**TAC DOCA surgery and *Leprdb/db* mice**

Minimally invasive transverse aortic constriction (TAC) was performed on ~ 12 week old male C57BL/6J mice as described previously with modification1. Briefly, mice were anesthetized using a single injection of ketamine and xylazine (120mg/kg and 12mg/kg, I.P.) and a 5mm horizontal incision was made at the first left intercostal space. The thymus was temporarily retracted to visualize the aortic arch and a 7-0 silk suture was passed under the aorta between the right innominate and left carotid arteries. The suture was ligated around a blunted 27 gauge needle and the needle was quickly removed. The chest wall and skin were closed. Sham animals underwent the same procedure except the suture was not ligated around the aorta. An additional incision was made in the right flank of the animal and a subcutaneous pocket was created by blunt dissection. A deoxycorticosterone acetate (50mg/pellet, 21 day release) or placebo pellet (Innovative Research of America) was implanted. The skin was closed and the mice were allowed to recover in a ThermoCare warmer.

Male B6.BKS(D)- *Leprdb/J* mice homozygous for the diabetes spontaneous mutation (*Leprdb*) andheterozygotes (*Leprdb*/+) littermates were purchased from Jackson Laboratories (Bar Harbor, ME).All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Arizona and the NIH “Using Animals in Intramural Research“ guidelines.

**Osmotic mini-pumps and vehicle**

For chronic inhibition studies. PF-4449613 ( Pfizer Inc ) was dissolved in 50% [dimethyl sulfoxide](http://www.sciencedirect.com/science/article/pii/S0014488614003379#200015907) (DMSO) and 50% polyethylene glycol (PEG) and was administered via subcutaneously implanted osmotic mini-pumps (Alzet osmotic pump, model 2004). Mice were implanted, at 1 week after TAC-DOCA/sham surgery, with osmotic mini-pumps that released PF-4449613 at concentration of 1 or 5 or 8 mg/kg/day for 28 days. The control animals were implanted with osmotic mini-pumps containing vehicle (DMSO and PEG (1:1)) at an equivalent volume. At the end of week 5 after surgery (or the end of week 4 after osmotic mini-pumps implantation), mice were used for invasive hemodynamic assessment.

In *Leprdb* model, male B6.BKS(D)- *Leprdb/J* mice at 3.5 months of age were implanted with osmotic mini-pumps that released PF-4449613 at concentration of 8 mg/kg/day or vehicle for 28 day, then were used for invasive hemodynamic studies.

The effect of early initiation of PDE9a inhibition was tested in adult male C57BL/6J mice. Mice were implanted, at 1 week prior to TAC-DOCA/sham surgery, with osmotic mini-pumps that released PF-4449613 at concentration of 8 mg/kg/day or vehicle and were followed up for 6 weeks. At 5 weeks post-surgery (or the end of week 6 after mini-pumps implantation), mice were used for invasive hemodynamic assessment.