Analysis of AVP functions via V1a and V1b receptors with knockout mice

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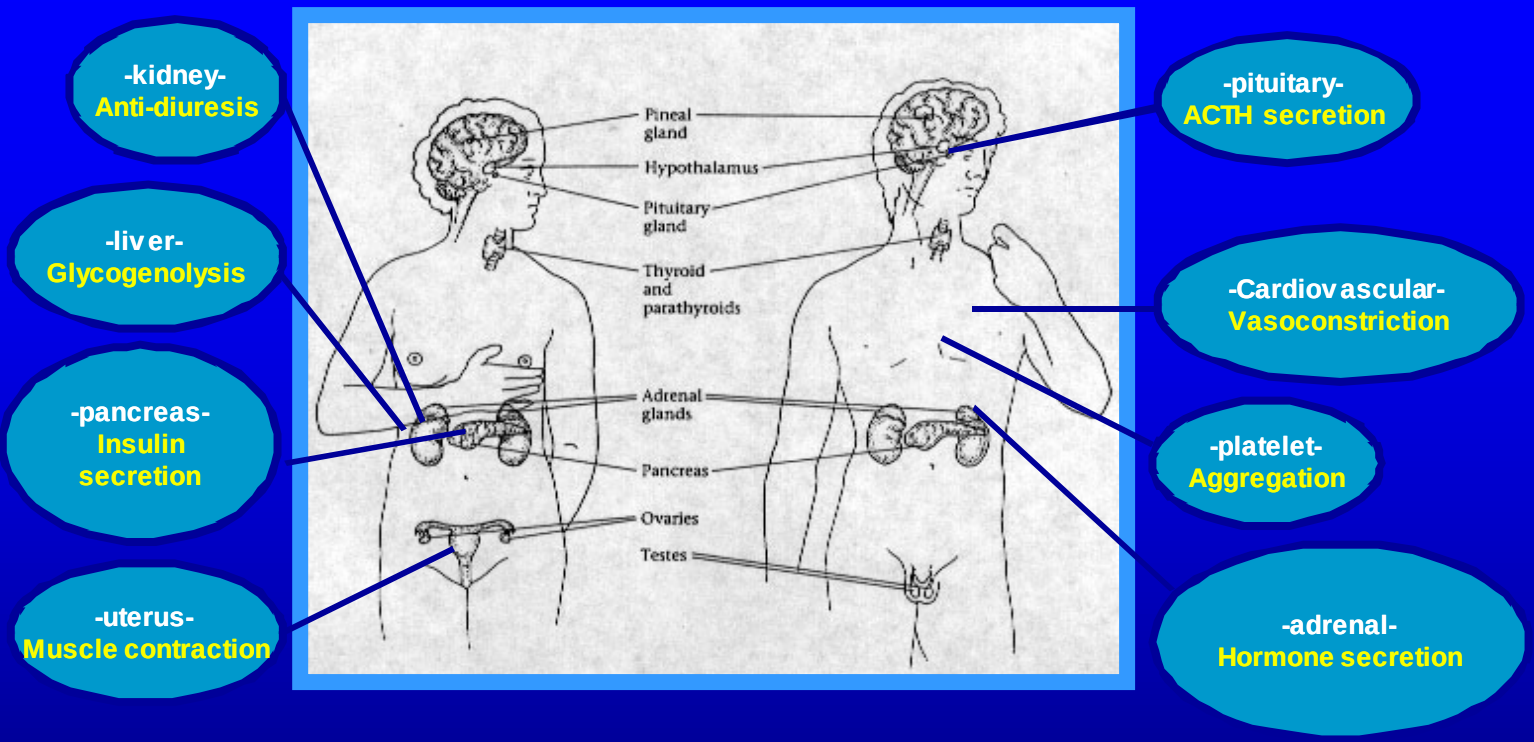
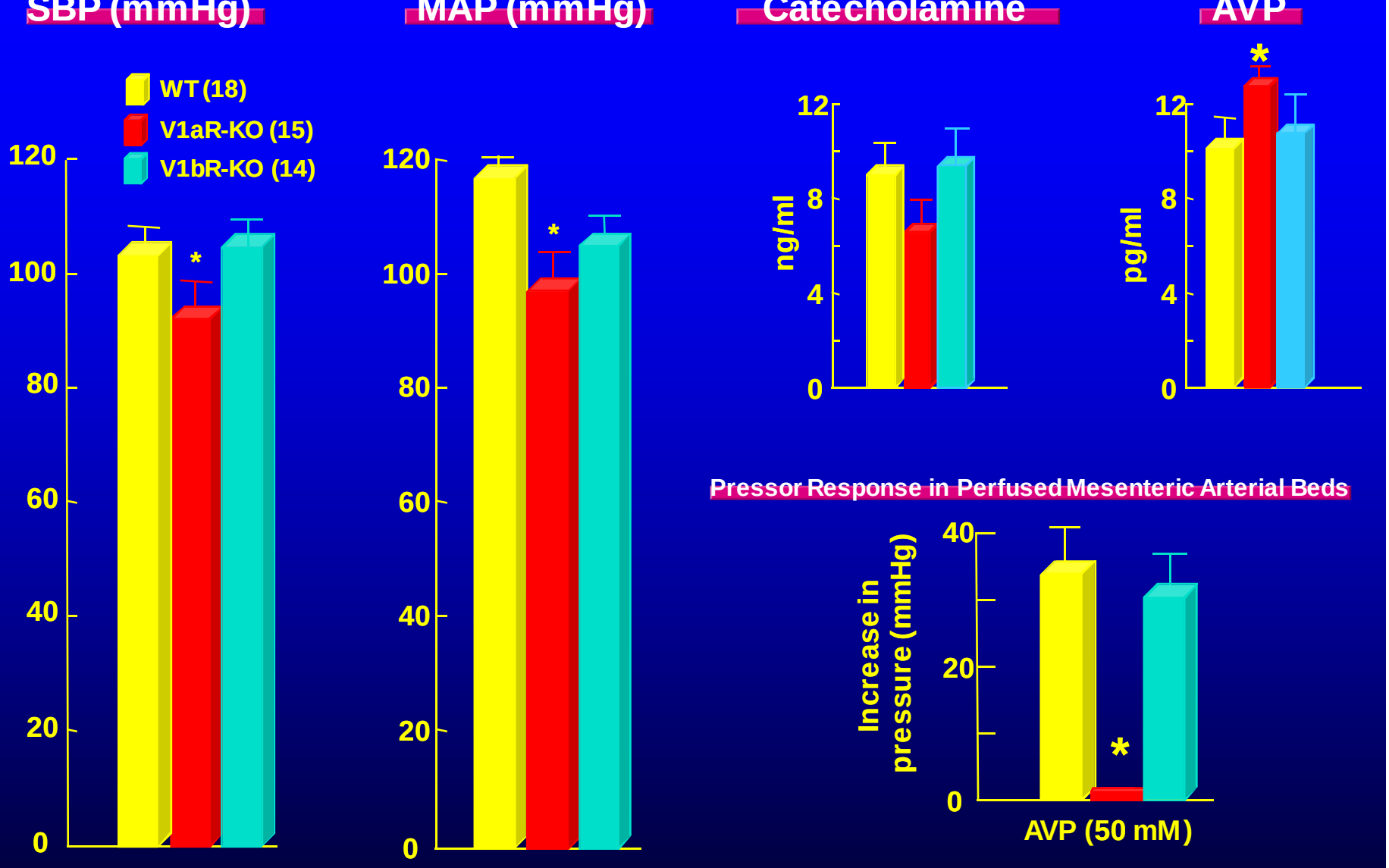
Arginine-Vasopressin (AVP) is involved in regulating diverse functions



These physiological effects of AVP are mediated via the AVP receptor subfamily.

Subtype	V1a	V1b	V2
Expression site	Vessels	Anterior pituitary	Renal tubules
action	vasoconstriction	ACTH secretion	antidiuresis

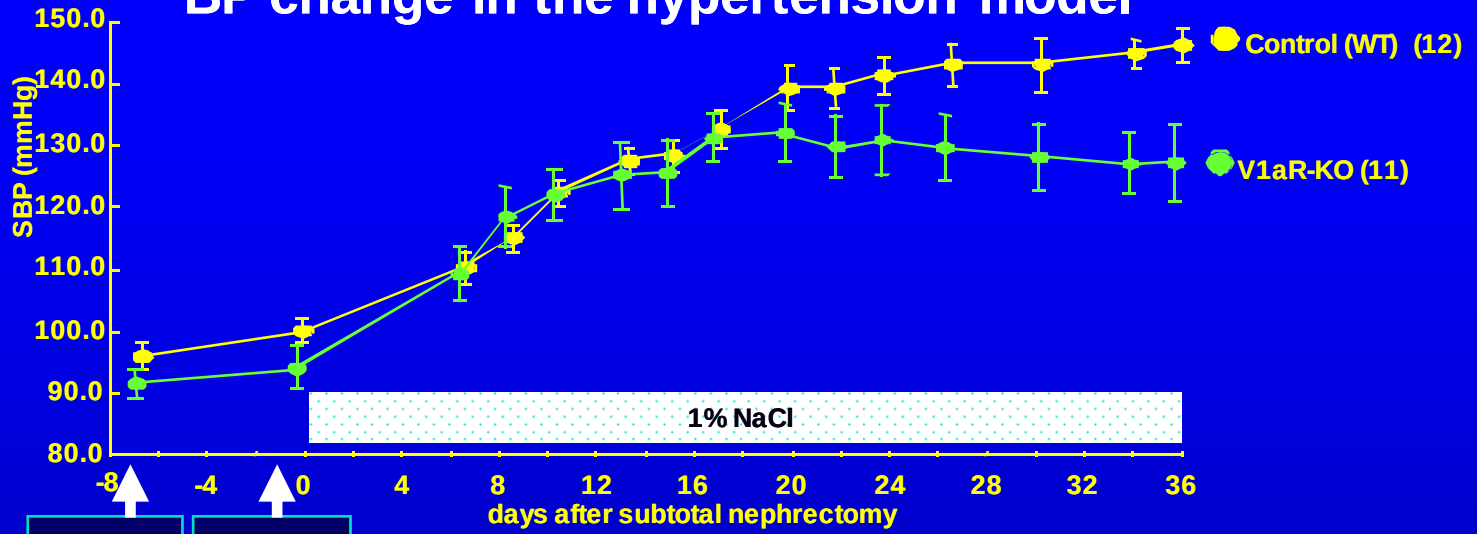
Reduced Blood Pressure (BP) in V1aR-KO

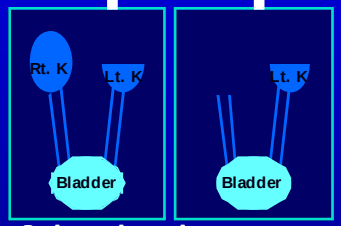


Koshimizu et al., *Proc Natl Acad Sci U S A. 2006*

1. The decreased BP in V1aR-KO mice could result from the decreased vascular tonus.

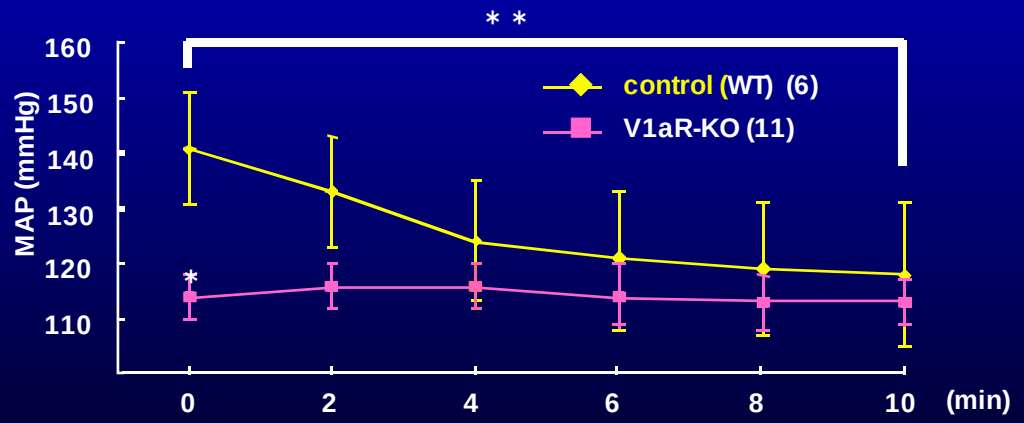
BP change in the hypertension model





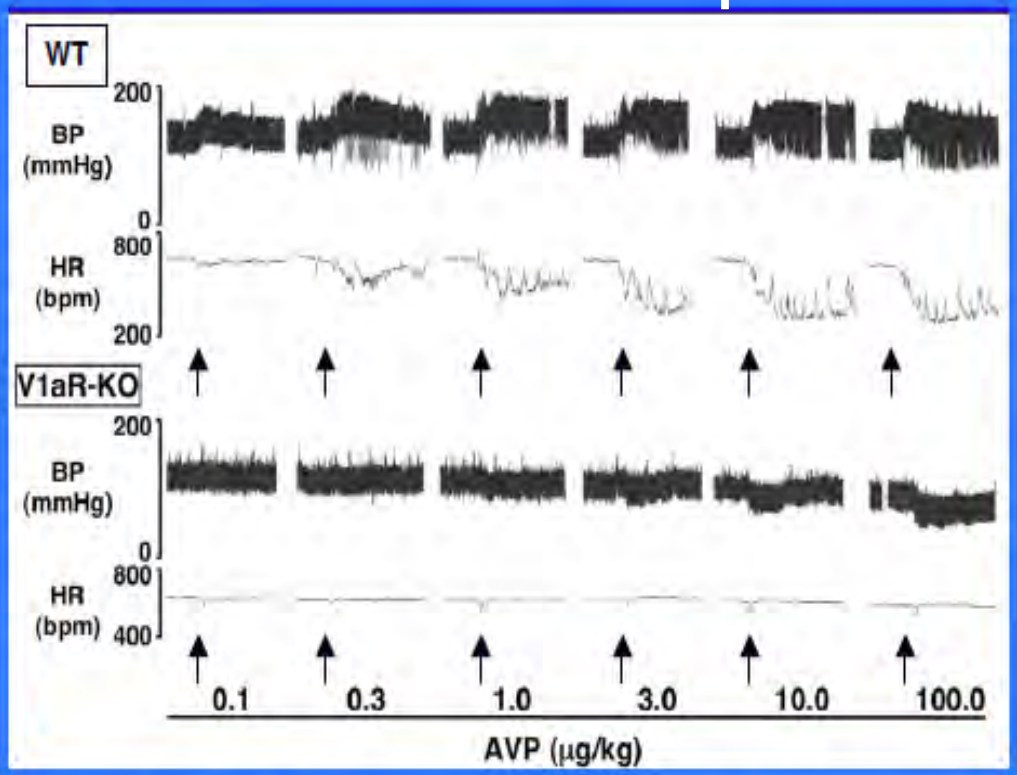
Subtotal nephrectomy

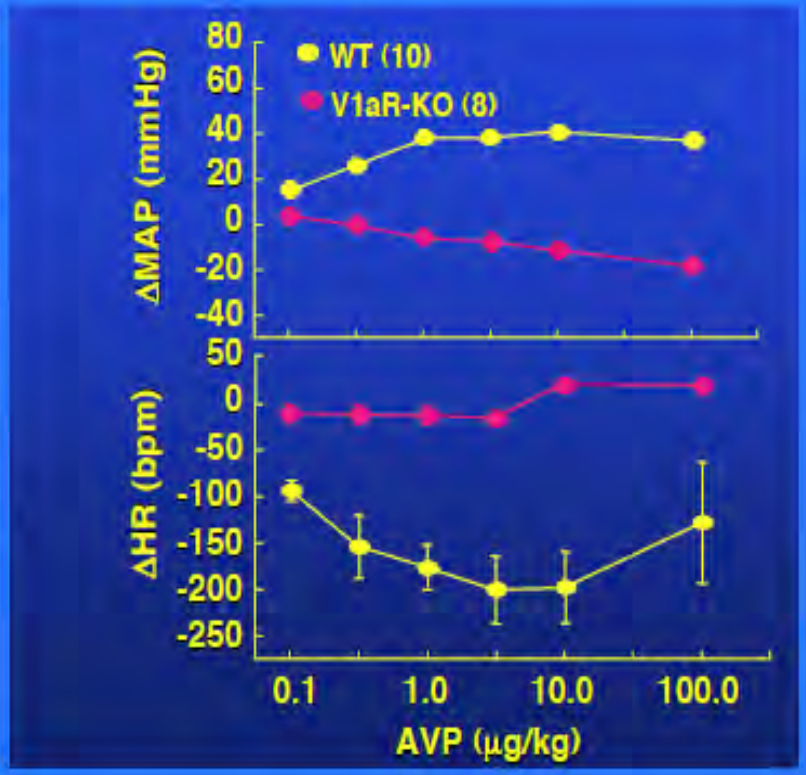
Effect of the V1aR antagonist (10μg/kg, i.v.) on BP in the hypertensive mice

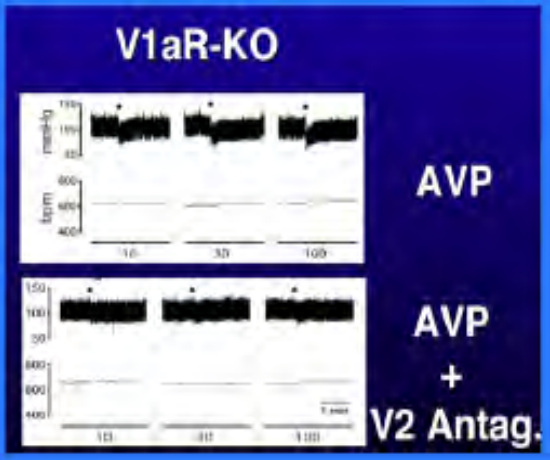


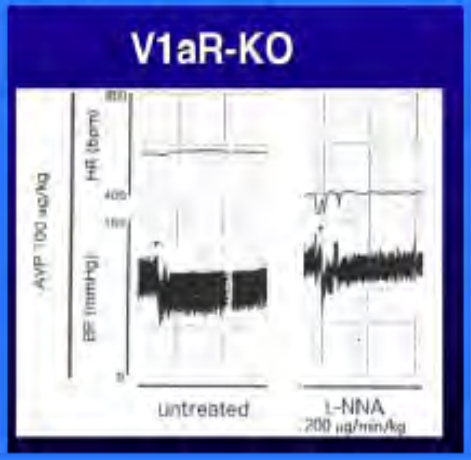
The V1a receptor is involved in developing and/or maintaining hypertension, and blockade of the V1a receptor results in decreasing BP in the hypertensive mice.

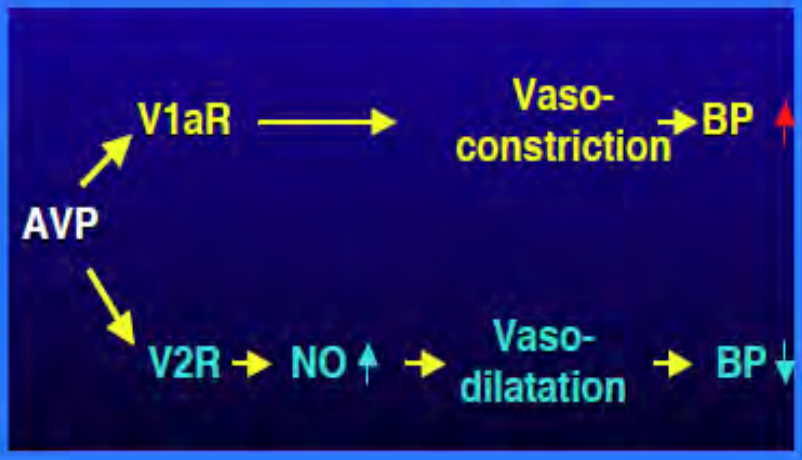
BP and HR response to the AVP stimulation







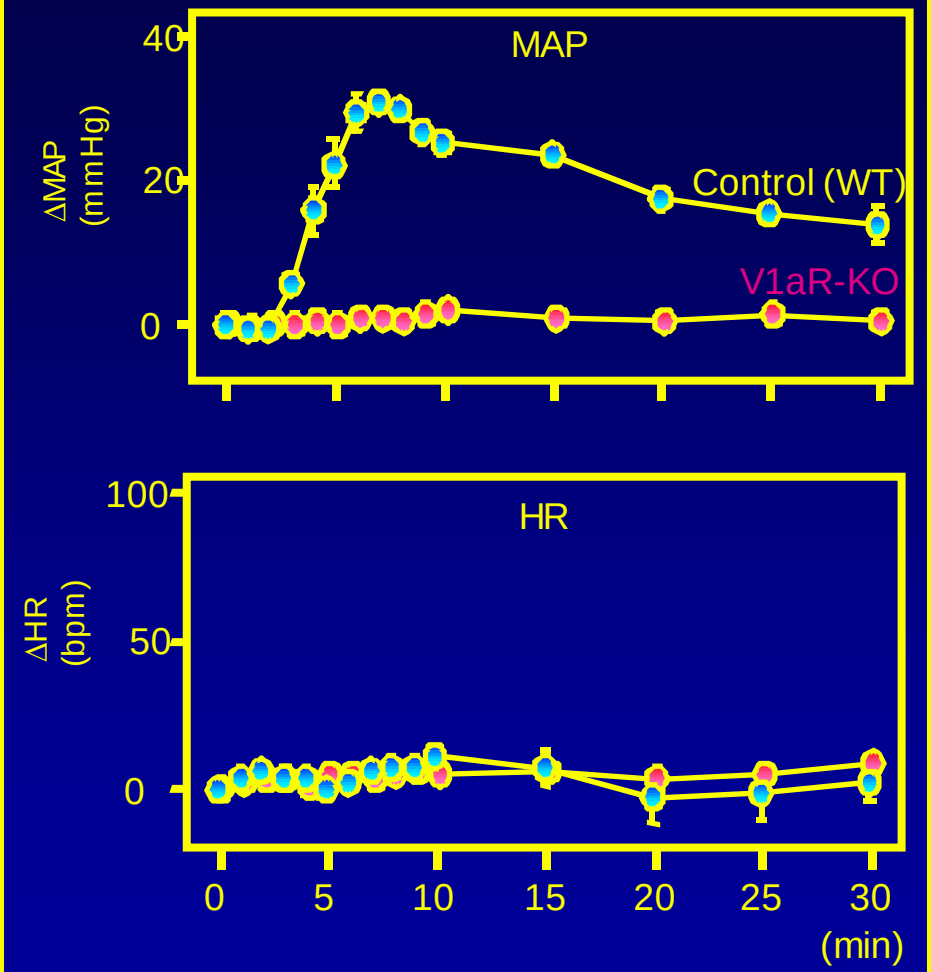




2. AVP stimulates vasoconstriction via V1aR and also stimulates vasodilatation via V2R, and the decreased pressor response to the AVP stimulation in KO mice could result in the decreased BP.

Decreased sypatethic nerve activity in CNS of V1aR-KO

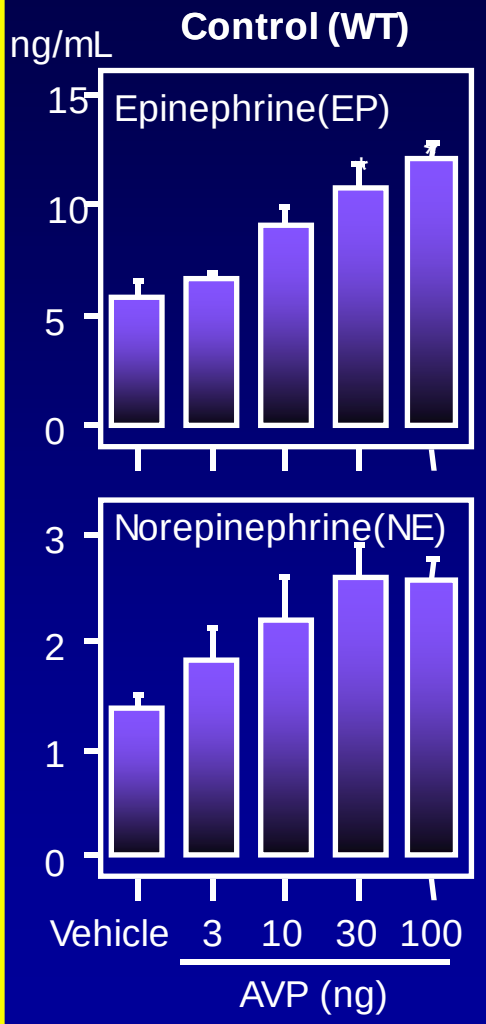
BP and HR change after the AVP injection into the intra-cereberoventricle (icv)

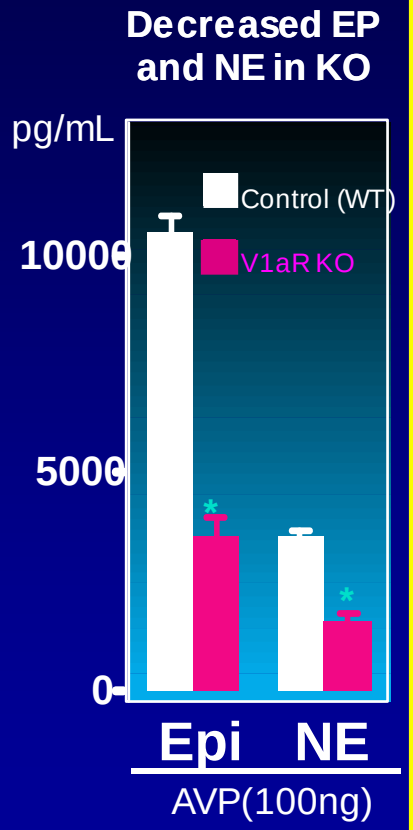


AVP 10 ng (icv) was injected into icv.

Oikawa et al., Eur J Pharmacol. 2007

Catecolamines after the AVP injection (icv)

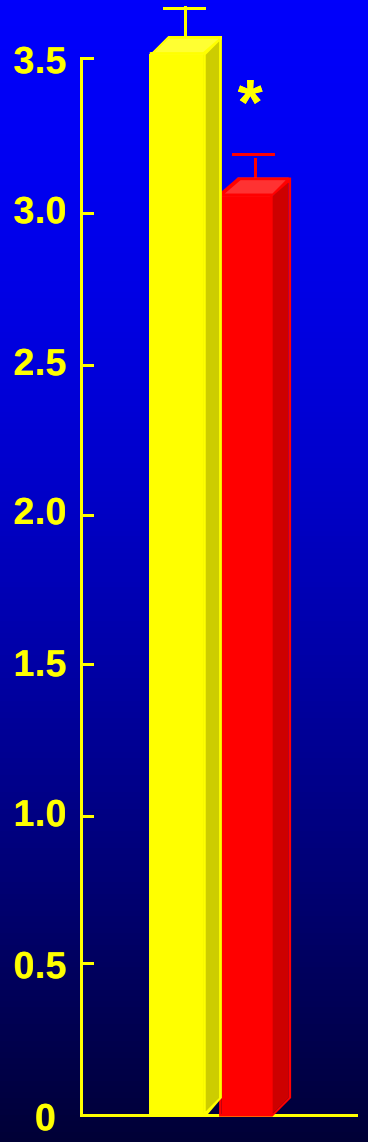




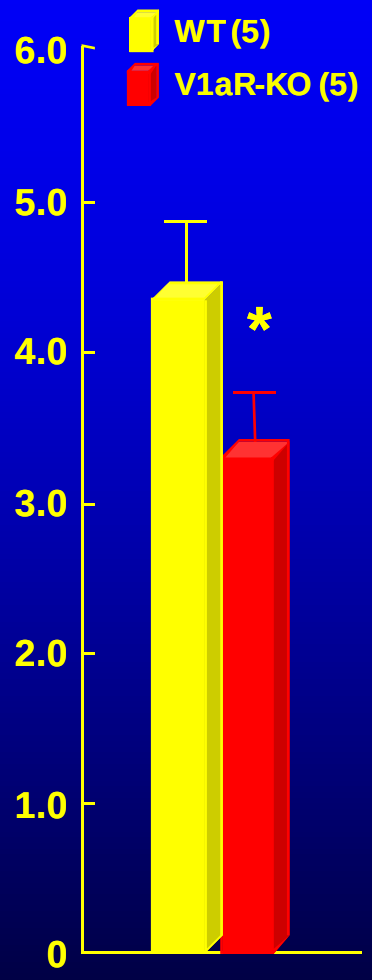
3. Decreased sympathetic nerve activity in response to AVP could cause the decreased BP in KO mice.

Reduced Blood Volume and Plasma aldosterone level in V1aR-KO

Blood volume (ml)

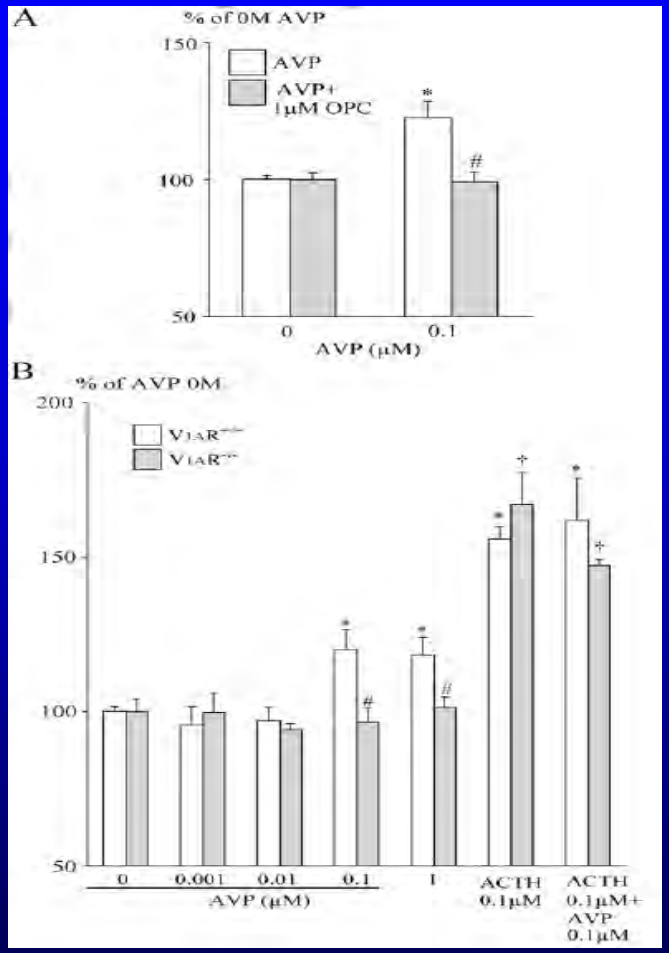


Aldosterone (ng/ml)



Aoyagi et al., *Endocrinology. 2007*

AVP stimulates aldosterone release from adrenal gland cells via V1aR.

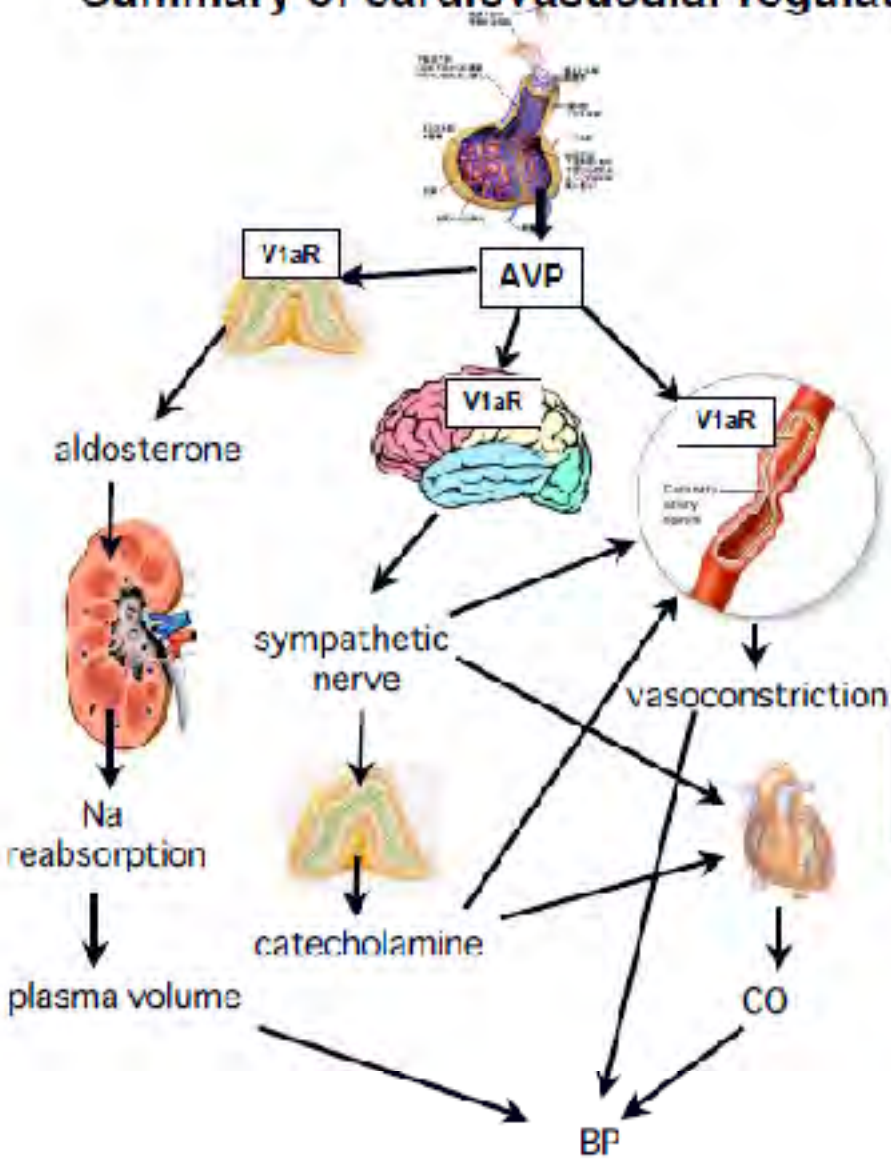


Impaired aldosterone release in V1aR-KO adrenal cells

Birumachi et al. *Eur J Pharmacol. 2007*

4. AVP-stimulated aldosterone release was impaired in V1aR-KO mice, and impaired aldosterone release could result in the lower plasma aldosterone level and consequent lower blood volume and BP.

Summary of cardiovasucular regulation of AVP via V1aR

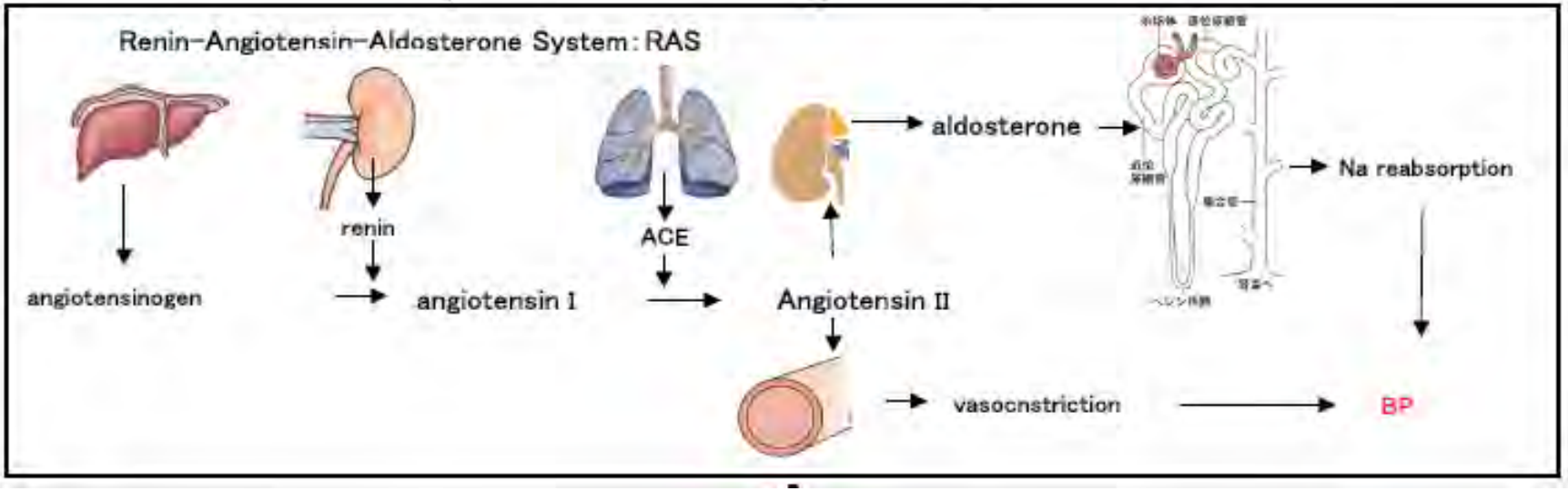


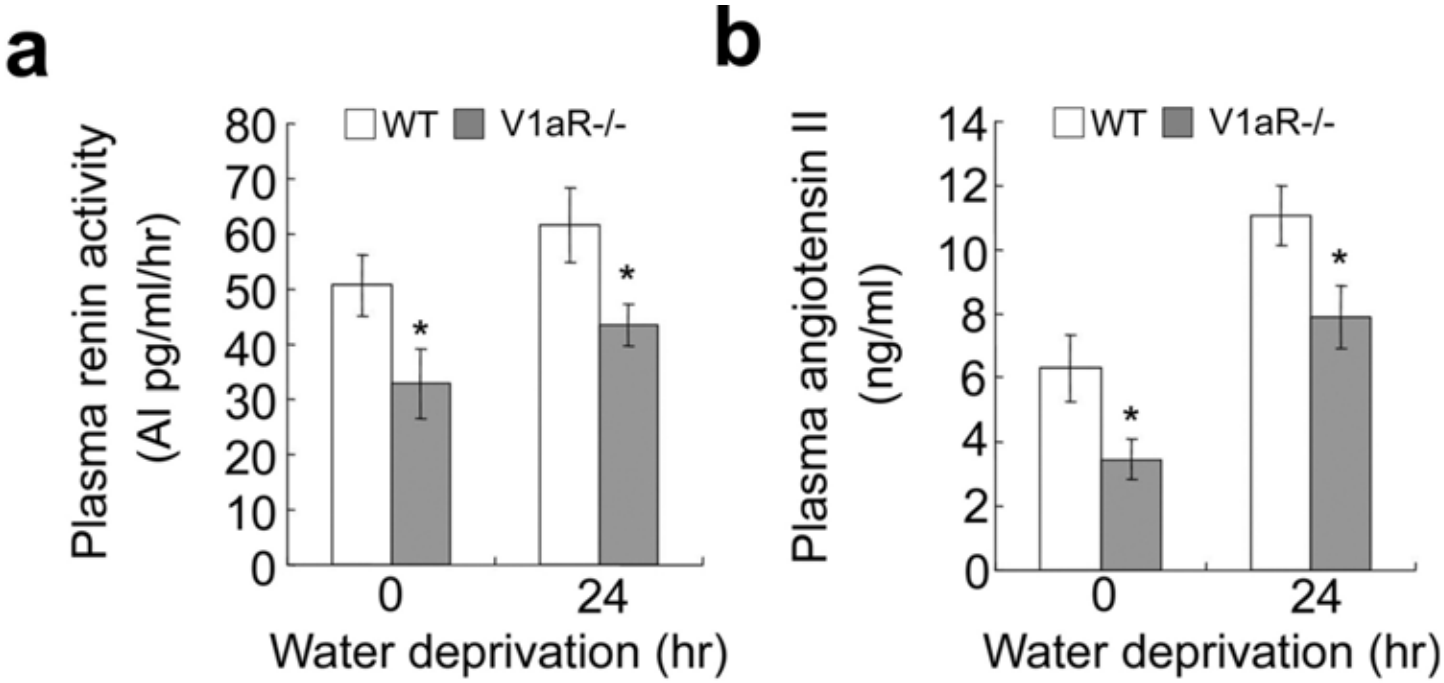
Blockade of the V1a receptor

1.Decreased aldosterone and plasma volume
2.Decreased sympathetic nerve activity
3.Decreased vascular resistance and pressor response

Decreased BP

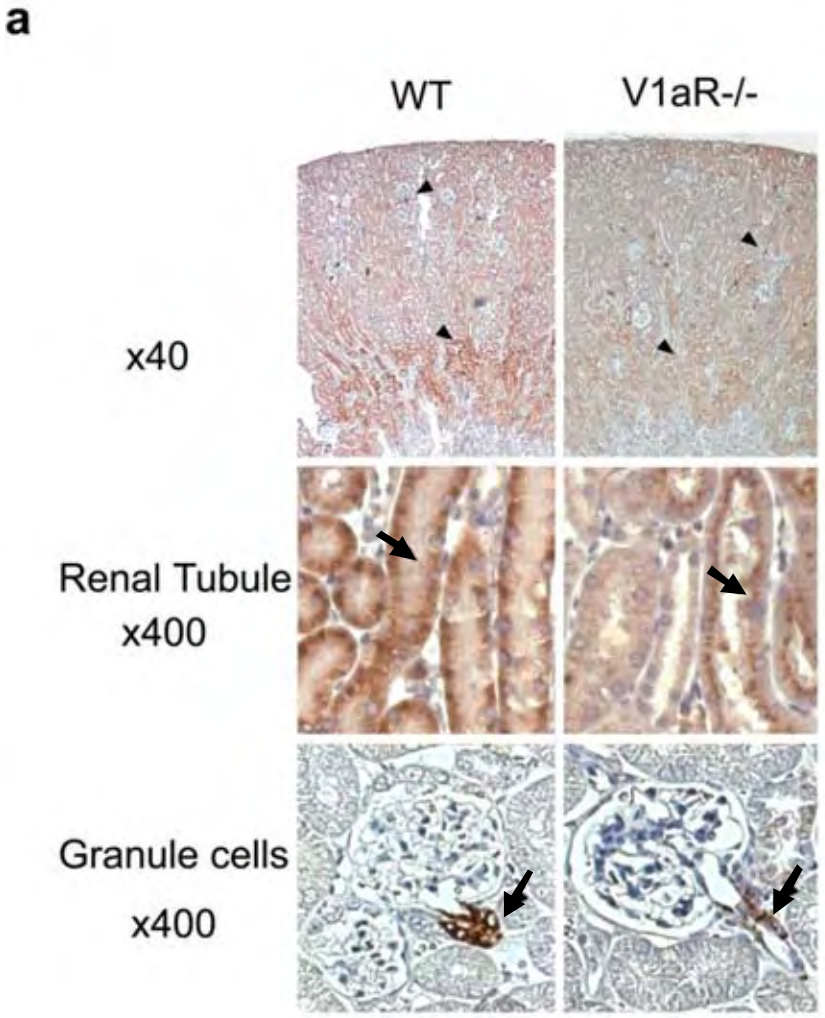
Decreased plasma renin activity and angiotension II in V1aR-KO



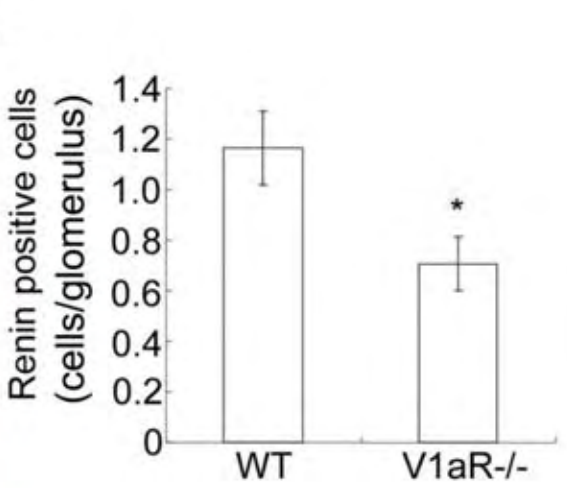


Aoyagi et al., *Amer J Physiol* 2008

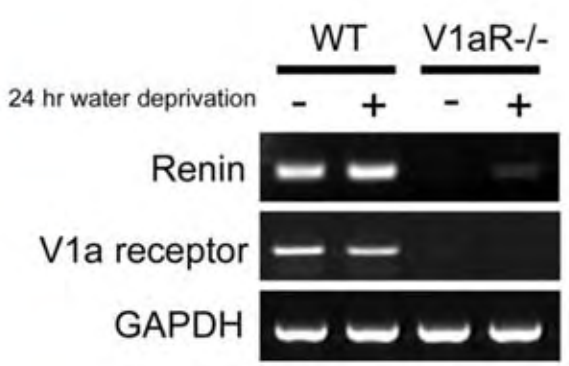
Decreased renin expression in the kidney of V1aR-KO



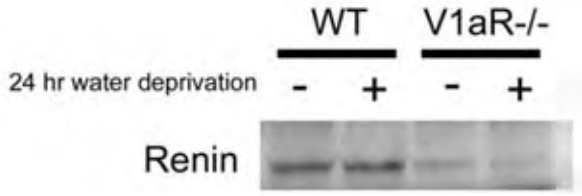
Immunohistochemistry with renin antibody in V1aR-KO



Number of renin positive cells in the kidney



Renin RNA expressions in the kidney

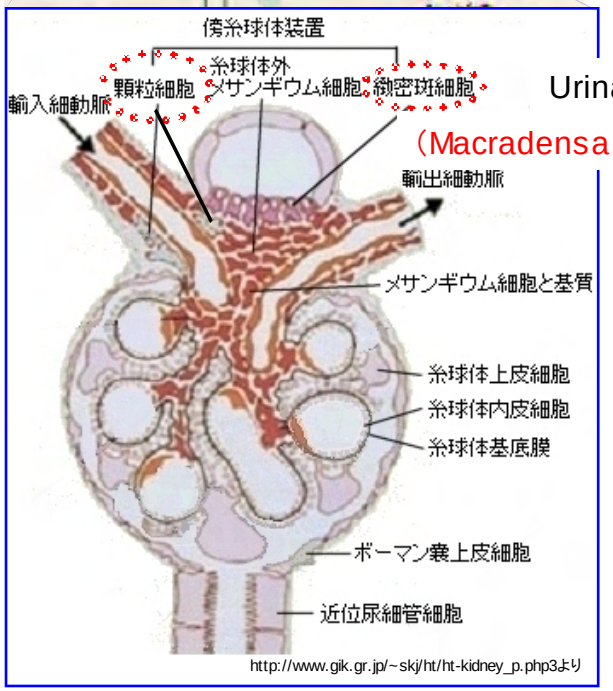


Renin expressions in the kidney

Aoyagi et al., *Amer J Physiol* 2008

Decreased expression of nNOS and COX-2 in the kidney of V1aR-KO

Regulation of renin secretion by NO and PGE2 in MD cells



(Macradensa cell)

Urinary Cl^- concentration↓

↓

nNOS, COX2 ↑

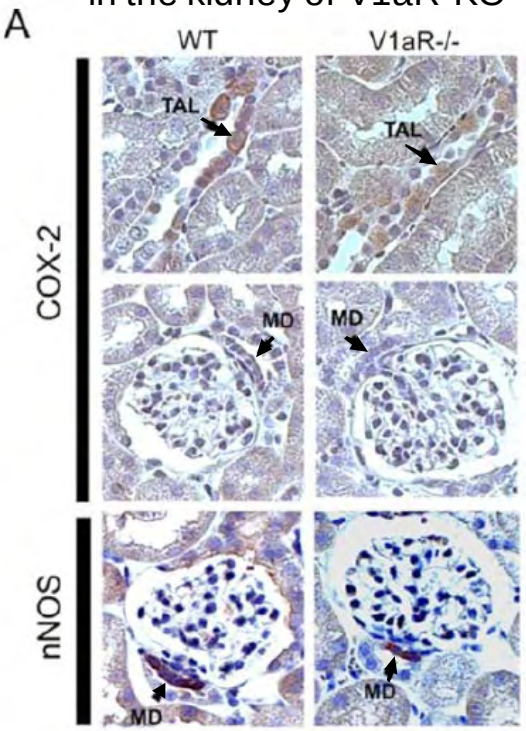
↓

NO, PGE_2 ↑

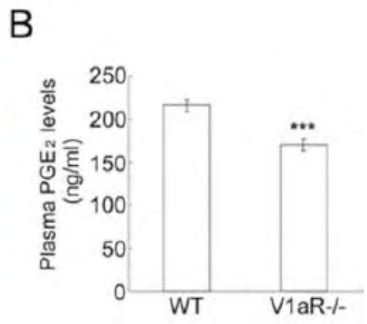
↓

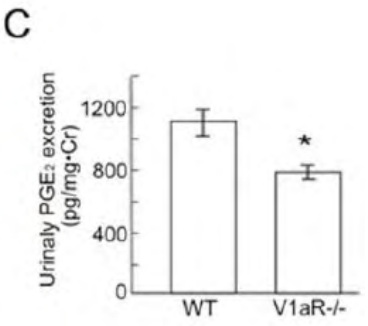
renin↑

Decreased expression of nNOS and COX-2 in the kidney of V1aR-KO

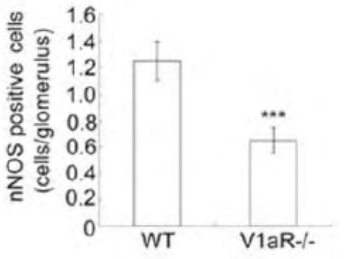


Immunohistochemistry with COX2 and nNOS antibody

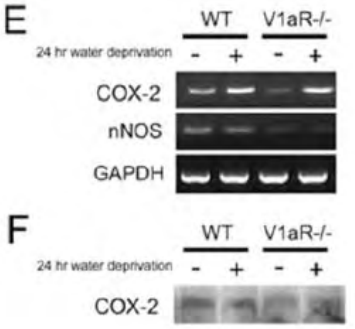




PGE2 levels in V1aR-KO



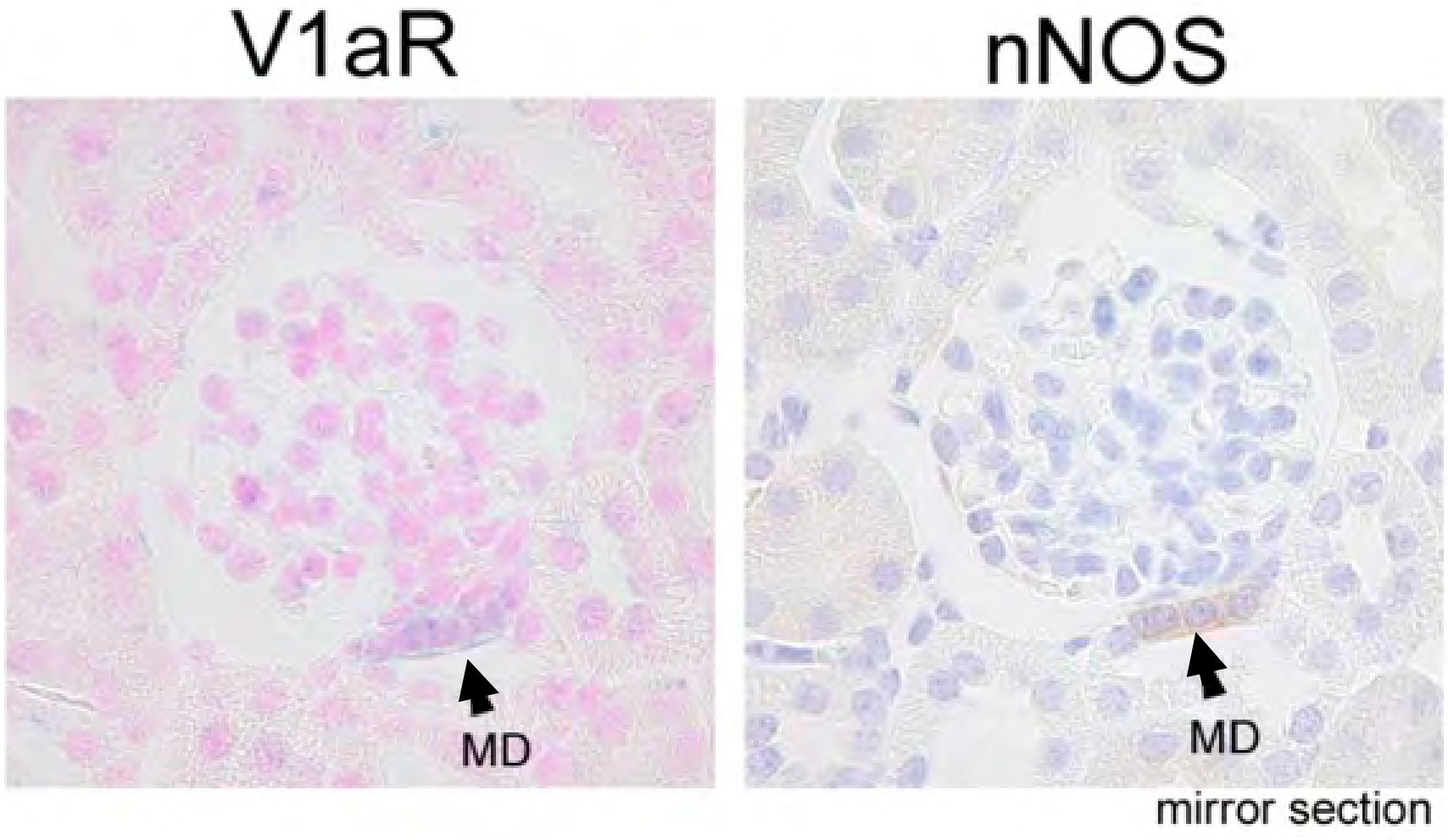
No. of nNOS positive cells in the kidney



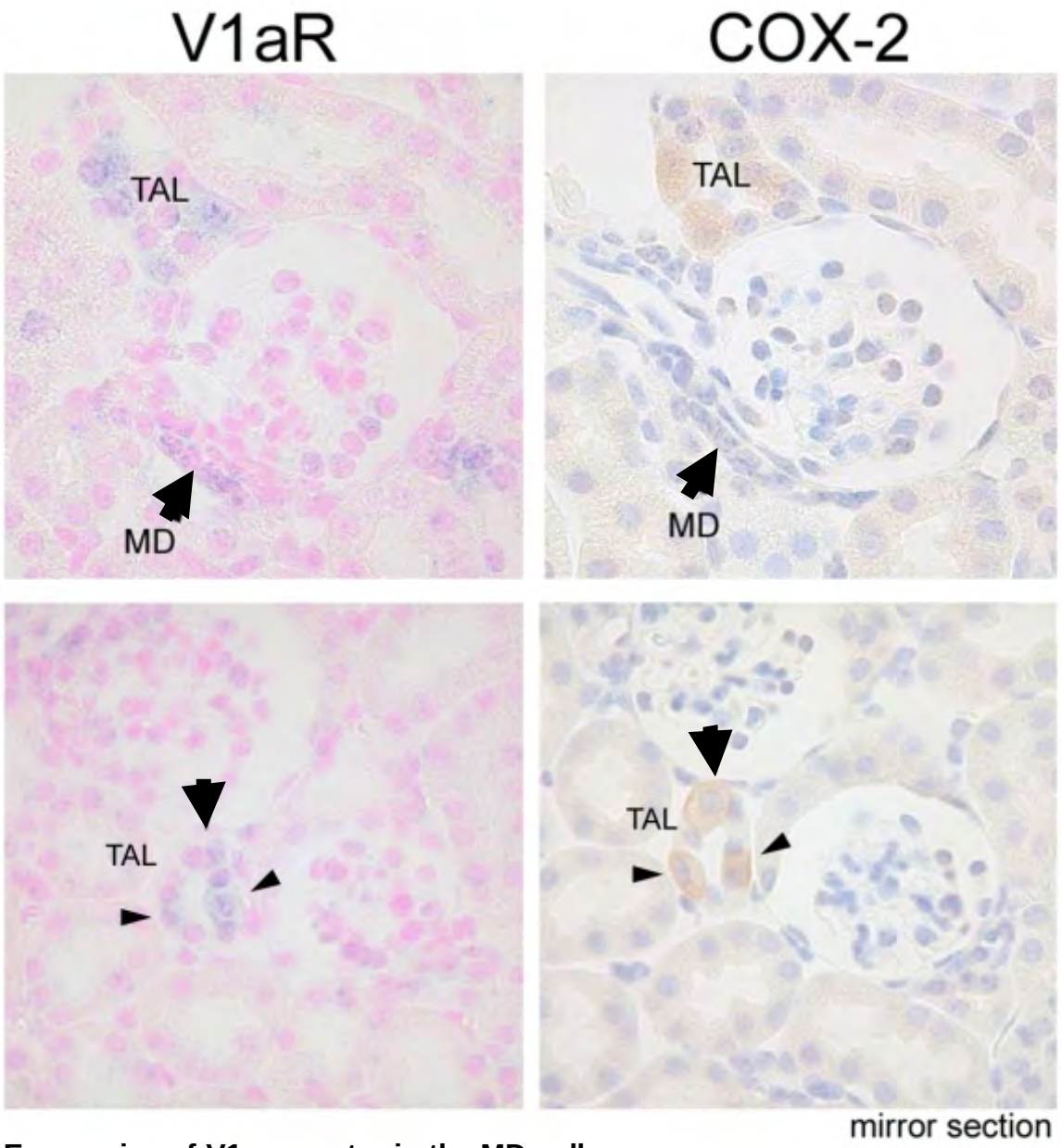
COX2 expressions in the kidney

V1aR is involved in regulating NOS and COX2, and decreased expressions cause the reduced renin production

Co-localization of nNOS with V1aR in Macradensa (MD) cell



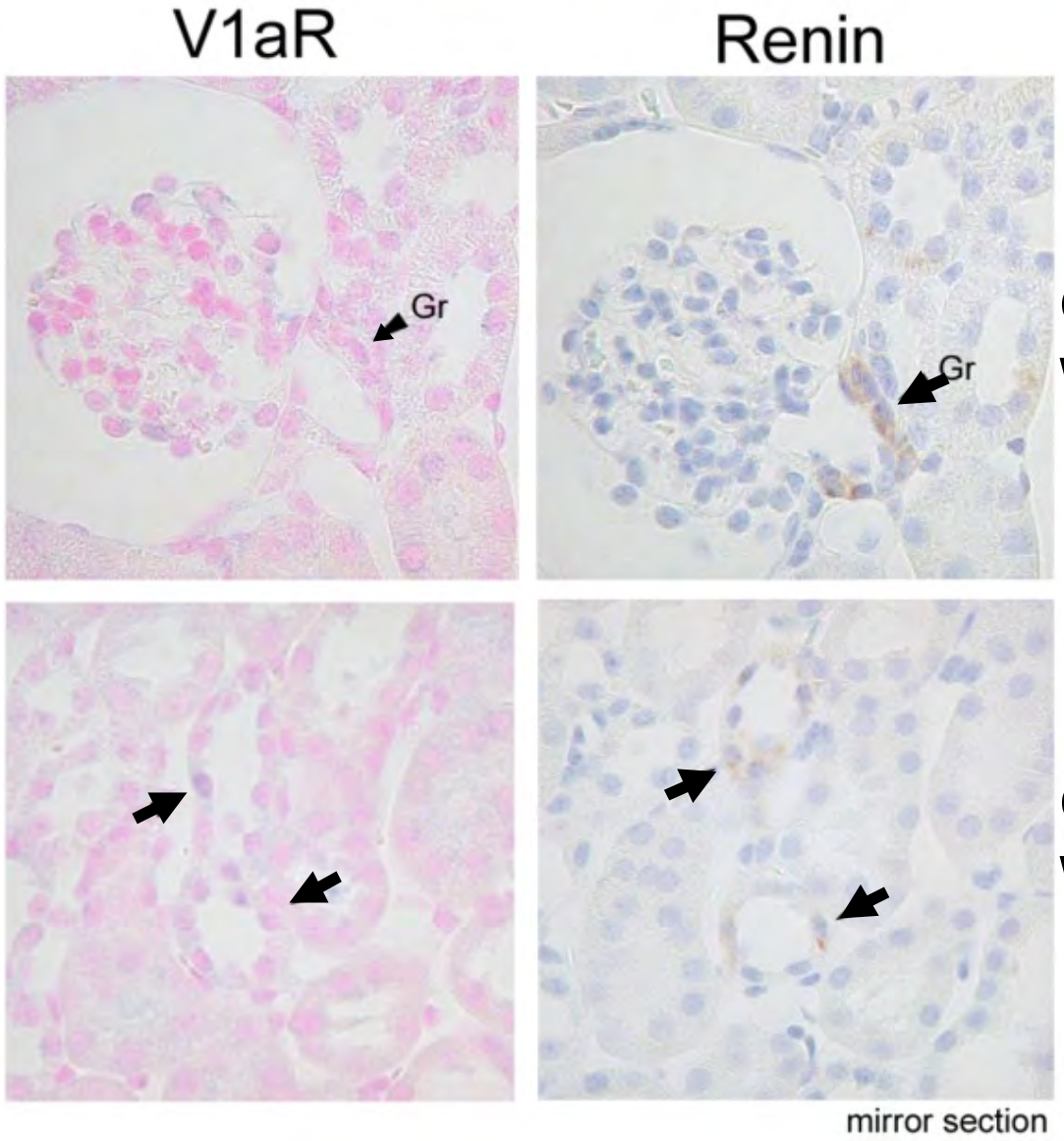
Expression of V1a receptor in the MD cell.
The co-localization of the V1aR mRNA and nNOS were determined by *in situ* hybridization and immunostaining in kidney mirror sections. Arrowheads indicate MD cells, where the V1aR mRNA was co-localized with nNOS.



Co-localization of COX-2 with V1aR in MD cell

Co-localization of COX-2 with V1aR in TAL

Expression of V1a receptor in the MD cell.
The co-localization of the V1aR mRNA and COX-2 were determined by *in situ* hybridization and immunostaining in kidney mirror sections. Arrowheads indicate MD cells, or renal tubule cells where the V1aR mRNA was co-localized with COX-2.



Co-localization of renin with V1aR in granule cells

Co-localization of renin with V1aR in renal tubles

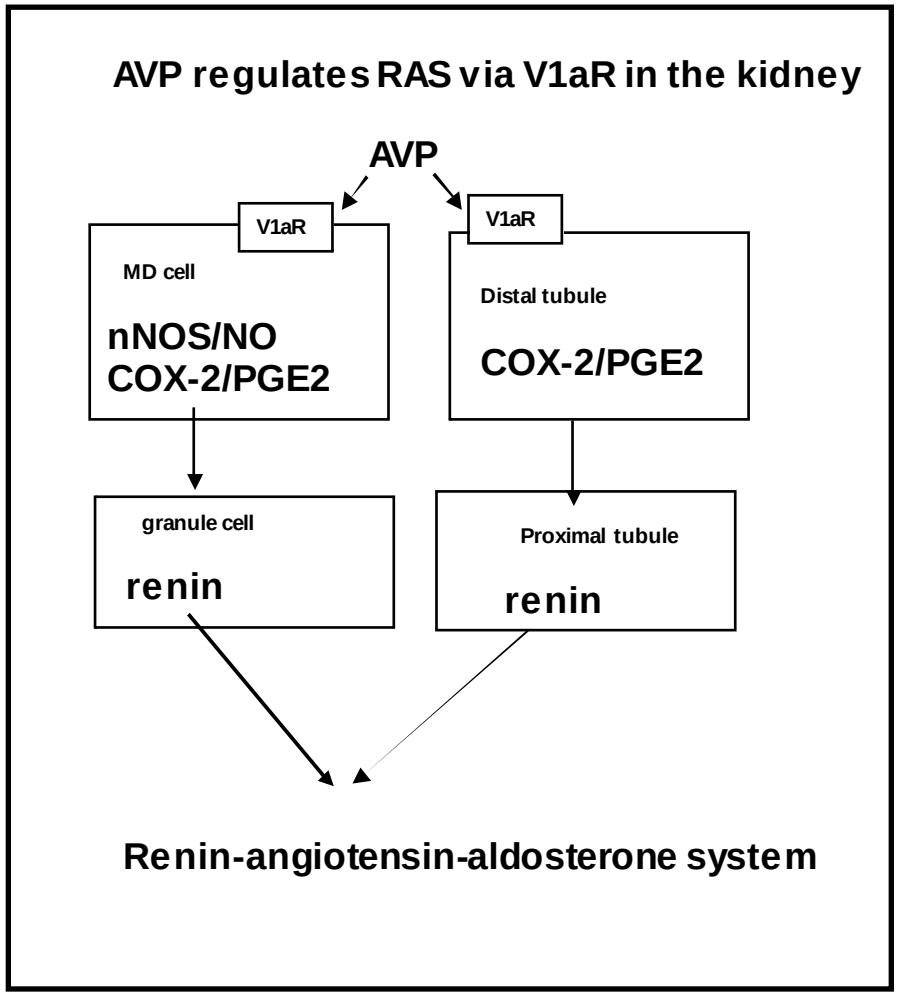
Expression of V1a receptor in the MD cell.
The co-localization of the V1aR mRNA and renin were determined by *in situ* hybridization and immunostaining in kidney mirror sections. Arrowheads indicate MD cells, or renal tubule cells where the V1aR mRNA was co-localized with renin.

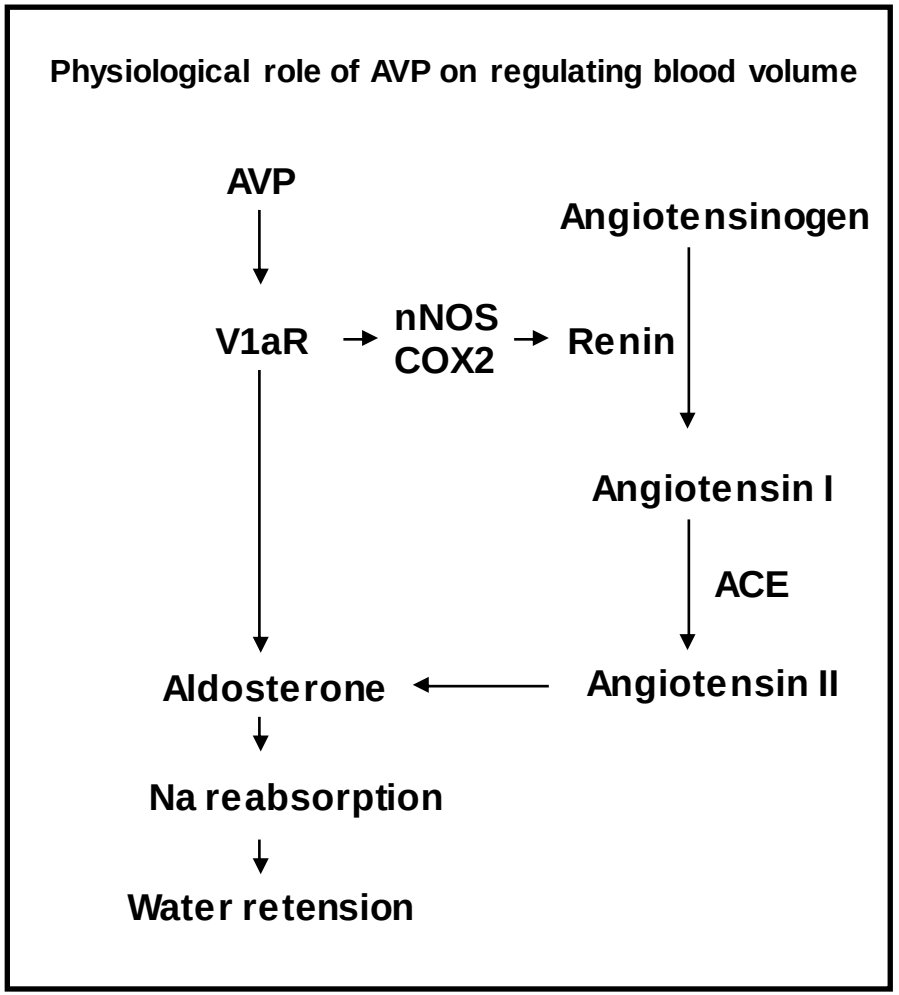
Summary of AVP function on regulating RAS and blood volume

① V1aR mediates the renin production by regulating the nNOS and COX-2 in MD cells.

② ・AVP-aldosterone system
・Renin-angiotensin-aldosterone system

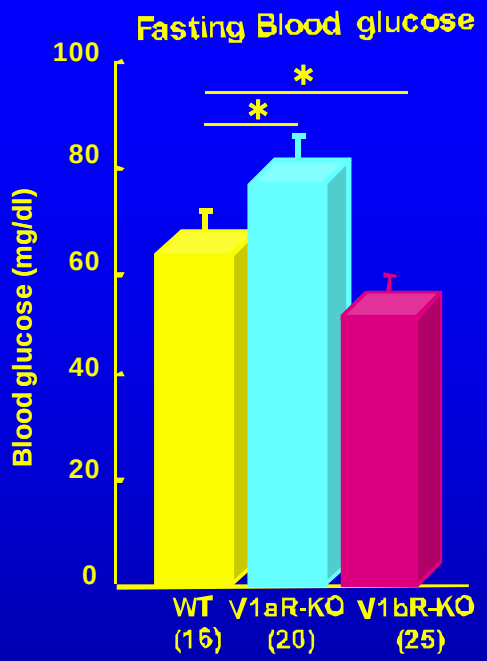
Which are impaired in V1aR-KO, leading to decreased aldosterone and blood volume

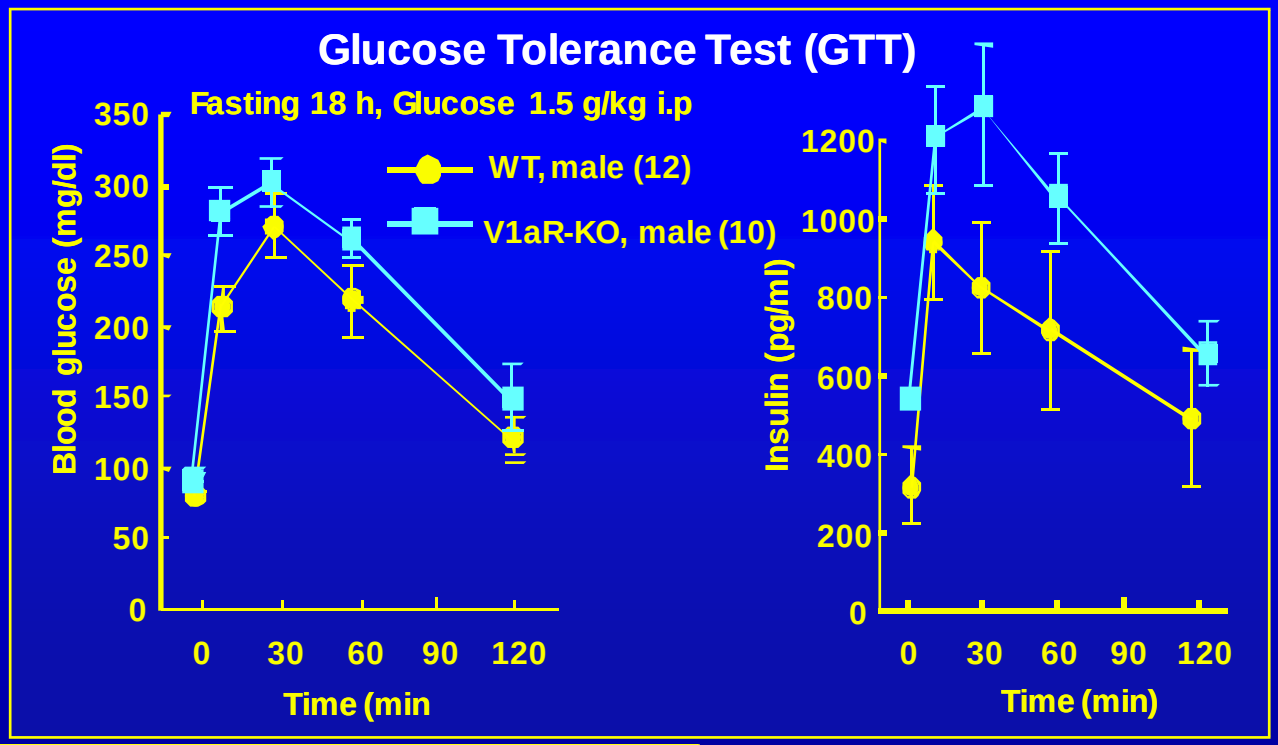


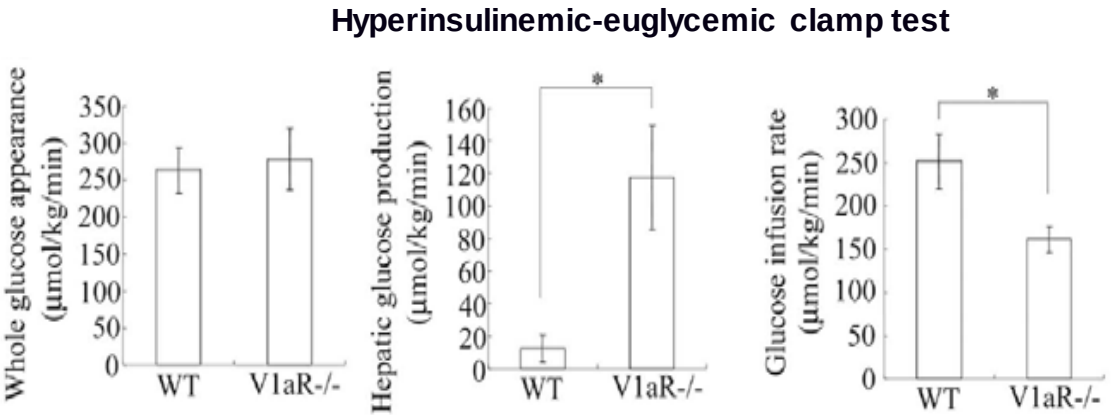


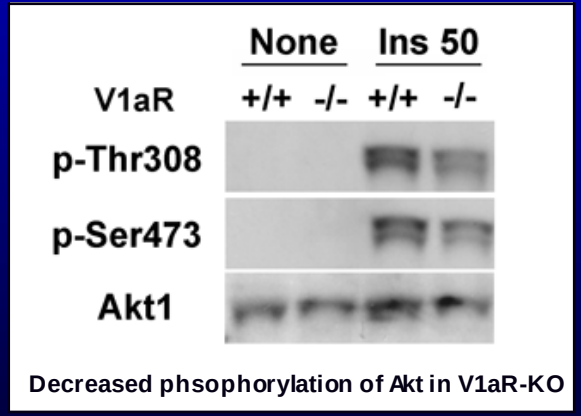
AVP not only stimulates aldosterone release directly from adrenal cortex via the V1a receptor, but also regulates nNOS, COX2 and renin via the V1a receptor in the kidney.

Impaired glucose tolerance in V1aR-KO mice







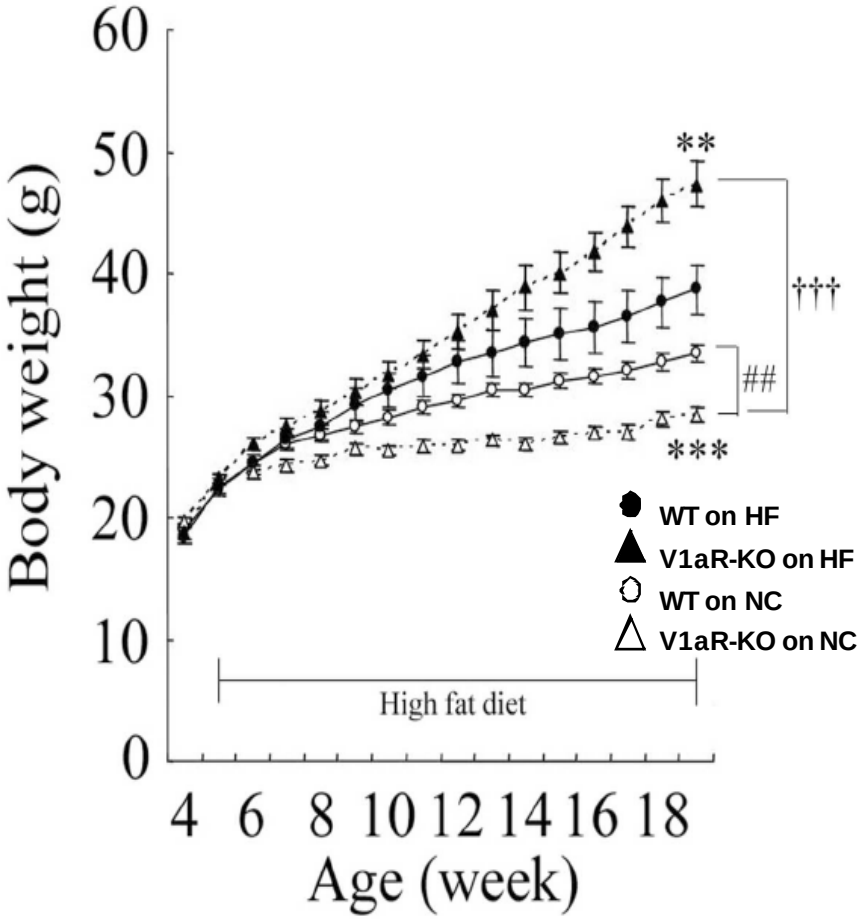


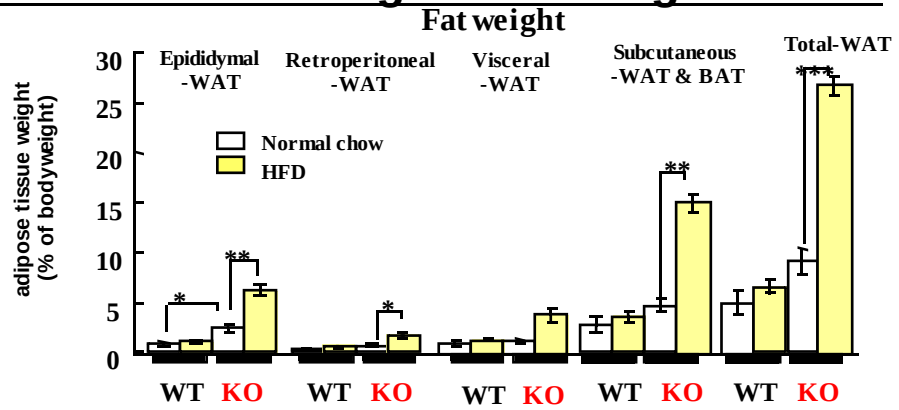
Decreased phsophorylation of Akt in V1aR-KO

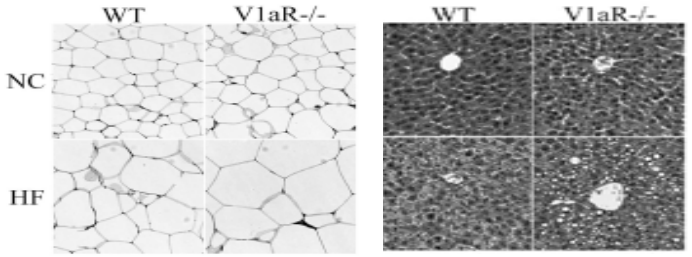
Hiroyama et al., *J Physiol* 2007

Glucose tolerance was impaired due to increased hepatic glucose production, and suppressed insulin signal in V1aR-KO.

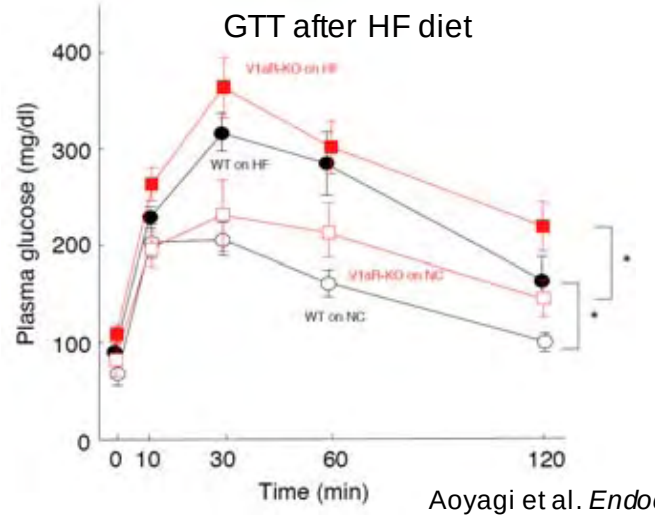
BW, fat weight and glucose tolerance after feeding with the high fat diet







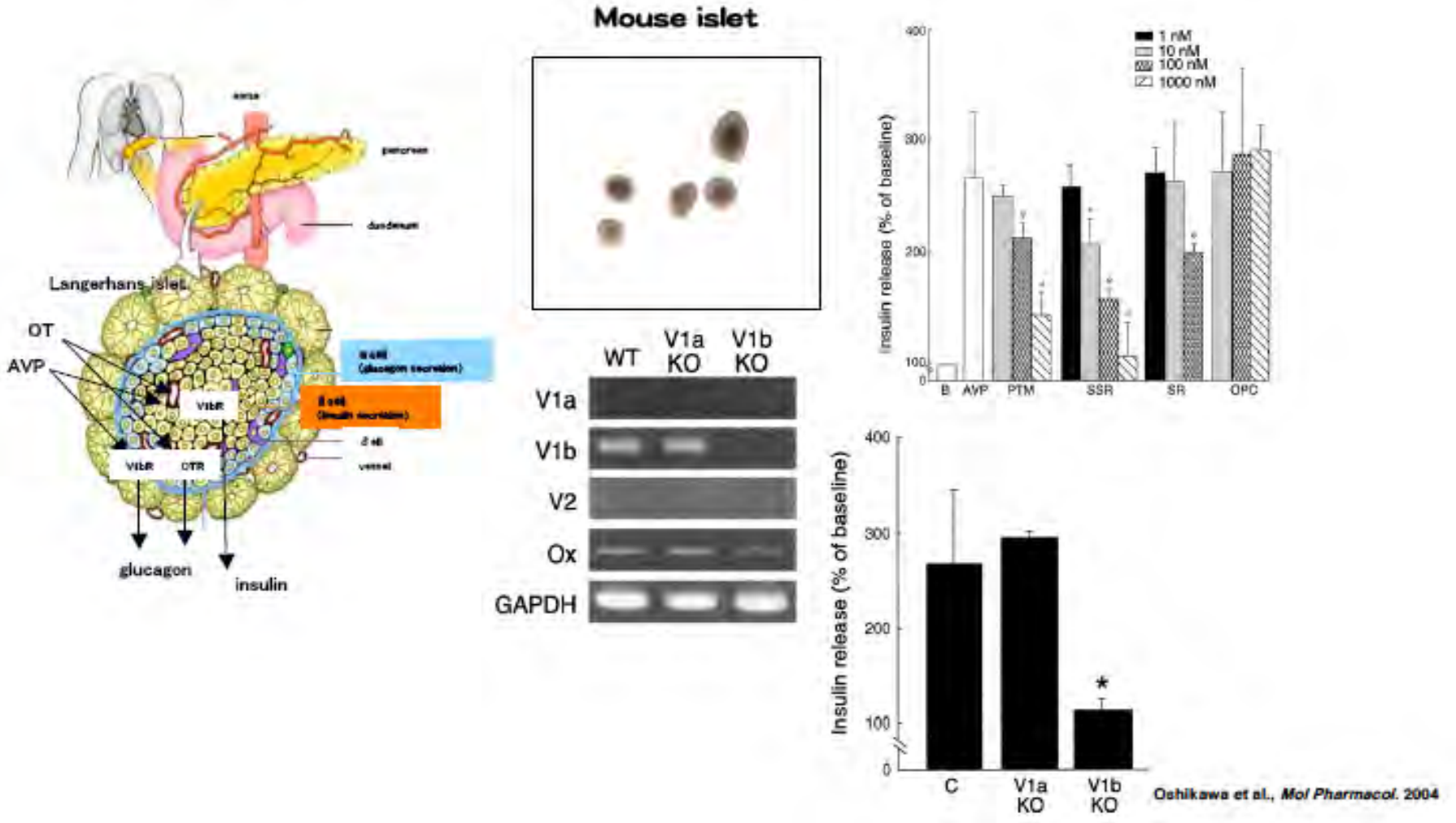
Histology of fat and liver after loading with HF diet



Aoyagi et al. *Endocrinology* 2007

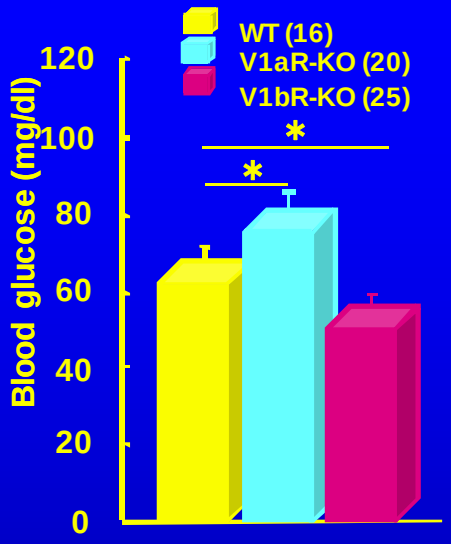
Glucose intolerance was accelerated by the HF diet, leading to hyperglycemia, excessive obesity, and fatty liver in V1aR-KO.

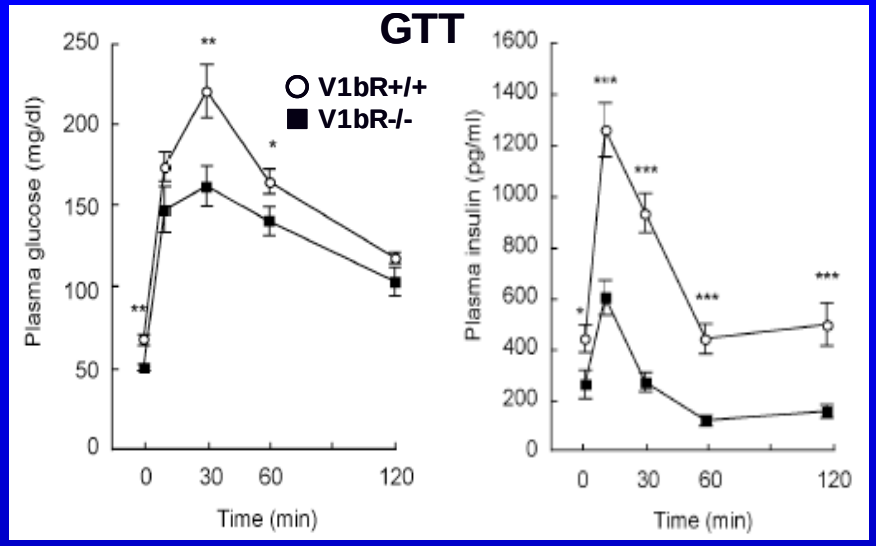
Impaired insulin release from cultured islets in V1bR-KO

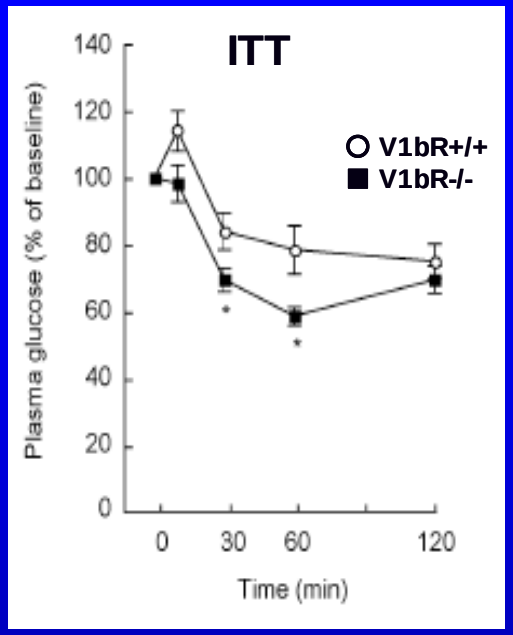


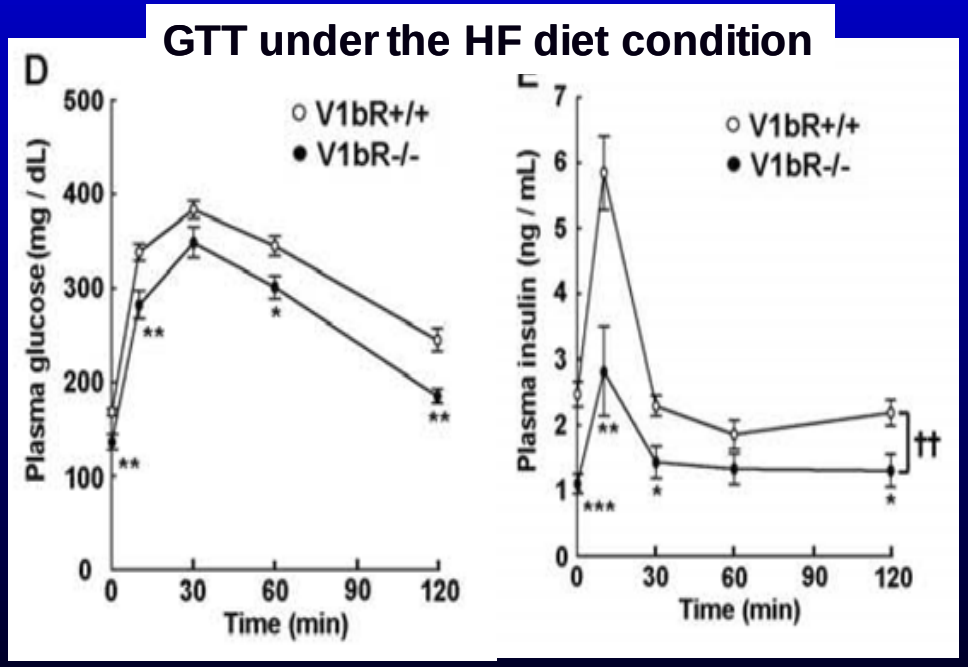
AVP mediates the insulin secretion via the V1b receptors and AVP-stimulated insulin secretion was impaired in V1bR-KO.

Increased insulin sensitivity in V1bR-KO mice









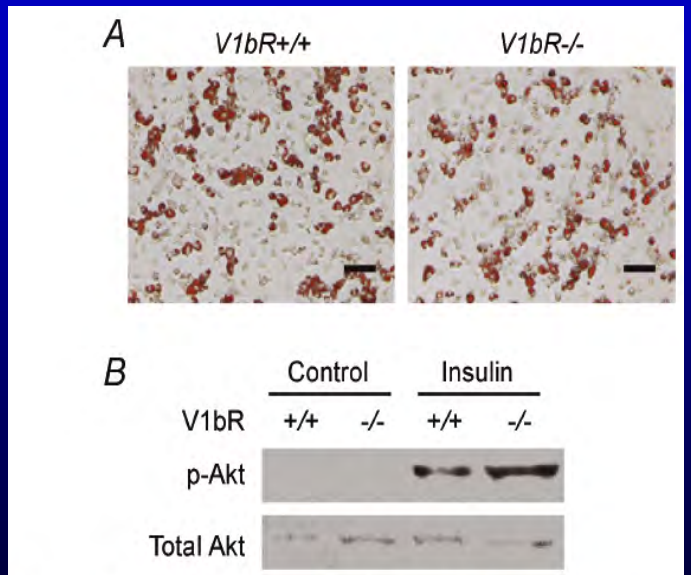
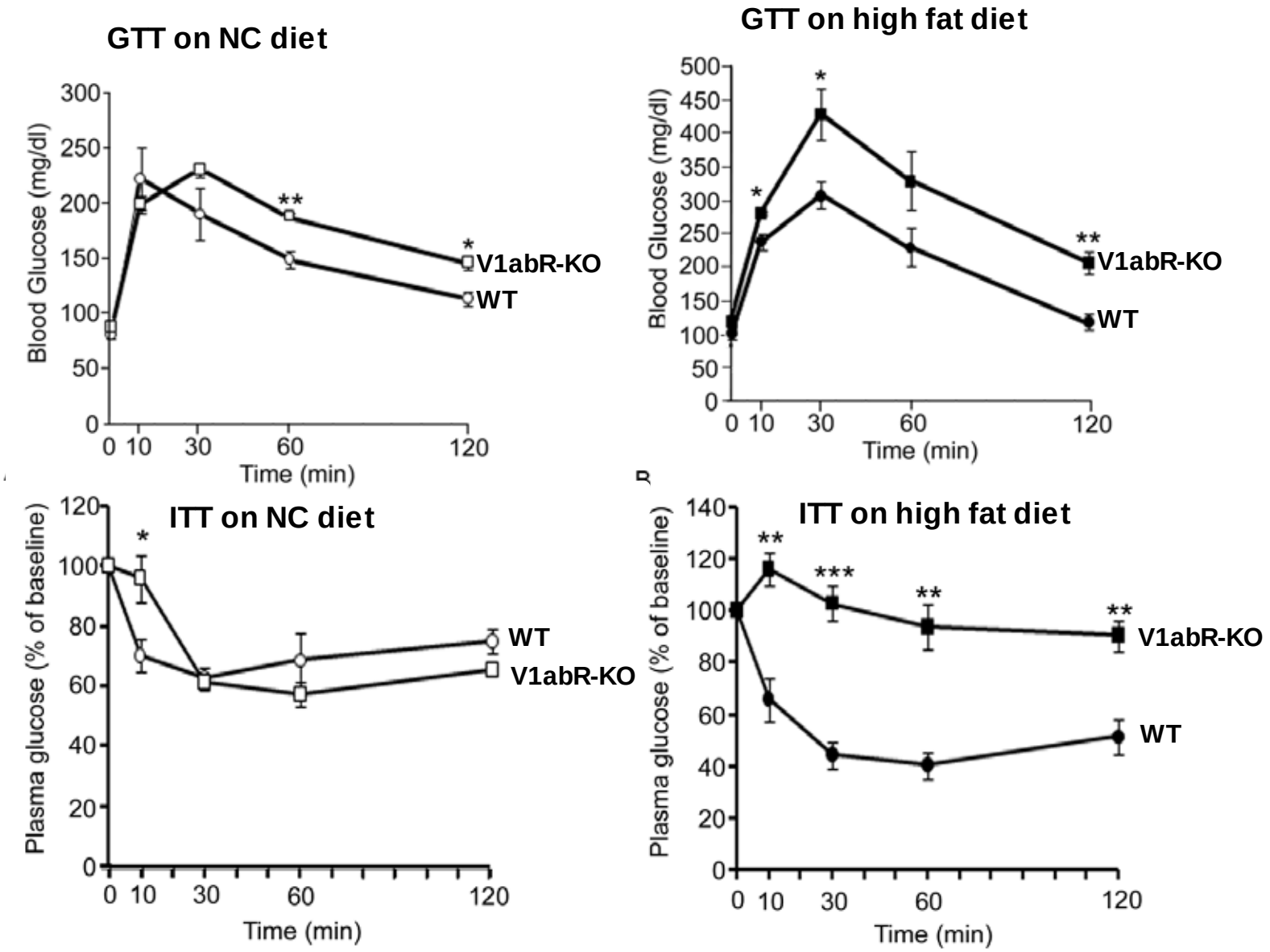


Figure 5. Effect on phosphorylation of Akt by insulin stimulation

Fujiwara et al., *J Physiol. 2007*

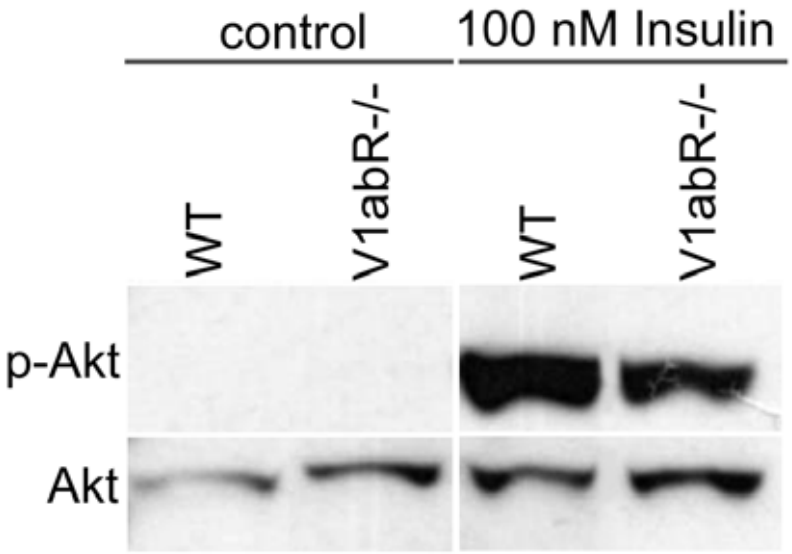
Insulin sensitivity was enhanced in V1bR-KO due to the enhanced insulin signal in adipocytes.

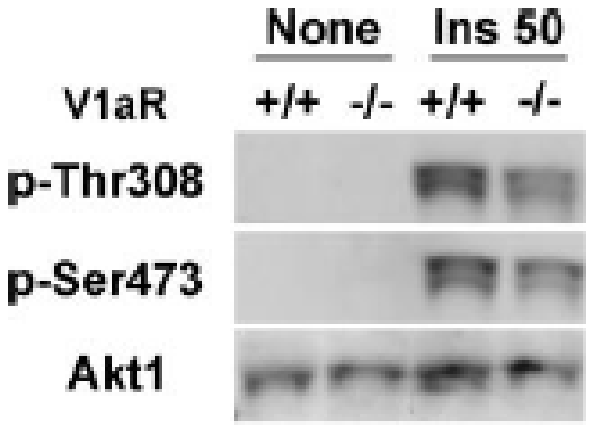
Decreased insulin sensitivity in V1abR-KO



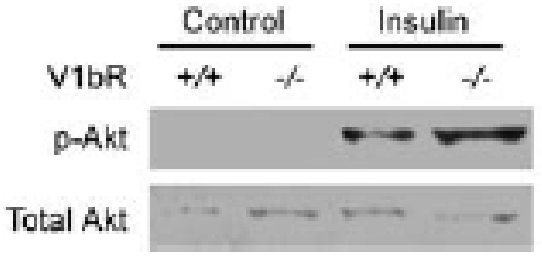
Insulin sensitivity was decreased in V1abR-KO, similar to V1aR-KO.

Decreased phosphorylation of Akt by the insulin stimulation in V1abR KO





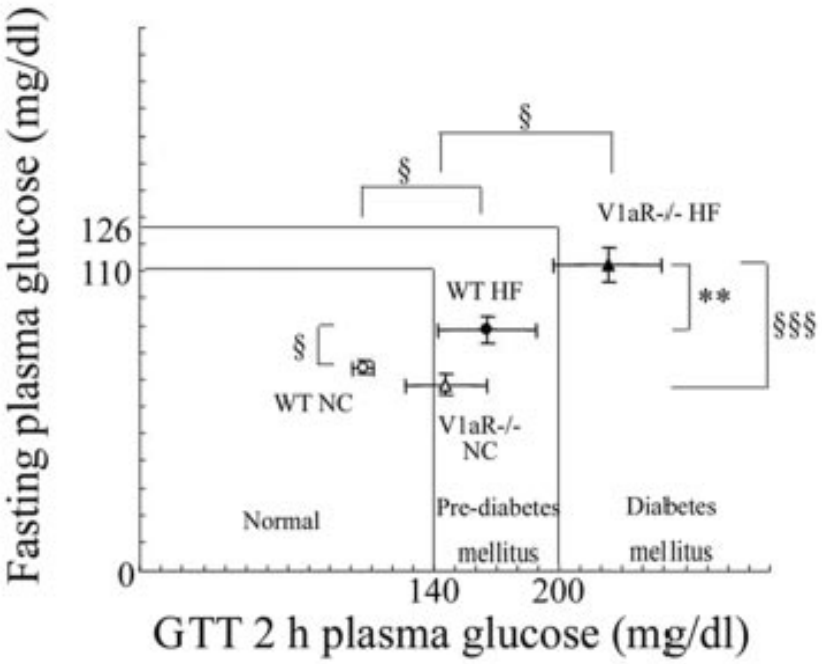
Hiroyama et al., 2007

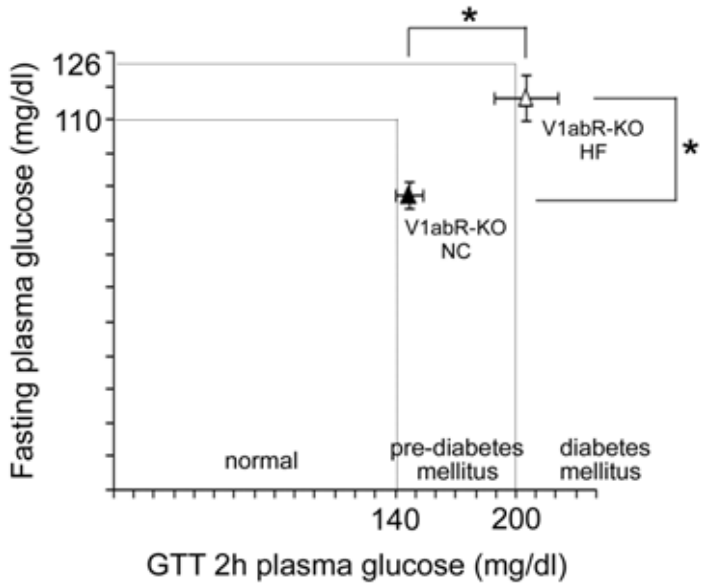


Fujiwara et al., 2007

Insulin sensitivity was decreased in V1abR-KO due to the suppressed insulin signal similar to V1aR-KO.

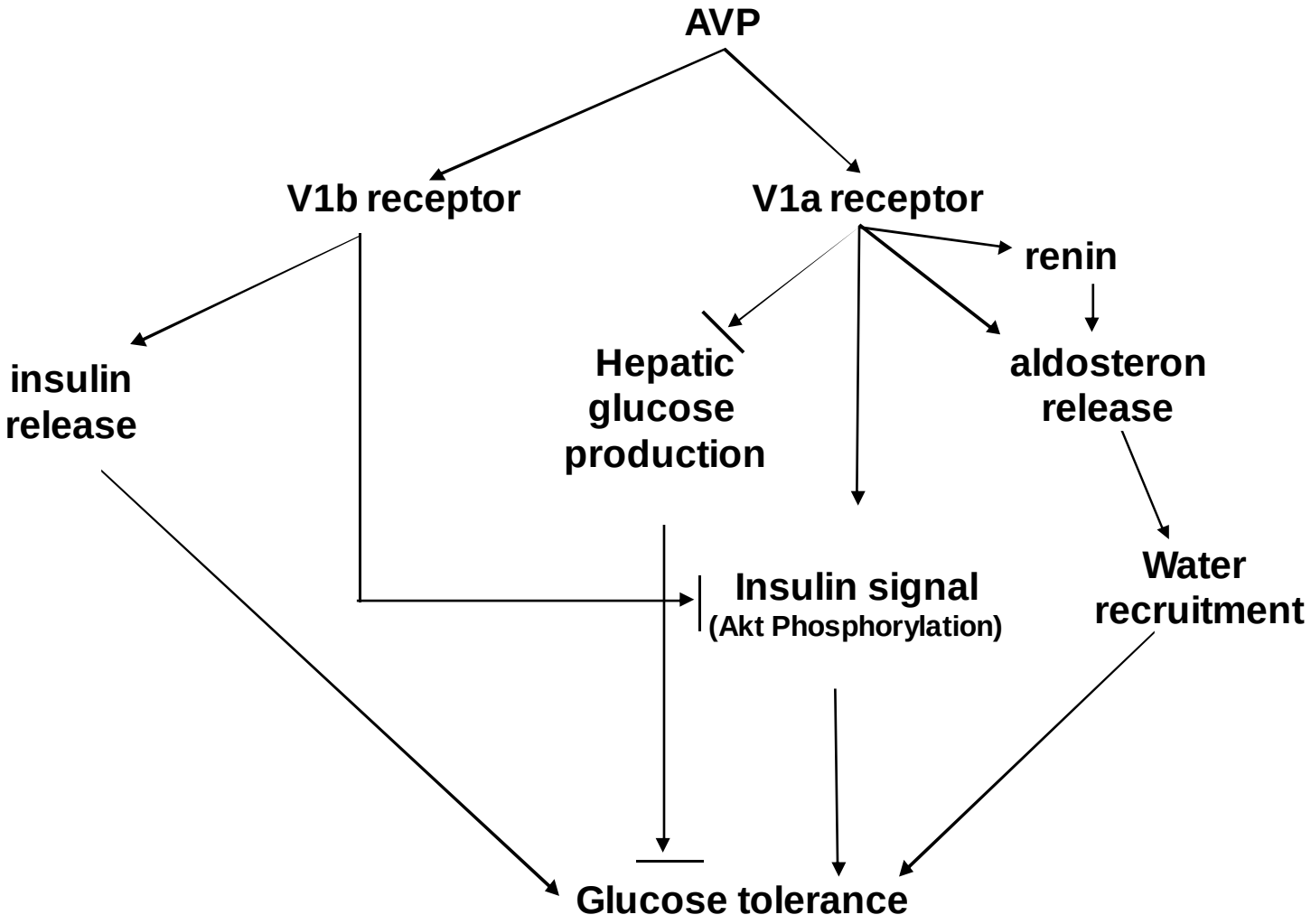
Classification of glucose intolerance in V1aR-KO or V1abR KO mice





V1aR-KO and V1abR-KO are pre-diabetic on NC diet and diabetic on HF diet

Possible mechanism for regulating the glucose tolerance by AVP



AVP regulates the insulin secretion from the pancreas and insulin signal in fat via the V1b receptor, and AVP regulates hepatic glucose production, insulin signal and aldosteron secretion via the V1a receptor, which consequently affect the glucose tolerance *in vivo*.

Aoyagi et al., *Endocrinology* 2007 modified

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