Improvement of physical performance in 5/6 nephrectomized CKD model mice through epigenetic modulation of PGC-1α expression by ghrelin treatment.

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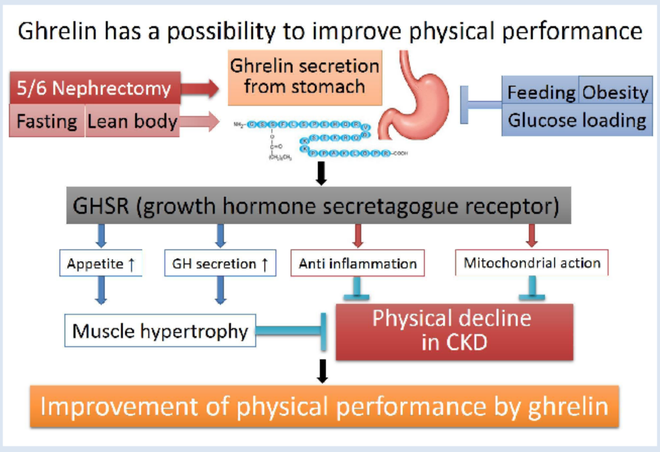
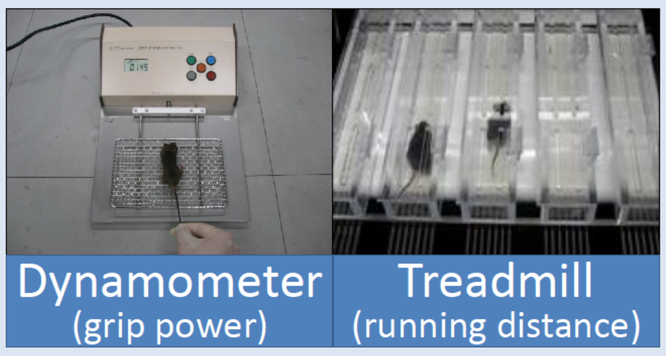
Introduction

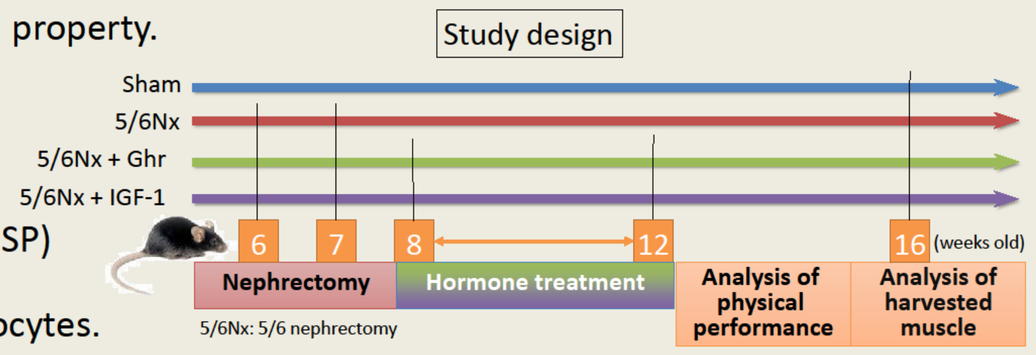
- An improvement of physical performance is expected to bring significant clinical benefits. A physical decline due to chronic kidney disease (CKD) is known to predict a wide range of diseases and morbidity.
- Our recent study revealed that muscle mitochondrial dysfunction could strongly spoil physical 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).*
- Ghrelin, a gastric hormone, is known to have muscle anabolic effect through growth hormone / insulin like growth factor-1 (IGF-1) axis; furthermore, previous reports indicated that ghrelin have beneficial effect for muscle mitochondria.
- Mitochondrial amount is regulated by a representative mitochondrial activator gene, peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α). Recently, epigenetic modifications of the promoter region in upstream of initiation point of the gene was revealed to critically control the expression.
- The usefulness of ghrelin treatment for a recovery of physical decline was examined by using 5/6Nx CKD model mice, in comparison with IGF-1 treatment, focusing on mitochondria and epigenetic modification of PGC-1α.





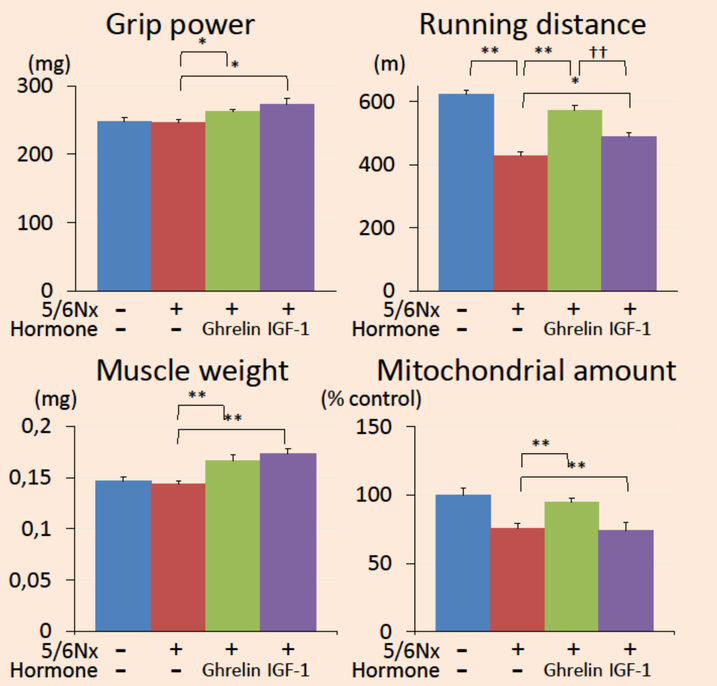
Methods

- Male C57Bl/6 mice were undergone 5/6 nephrectomy (Heminephrectomy at 6 weeks old and polectomy at 7 weeks old). Ghrelin or IGF-1 (0.3 μg/gBW; 3 times per week) were administered intraperitoneally, respectively.
- Physical performance (muscle strength and exercise endurance; determined by measuring grip power and running distance, respectively) was examined after the treatment by ghrelin or IGF-1 for a month.
- Skeletal muscle were harvested to evaluate the mitochondrial property.
- Epigenetic regulation of PGC-1α expression was evaluated by using of PCR analysis. The alteration in the methylation ratio of cytosine residue at 260 base pairs upstream (C-260), a representative methylation site that decrease PGC-1α expression, was examined by using methylation specific PCR (MSP) and bisulfite genomic sequence (BGS) analysis in the skeletal muscle of mice and ghrelin-treated C2C12 cultured myocytes.

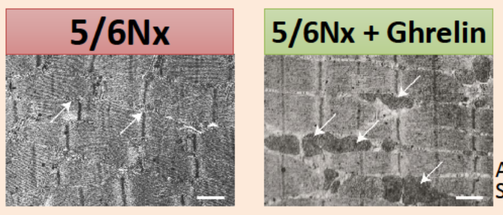


Results

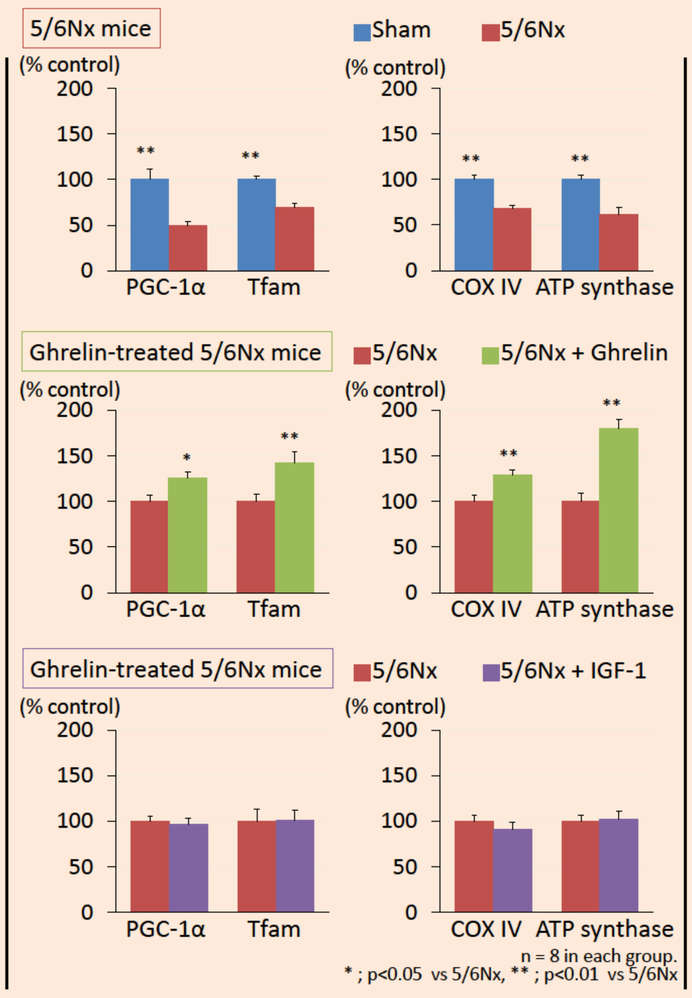
Sham 5/6Nx 5/6Nx + Ghrelin 5/6Nx + IGF-1



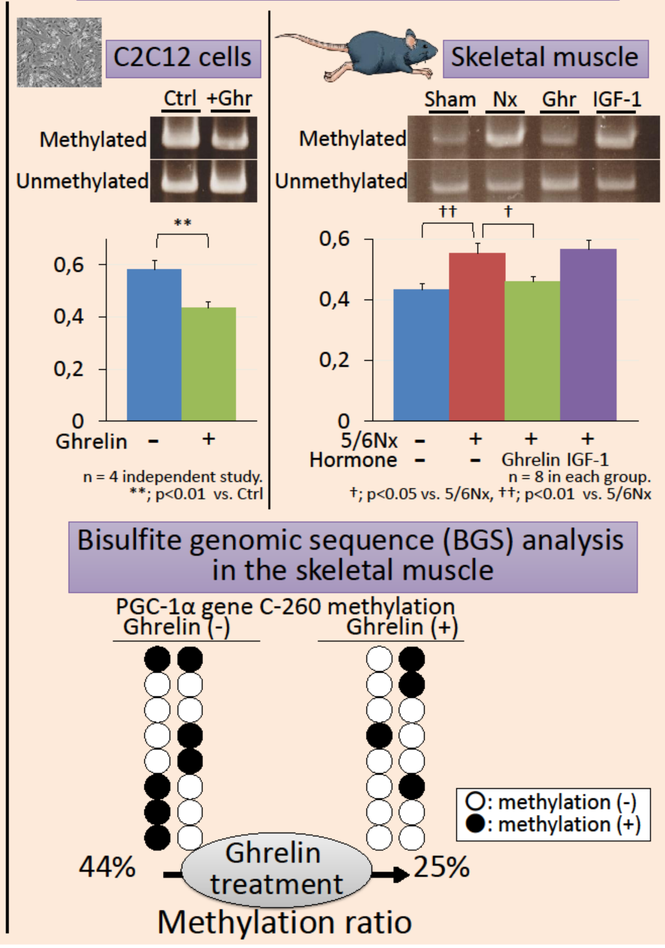
[Electron microscopy of the gastrocnemius muscle]



[Qualitative PCR in the skeletal muscle]



[Analysis of the methylation ratio of the promoter region of PGC-1α gene]

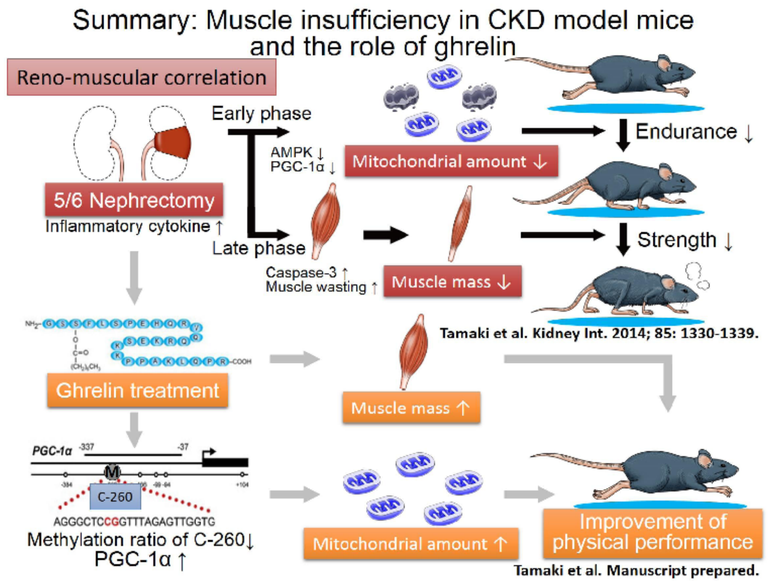


Summary and Conclusion

- 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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