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学位論文名	A novel immunosuppressant FTY720 ameliorates proteinuria and alteration of intrarenal adrenomedullin in rats with autoimmune glomerulonephritis （新規免疫抑制剤FTY720はラット腎炎モデルにおける尿蛋白を減少させ、腎組織アドレノメデュリン産生に影響する）
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論文内容の要旨

objective

FTY720 has been originally developed as a new immunosuppressive agent, which prolongs graft survival in organ transplantation. Induction of apoptosis in resting and activated lymphocytes is considered to be a mechanism of action. In the present study, using the $HgCl_2$-induced autoimmune glomerulonephritis model, we investigated the effect of FTY720 thereon. Adrenomedullin (AM) and its gene expression have been reported to be observed in the kidney, participated in the regulation of sodium homeostasis and had renoprotective effects. However, the pathophysiological significance of renal AM and the possible involvement of renal AM in the effect of immunosuppressant in rats with glomerulonephritis have not been elucidated. In the present study, we evaluated the pathophysiological significance of renal AM in glomerulonephritis and whether a novel immunosuppressant FTY720 alters renal AM synthesis.

Materials and Methods

Animals were randomly divided into 5 groups : group 1 (rats received vehicle only), group 2 (disease group, rats were treated with $HgCl_2$ only), Co-administrated ($HgCl_2$ and FTY720) group (group 3 : FTY720 at 3 mg/kg body weight ; group 4 : FTY720 at 10 mg/kg body weight), group 5, FTY720 (10 mg/kg body weight) alone.

$HgCl_2$ (1 mg/kg body weight, 3 times/week) and FTY720 (daily) was inoculated subcutaneously for 2 weeks. Animals were sacrificed on day 14, and renal function targets were analyzed. Radioimmunoassay was used for measuring renal AM level, and Northern blot analysis was performed for checking the AM mRNA expression.

Result

A progressive proteinuria developed from 7 days onwards in $HgCl_2$ only group (group 2). Proteinuria

stabilized at around 600 mg/24 h, and a severe drop in serum albumin level reached around 2 g/dl at day 14. A concomitant rise in serum total cholesterol was observed (above 200 mg/dl) at the end of experiment. Treatment with FTY720 (10 mg/kg body weight) resulted in a significant reduction in the urinary protein excretion, total cholesterol levels and the urinary excretion of NAG. The effects of FTY720 on these parameters were dose dependent. Despite the reduction in proteinuria, serum albumin levels were reduced in the treated rats (groups 3 and 4) compared with controls (group 1). The reduced albumin levels were also noted in rats treated only with FTY720 (group 5). $HgCl_2$ and FTY720 independently increased renal tissue AM levels significantly. Co-administration of $HgCl_2$ and FTY720 resulted in a synergistic increase of plasma and renal tissue AM levels. AM mRNA expressions in the renal cortex was also higher in the rats of groups 2, 4 and 5, the highest being in group 4. Significant correlations were found between renal cortical and medullary mature AM levels and urinary NAG excretion and creatinine clearance. Although similar positive correlations existed between renal AM levels and urinary sodium excretion, they did not reach a statistical significance.

Conclusion

FTY720 has been shown to ameliorate HgCl2-induced autoimmune glomerulonephritis in a dose-dependent manner, which indicated FTY720 might be considered as a drug of choice for glomerulonephritis when other more potent immunosuppressants are not effective or when they should be withdrawn because of serious side effects. In addition, FTY720 additionally increased renal AM levels in the rats with autoimmune glomerulonephritis, although it suppressed renal damage; suggest that the alteration of renal AM levels under FTY720 administration might not reflect its effect on HgCl2-induced autoimmune glomerulonephritis. There may be a possibility that FTY720 increases renal AM production directly and the increased AM may participate in the reduction of proteinuria by FTY720 administration in the rats with HgCl2-induced autoimmune glomerulonephritis.

論文審査の結果の要旨

FTY720はリンパ球のホーミングというユニークな免疫抑制機序を有し、拒絶反応を抑制し、移植組織の寿命を延長するが、自己免疫性腎炎の尿蛋白抑制効果の有無については不明であった。本研究において、FTY720は用量依存的に尿中蛋白排泄量を減少させた。一方、アドレノメデュリンは腎臓でも産生され、腎保護作用を有するが、腎炎における生理学的意義の報告は少ない。腎炎では腎組織のアドレノメデュリン遺伝子発現が亢進し、濃度増加を認め、クレアチニンクリアランスと負の相関を有していることが本研究において確認された。さらに、FTY720投与により腎炎所見は改善したにもかかわらず、アドレノメデュリン遺伝子発現や濃度はむしろ増加した。この増加は、既報の尿蛋白減少作用を併せて考えると、FTY720の尿蛋白減少効果に協調的に関与している可能性がある。今回の研究結果は、通常の薬物治療が無効である難治性腎炎の新たな治療戦略を考える過程で基盤となる情報を提供する。従って、本論文は学位論文に値する内容であると判定した。