Improvement of physical decline through combined effects of muscle enhancement and mitochondrial activation by a gastric hormone ghrelin in 5/6Nx CKD model mice

Masanori Tamaki[1,2], Aika Hagiwara[1], Kazutoshi Miyashita[1], Shu Wakino[1], Hiroyuki Inoue[1], Kentaro Fujii[1], Chikako Fujii[1], Sho Endo[1], Asuka Uto[1], Masaaki Sato[1] and Hiroshi Itoh[1]

1)Department of Internal medicine, School of medicine, Keio University
2) Department of Nephrology, Tokushima University Hospital

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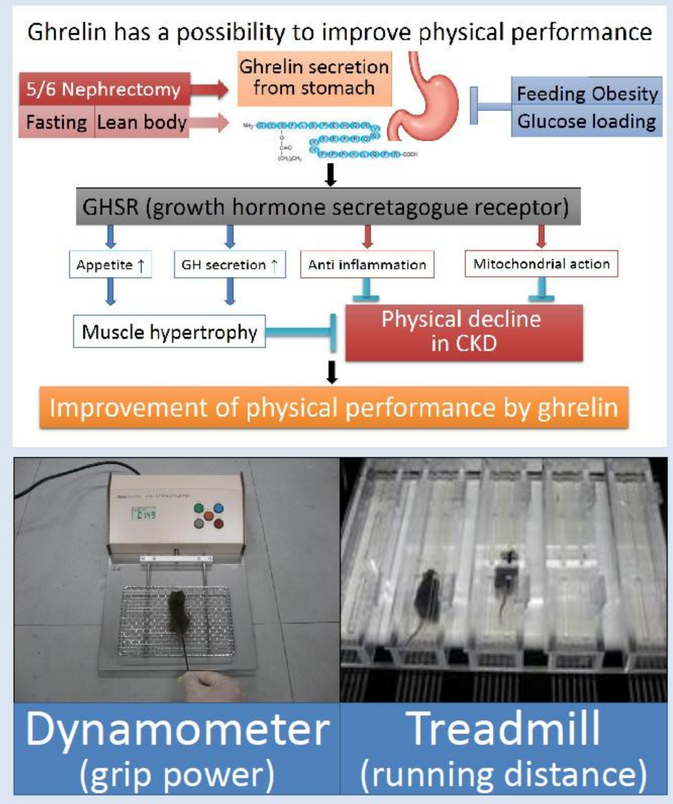
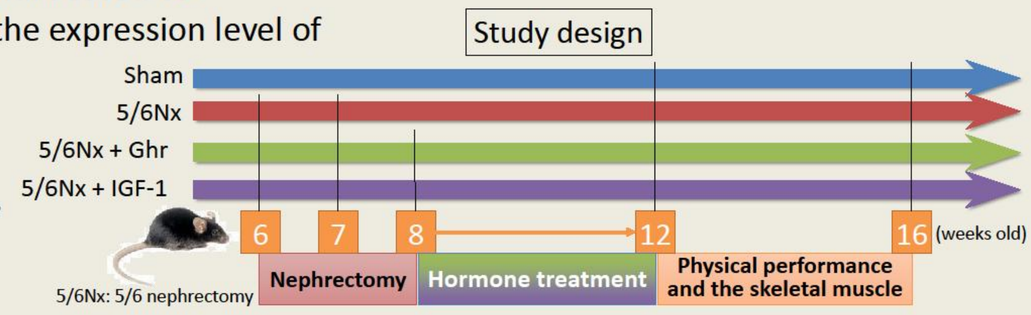
Introduction

- A physical decline due to chronic kidney disease (CKD) is known to predict a wide range of diseases and morbidity. An improvement of physical performance is expected to bring significant clinical benefits.
- The principal cause of physical decline has been regarded as a decrease in muscle mass. However, our previous study revealed that decreased muscular mitochondrial amount (known as mytopenia) could strongly spoil physical performance in 5/6 nephrectomized (5/6Nx) CKD model mice, even when the muscle mass was maintained. *(Tamaki et al. Kidney Int 2014; 85: 1330-1339).*
- Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) gene, which was a representative mitochondrial activator gene, was known to regulate mitochondrial amount in the skeletal muscle. The expression level of PGC-1α was decreased in the skeletal muscle of 5/6Nx mice in association with increase in TNF-α, a representative inflammatory cytokine which was elevated in CKD. Recently, a DNA methylation of the cytosine residue at 260 base pairs upstream (C-260) of initiation point of the PGC-1α gene was demonstrated to significantly decrease the gene expression.
- Ghrelin, a gastric hormone, was known to have muscle anabolic effect which is independent to the growth hormone (GH)/ insulin like growth factor-1 (IGF-1) axis; furthermore, previous reports indicated that ghrelin promote muscle mitochondrial oxidation.
- In the present study, we examined the usefulness of ghrelin treatment for a recovery of physical decline in 5/6Nx mice, in comparison with IGF-1 treatment, focusing on mitochondria and epigenetic modification of PGC-1α.



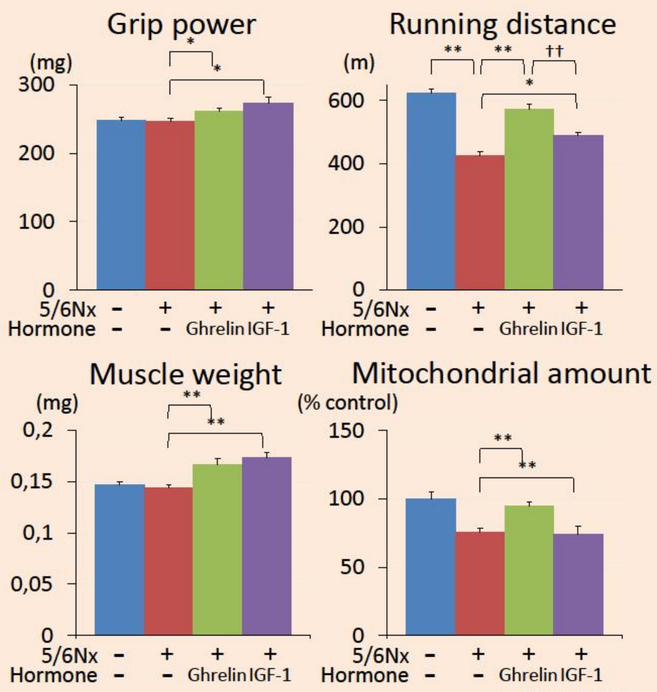
Methods

- Male C57Bl/6 mice were undergone 5/6 nephrectomy (heminephrectomy at 6 weeks old and polectomy at 7 weeks old).
- Acylated ghrelin (0.1 nmol/gBW; 3 times per week) or a representative muscle anabolic factor, IGF-1 (0.1 nmol/gBW) were administered intraperitoneally for a month.
- To evaluate physical performance (muscle strength and exercise endurance), grip power and running distance were measured by using a dynamometer and a treadmill for mice, respectively. The gastrocnemius muscle was harvested to evaluate muscle mass and mitochondrial property. Mitochondrial DNA copy number and the expression level of PGC-1α were determined by quantitative PCR analysis.
- The methylation ratio of the cytosine residue at 260 base pairs upstream (C-260) of initiation point of the PGC-1α gene was evaluated by using methylation specific PCR (MSP) analysis and bisulfite genomic sequence (BGS) analysis.
- Differentiated C2C12 cultured myocytes were examined after they were treated with or without ghrelin (100 nM) or TNF-α (1 ng/ml) for 24 hours.

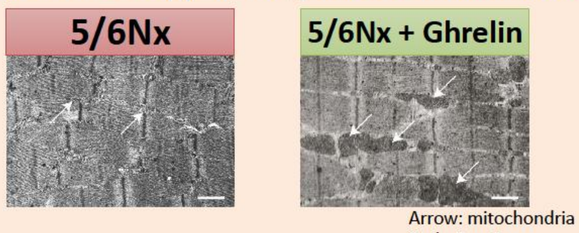


Results

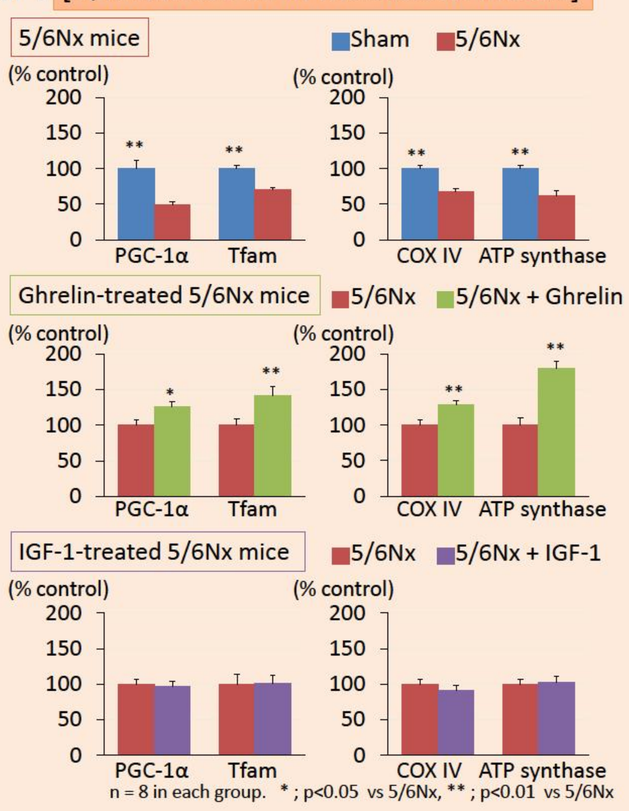
Sham 5/6Nx 5/6Nx + Ghrelin 5/6Nx + IGF-1



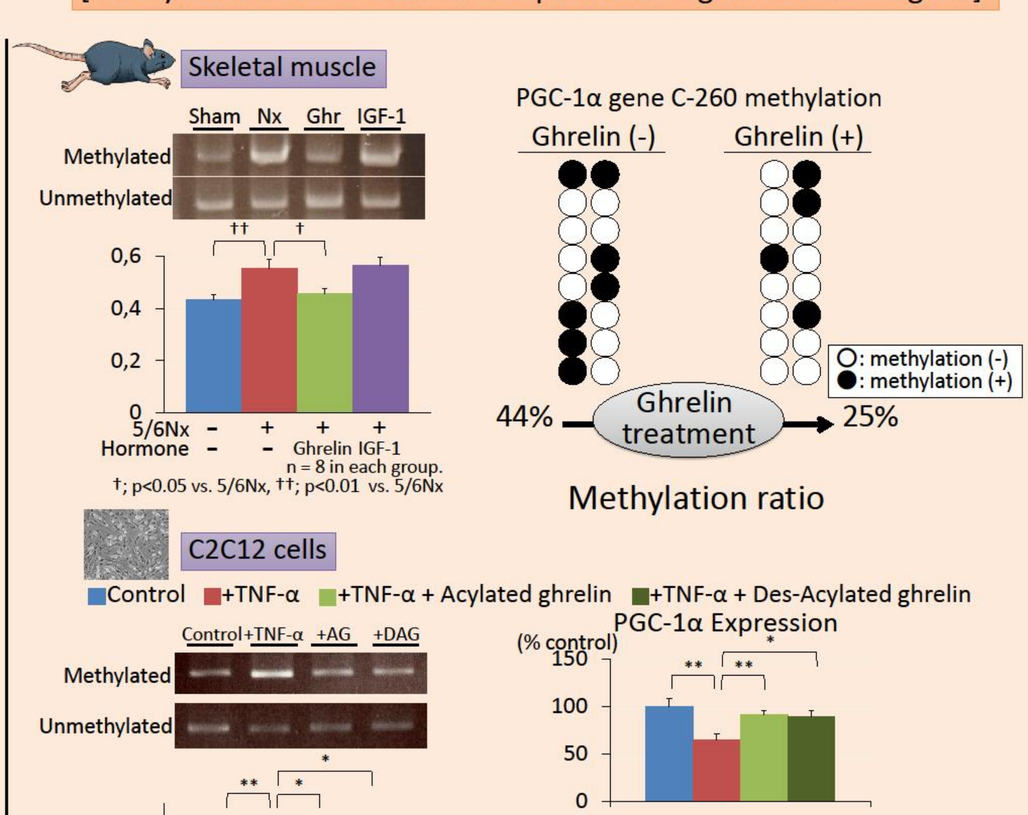
[Electron microscopy of the gastrocnemius muscle]



[Qualitative PCR in the skeletal muscle]



[Methylation ratio of C-260 at the promoter region of PGC-1α gene]

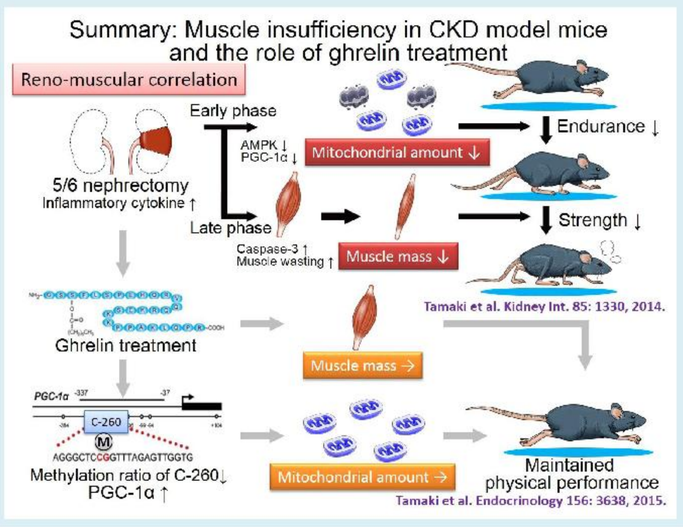


Summary and Conclusion

- Ghrelin treatment effectively improved physical decline of 5/6Nx mice through the combined effects to enhance muscle mass and mitochondrial amount, associated with epigenetic modification of muscle PGC-1α expression.

5/6Nx mice (Young)	Muscle power	Muscle weight
5/6Nx	No change	
+ Ghrelin	Increased	
+ IGF-1	Increased	

5/6Nx mice (Young)	Exercise endurance	Mitochondrial amount
5/6Nx	Decreased	
+ Ghrelin	Increased	
+ IGF-1	Slightly increased	No change



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