].

Despite Ballardie’s work, there continues to be reluctance to recommend cyclophosphamide therapy for progressive IgA nephritis. The rationale is that of the three randomized trials of oral cyclophosphamide [6, 7, 10], only the Ballardie