Insulin resistance and altered mTORC1 signaling expression in experimental uremia

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Background

- Insulin resistance (IR) plays a central role in the metabolic syndrome (MetS) and is associated with increased risk for chronic kidney disease (CKD) in nondiabetic patients. The mammalian target of rapamycin complex 1 (mTORC1) pathway senses and integrates a variety of environmental cues to regulate organismal growth and homeostasis. However, the role of mTORC1 in insulin signaling pathway in CKD is less clear. This study was intended to investigate the role of mTORC1 signaling pathway in adipose tissue and muscle under the condition of IR) in experimental uremia.

Methods

Fourteen male SD rats were divided into 5/6 nephrectomy (CKD group) and sham operation (control group) groups for 20 weeks. Insulin sensitivity was assessed using the intraperitoneal glucose tolerance test (IPGTT) and the insulin sensitivity index HOMA (HOMA-IR). Expression of critical proteins in insulin and mTORC1 signaling pathway in adipose tissue and muscle were detected.

Results

1. Biochemical results

A

	CON (n=7)	CKD (n=7)	P value
WEIGHT (g)	632.57±56.81	566.67±47.20	<0.05
UV(ml)	19.50±7.38	14.24±3.27	0.11
UP(mg)	11.17±4.06	45.32±11.68	<0.05
GLU(mmol/l)	5.50±0.28	5.86±0.35	0.44
CHOL(mmol/l)	1.56±0.07	2.73±0.29	<0.05
TRIG(mmol/l)	1.13±0.27	1.58±0.24	0.24
HDL(mmol/l)	1.27±0.07	2.14±0.21	<0.05
LDL(mmol/l)	0.32±0.03	0.72±0.09	<0.05
Cr(umol/l)	35.10±4.07	93.63±8.05	<0.05
BUN(mmol/l)	5.55±0.35	15.81±2.07	<0.05
UA(umol/l)	77.27±4.34	90.33±3.26	<0.05
ALB(g/l)	36.57±0.55	31.69±1.19	<0.05

2. Insulin sensitivity

	CON (n=7)	CKD (n=7)	P value
GLU(mIU/l)	**7.64±2.15**	**16.88±2.39**	**<0.05**
HOMA-IR(mmol/l×mIU/l)	**1.87±0.54**	**4.45±0.73**	**<0.05**

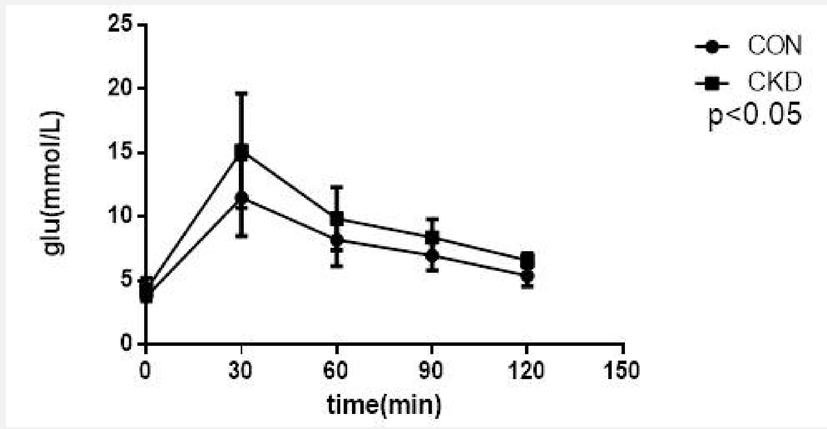

Fig. 1 Insulin sensitivity was assessed by intraperitoneal glucose tolerance test (IPGTT) and insulin sensitivity index HOMA (HOMA-IR).
HOMA-IR(mmol/l×mIU/l) =FPG(mmol/l)×FINS (mIU/l)/22.5. The CKD group were glucose intolerance and lower insulin sensitivity. ($p<0.05$)

3. Insulin signaling pathway in adipose tissue and muscle

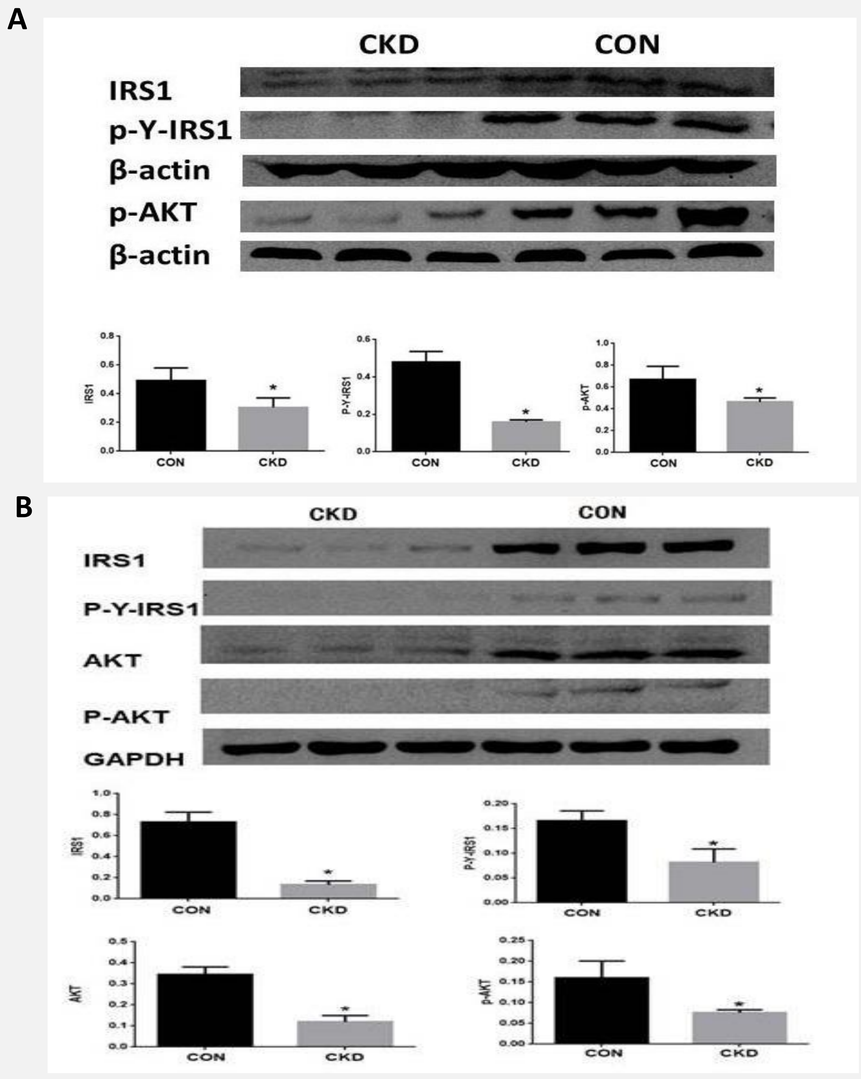

Fig.2 IRS1、p-IRS1、AKT、p-AKT protein expression in adipose tissue（A） and muscle(B) of 5/6 nephrectomy rats .($p<0.05$)

4. mTORC1 signaling pathway in adipose tissue and muscle

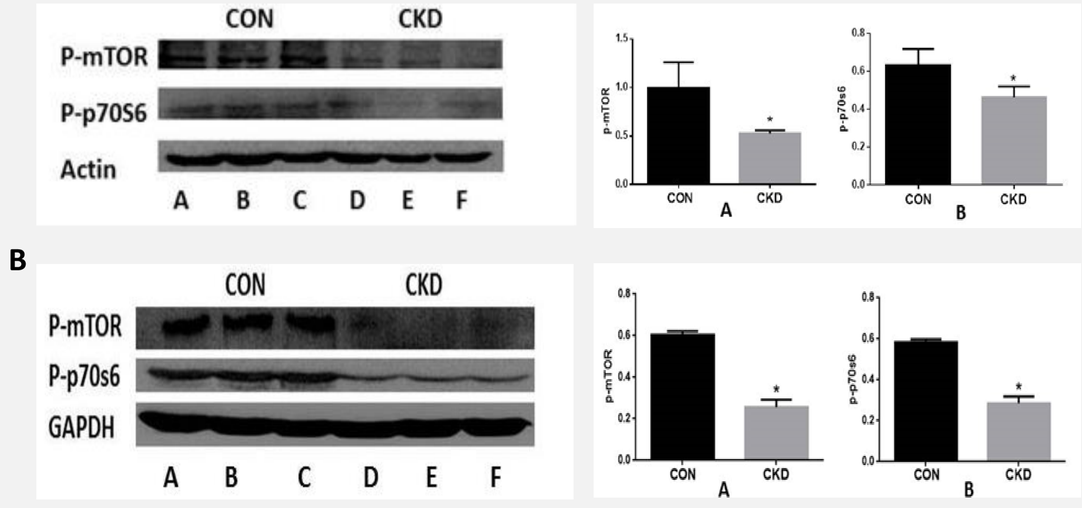

Fig.3 Decreased expression of p-mTOR and p-p70s6 in adipose tissue（A） and muscle(B) of 5/6 nephrectomy rats .($p<0.05$)

Conclusion

5/6 nephrectomy rats displayed insulin resistance. mTORC1 signaling pathway was downregulated in adipose tissue and muscle. Reduced mTORC1 signaling pathway is associated with IR in CKD.

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