

The Apolipoprotein E knockout mice: an attractive new model of ED

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OBJECTIVES

- Erectile dysfunction (ED) and cardiovascular diseases share the same risk factors including hypercholesterolemia and atherosclerosis, but there are few available animal models allowing to study hypercholesterolemia-associated ED.
- Although the use of hypercholesterolemic rabbit models has proven to be useful to illustrate the link between ED and hypercholesterolemia, the cost of daily maintenance of the animals and necessity for important amounts of drug in view of proof of concept studies to prevent or slow down these disorders have limited their use.

We aimed to develop a new model of atherosclerosis-associated ED in a well-known experimental model of atherosclerosis, the ApoE KO mice.

MATERIALS & METHODS

Experimental animals

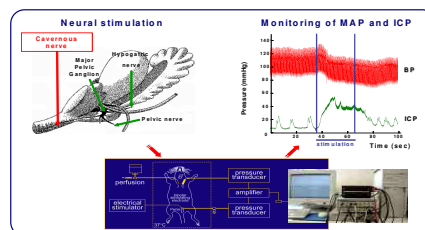
26, 32, and 38 weeks-old ApoE KO mice (Jackson laboratory, Bar Harbour, ME, USA) fed a western-type diet (0.15% cholesterol, 42% milk fat by weight, Teklad diet TD88137, WI, USA) from 4 weeks of age (n=9, 13, and 11 respectively) and age-matched C57BL6/J mice (n=9, 14, and 18 respectively).

In vivo evaluation of erectile function

Mice under isoflurane anesthesia were subjected to electrical stimulation of the cavernous nerve in vivo (square-wave pulses 6 V, 0.3ms pulse duration for 30 s, 0 to 15 Hz frequency). Simultaneous computerized measures of mean arterial blood pressure (MAP) and intracavernous pressure (ICP) were recorded. Erectile responses were expressed as Δ ICP/MAP (%), Δ ICP being the difference between ICP in the flaccid state and ICP during the plateau phase of erectile response, and MAP, the mean arterial pressure during the plateau phase.

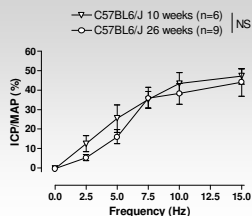
Quantification of atherosclerotic lesions

Atherosclerotic lesions were evaluated by planimetry in Oil Red O stained aortas. The total area of lesions visible from the right common carotid artery bifurcation to the iliac bifurcation was quantified using Lucia G 4.81 imaging analysis software. The results were expressed as percentage of the total luminal surface area.



RESULTS

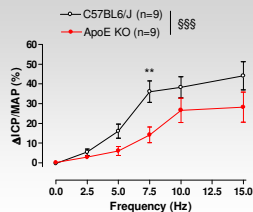
C57BL6/J mice



NS, two-way ANOVA

- Unchanged profile of erectile responses in C57BL6/J mice of 10 and 26 weeks of age.

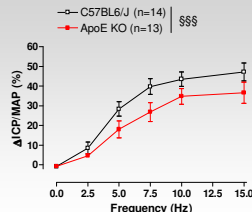
26 weeks-old mice



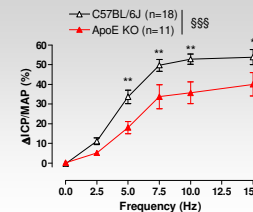
§§§ P<0.001, two-way ANOVA followed by a Bonferroni's post-test (*P<0.05, **P<0.01)

- The magnitude of erectile response was markedly reduced in 26 weeks-old ApoE KO mice compared to age-matched C57BL6/J mice.
- The impairment of erectile response was confirmed in older mice at 32 and 38 weeks of age, but the difference between ApoE KO and C57BL6/J mice did not appear to increase with age.

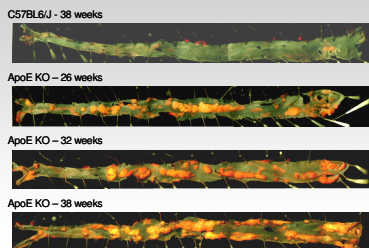
32 weeks-old mice



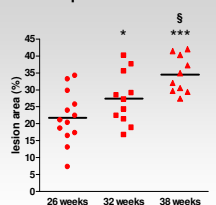
38 weeks-old mice



Oil red O stained aortas



Atherosclerotic lesions quantification



P<0.001 One-way ANOVA, followed by a Newman-Kuls post test: *P<0.05, **P<0.01 vs. 26 weeks, §P<0.05 vs. 32 weeks

- No atherosclerotic plaque was detected in C57BL6/J mice.
- The extent of atherosclerotic plaque area developed within 26 weeks of age in ApoE KO mice, thus covering 21.8% of the total luminal surface of the aorta
- A significant progression of atherosclerotic lesion extent was found with age in ApoE KO mice (27.4% at 32 weeks of age, and 34.5% at 38 weeks of age).

CONCLUSIONS

- The present study provides the first evidence that, using electrical stimulation of the cavernous nerve at increasing frequencies, anesthetized ApoE KO mice fed a Western-type diet demonstrate significantly impaired penile erection compared to age-matched C57BL6/J mice.
- We propose that the ApoE KO mouse could therefore constitute a relevant model for the study of hypercholesterolemia and atherosclerosis-associated ED, and provides an attractive tool to investigate the disease-modifying effects of new therapeutic agents targeting these disorders.

This study represents experimental support to investigate common therapeutic strategies targeting both the progression of systemic consequences of atherosclerosis and ED in both the systemic vascular system and the penis as a target end-organ.