FK506: Mechanism of immunosuppression and adverse-effects.

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FK506 (Tacrolimus), a macrolide antibiotic produced from Streptomyces tsukubaensis, is a powerful immunosuppressant. Its pharmacological mechanism is similar to that of Cyclosporine (CsA), although the two are structurally distinct. Like CsA, FK506 inhibits early T-cell activation gene transcription such as interleukins, which results from its inhibition of phosphatase (calcineurin) in activated T cells. Calcineurin is considered to dephosphorylate NF-ATc/p which associates with AP-1 to activate the transcription of lymphokine genes. Both immunosuppressants bind to their respective cytoplasmic receptor called immunophilins (FKBP, cyclophilin), and gain new ability to associate with calcineurin and inhibit its phosphatase activity.

FK506 has proved to be an effective drug for the prevention of allograft rejection in various animals and in human, however, adverse effects similar to those of CsA have been observed. One of the main adverse effects was hyperglycemia. We investigated the mechanism and the reversibility of hyperglycemia caused by FK506. FK506 did not affect the glucose uptake by insulin into rat strio-muscle cell line, but
suppressed insulin production in rat insulinoma cells. Two-week oral administration of FK506 at 10 mg/kg/day suppressed insulin production time-dependently at the transcriptional step in pancreatic β-cells, while glucagon content in pancreatic α-cells was not affected. When FK506 administration was stopped in these rats, insulin mRNA transcription and insulin production returned to normal. This recovery indicates that the adverse effect of FK506 on the pancreas is reversible. The localization of FKBP-12 and calcineurin in rat pancreas was analyzed immunohistochemically. Both FKBP-12 and calcineurin were localized in the pancreatic β-cells, but the content of FKBP-12 was less in the pancreatic α-cells. Scarcely any staining was noted both for FKBP-12 and calcineurin in the acinar cells. Thus, as in the case with NF-AT in T-cells, these findings suggest that a reduction of unidentified nuclear factors for insulin mRNA transcription occurs owing to the binding of FK506 to FKBP-12 and a subsequent inhibition of calcineurin in the β-cells.

The renal impairment by FK506 is also a frequent adverse effect, as in the case of CsA. We could reproduce a similar nephrotoxic profile in low sodium diet rats administered with FK506 to those obtained in clinical trials. FK506 increased BUN and S-Cr, and decreased CcR, clearly showing the reduction of GFR. FK506 also caused an increase in the urinary excretion of NAG and AAP, which indicated tubular injury. Renal histological analyses demonstrated proximal tubular vacuolation as observed in short-term toxicity, and tubulo-interstitial fibrosis and
inflammation in long-term toxicity. With those functional and pathological changes, FK506 induced plasma renin activity (PRA) dose- and time-dependently, and renin mRNA levels in juxtaglomerular apparatus paralleled the increase of PRA in FK506 dosed rat. NO syntase activity in macula densa was adversely decreased in these rats. The expression of renin mRNA induced by FK506 may have some relevance to the inactivation of NO syntase through the inhibition of calcineurin by FK506. These data suggest an involvement of the renin-angiotensin system in the nephrotoxicity of FK506. It is possible to speculate that the renal dysfunction and proximal tubular vacuolation as acute nephrotoxicity of FK506 resulted from the reduction of GFR and RBF through vasoconstriction, and that the tubulo-interstitial fibrosis as chronic lesions was caused by the growth stimulatory effects of Angiotensin II and subsequently induced TGF-β.