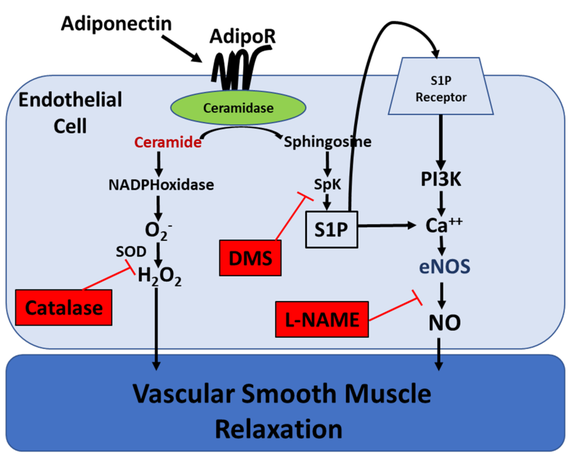
Age-related endothelial dysfunction reflects disruption of adiponectin-S1P mediated mechanotransduction

Steven Medarev[1], Tristan Driscoll[2], Judy Muller-Delp[3], and Jose Pinto[1]

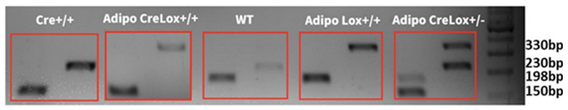
[1]Florida State University, College of Medicine; [2]Florida State University, College of Engineering; [3]Kansas State University, College of Veterinary Medicine

INTRODUCTION



Aging is associated with endothelial dysfunction, contributing to impaired microvascular function and increased cardiovascular disease risk. Adiponectin, an anti-inflammatory adipokine, supports vascular homeostasis by exerting ceramidase activity through its cell surface receptors, AdipoR1 and AdipoR2. This activity reduces ceramide accumulation and promotes sphingosine-1-phosphate (S1P) signaling, which enhances endothelial nitric oxide synthase activation and flow-mediated vasodilation. With aging, adiponectin activity declines, potentially disrupting this lipid signaling balance and impairing endothelial function.

ANIMAL MODEL



Cre+/+ mice were mated with **AdipoLox+/+** mice to produce heterozygous Adipo CreLox+/- mice, which were then bred to generate **Adipo CreLox+/+** mice. These Adipo CreLox+/+ mice have normal levels of circulating adiponectin, which can be depleted upon tamoxifen administration.

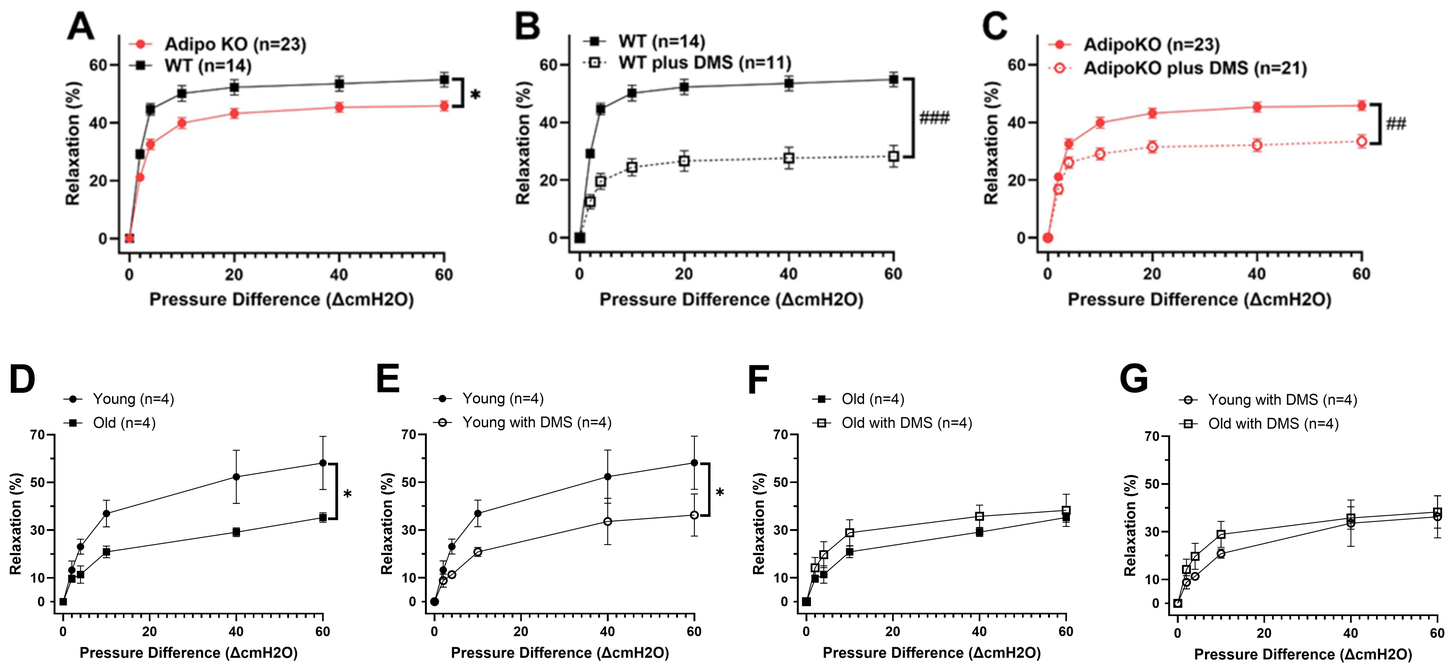
Table 1. Circulating Adiponectin in Genotypes

Group (n)	Adipo Lox+/+ (3)	Cre+/+ (3)	Cre+/+ post-TAM (4)	Adipo CreLox+/+ post-TAM (5)	Adipo CreLox+/- post-TAM (3)
Adiponectin (µg/mL)	6.58±2.44	6.81±1.96	6.76±1.27	0.88±0.39	4.49±0.44

HYPOTHESIS

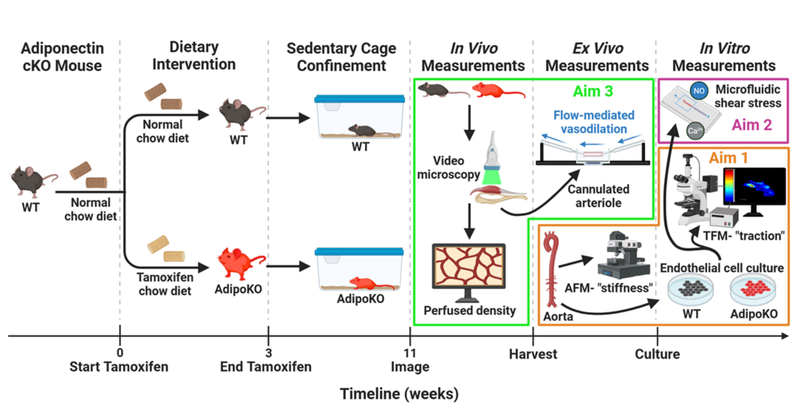
Aging and acute adiponectin depletion impair flow-mediated vasodilation in skeletal muscle arterioles through disruption of S1P signaling.

FLOW-MEDIATED DILATION IN YOUNG & OLD MICE UNDER DIFFERENT CONDITIONS



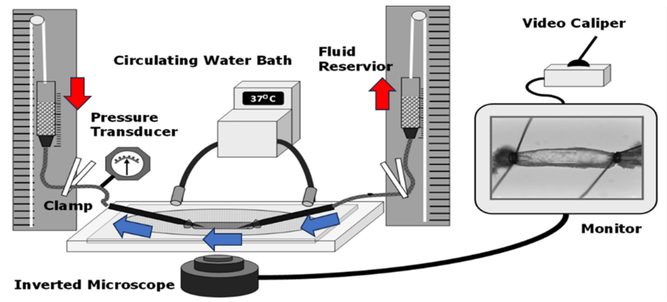
(**A**) Young WT mice exhibited significantly greater flow-mediated vasodilation (FMD) compared to young AdipoKO mice, highlighting the importance of adiponectin in endothelial function. (**B**) In young WT mice, DMS treatment significantly reduced FMD, bringing it to levels even lower than those observed in young AdipoKO mice, indicating that S1P signaling plays a crucial role in endothelial function (**C**) In young AdipoKO mice, DMS treatment also reduced FMD, though not as much as in young WT mice, suggesting that adiponectin deficiency already leads to a substantial impairment in flow-induced vasodilation, with only a partial additional effect from S1P inhibition. (**D**) Old WT mice showed significantly reduced FMD compared to young WT mice, indicating that aging impairs endothelial function. (**E**) In young WT mice, DMS treatment significantly reduced FMD, demonstrating the critical role of S1P signaling in maintaining endothelial function in response to flow. (**F**) In old WT mice, FMD was not significantly altered by DMS treatment, suggesting that aging is associated with a loss of S1P-dependent endothelial function that is not further impacted by S1P inhibition. (**G**) Young WT mice treated with DMS exhibited similar FMD responses to old WT mice treated with DMS, suggesting that aging results in a loss of endothelial function that is not further modulated by S1P inhibition. Values are averages ± SEM, where n is the number of mice. Three-way ANOVA with Bonferroni post hoc test, where *p<0.05, **p<0.01, ***p<0.001.

APPROACH

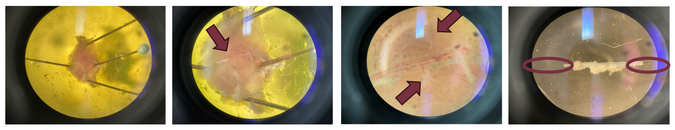


Workflow for adiponectin depletion studies and specific aims in **young (4-7months)** and **old (18-21 months)** mice.

ARTERIOLE DISSECTION & CANNULATION



Arterioles are cannulated and exposed to intraluminal flow by adjusting hydrostatic reservoirs in opposite directions, while diameter changes are measured using a video monitor and caliper.



SUMMARY

1. **Impaired Vasodilation in Aging and AdipoKO:** Arterioles from old WT and young AdipoKO mice showed reduced vasodilation compared to young WT mice.
2. **DMS Treatment Effects:** DMS treatment lowered vasodilation in young WT mice comparable to levels seen in old WT and AdipoKO mice.
3. **S1P-Dependent Dysfunction:** DMS had less or no additional effect in AdipoKO and old WT arterioles respectively, indicating impaired S1P-dependent vasodilation.

CONCLUSION

Aging disrupts adiponectin-S1P signaling, impairing flow-mediated vasodilation, likely due to a loss of adiponectin's ceramidase activity. Our findings establish adiponectin as a key regulator of endothelial function, with its decline contributing to vascular dysfunction. The greater reduction in vasodilation following N,N-dimethylsphingosine (DMS) treatment in WT mice compared to AdipoKO mice supports the role of adiponectin in S1P-mediated endothelial function. The partial preservation of vasodilation in old and AdipoKO mice suggests compensatory mechanisms, such as H_2O_2-mediated vasodilation, may help offset impaired S1P signaling. Future studies will test whether adiponectin agonists can restore endothelial function in aging and AdipoKO mice. Additional work will explore alternative vasodilatory pathways, including the roles of nitric oxide and H_2O_2, using L-NAME and catalase, to further understand vascular adaptation to adiponectin deficiency.

ACKNOWLEDGMENTS

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