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 研究課題名（和文） 腎臓リハビリテーション運動療法と組織再生療法、栄養療法の相乗効果の機序解明
 研究課題名（英文） Elucidation of the mechanism that combination therapy with long-term exercise, G-CSF and nutrition therapy effectively inhibits the aggravation of progressive renal disease.
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研究成果の概要：慢性腎不全モデルを作成し、12週間にわたり長期的運動とG-CSFの単独及び併用治療、また、これらの治療とアンジオテンシンⅡ受容体拮抗薬(ARB)との併用治療を行った。その結果、G-CSFと長期的運動の単独治療による降圧効果と腎保護効果を認め、ARBの併用により降圧効果と尿蛋白減少効果が増強した。さらに、3者の併用は、腎保護効果と降圧効果を発揮しながら運動耐容能を増強させる可能性が示唆された。以上より、長期的運動療法、G-CSF療法およびARB療法の併用効果を確認し、その機序を明らかにする有力な手がかりが得られた。

交付額

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研究分野：総合領域

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1. 研究開始当初の背景

G-CSFはサイトカインであり、腎不全における骨髄幹細胞動員作用、傷害細胞・血管内皮細胞・血管平滑筋細胞への分化誘導作用による組織再生療法への有効性に期待が集まっている。アンジオテンシンⅡ受容体拮抗薬(ARB)は、腎障害患者や腎障害動物モデルにおける有効な降圧作用と共に腎保護作用を

有することが報告され、運動療法との併用による腎保護作用の増強に期待が持たれている。しかし、これらの治療の有効性や詳細な機序に関する十分な解明がなされていない。

2. 研究の目的

エビデンス確立に向けた「腎臓リハビリテーション」の基礎的検証を行うと共に新たな

対策法の確立を目指す。部分腎摘慢性腎不全モデルを作成し、長期的運動療法による血圧、運動耐容能、臓器障害の改善作用について、その機序の解明を目指す。また、G-CSF療法、ARBとの相互作用による増強効果とその機序の解明を目指す。

3. 研究の方法

WKYラットで5/6腎摘慢性腎不全モデルを作成した。ラットを以下の8群に分け、12週間治療した。1) 非治療(C)群, 2) 運動(EX)群, 3) G-CSF群, 4) EX+G-CSF群, 5) EX+olmesartan(OLS)群, 6) G-CSF+OLS群, 7) EX+G-CSF+OLS群, 8) 偽手術(S)群。EXは速度20m/分の走行運動を1日1回60分間、1週間に5日間行った。G-CSF(5 μ g/kg)は連日皮下投与した。2週間毎に収縮期血圧(SBP), 24時間尿蛋白排泄量(UP)を測定した。治療開始週と最終週にトレッドミル運動負荷試験を行い、総走行可能距離(TRD)を測定した。最終日に断頭採血し、血清クレアチニン(Scr), 血液尿素窒素(BUN)を測定した。残存腎を摘出し、糸球体硬化指数(IGS)を評価した。

4. 研究成果

S群に比較して、C群のUP, Scr, BUN, IGSは有意に悪化した。一方、C群に比較して、G-CSF群とEX+G-CSF群のUP, EX+G-CSF群のScr, G-CSF群とEX+G-CSF群のBUN, EX群とG-CSF群およびEX+G-CSF群のIGSは有意に改善した。また、G-CSF群とEX+G-CSF群のIGSはEX群に比較して有意に改善した。特に、OLSの併用では最も良好なSBPとUPを示し、また、全てのEX治療群の12週間後のTRDは非EX治療群に比較して有意に延長した。その結果、G-CSFとEXの単独治療による降圧効果と腎保護効果を認め、OLSの併用により降圧効果と尿蛋白減少効果が増強した。さらに、3者の併用により、腎保護効果と降圧効果を発揮しながら運動耐容能を増強させる可能性が示唆された。以上より、長期的運動療法、G-CSF療法およびARB療法の併用効果を確認し、その機序を明らかにする有力な手がかりが得られた。

5. 主な発表論文等

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