

## THE EFFECT OF AN ARB, OLMESARTAN ON HYPERTENSION RELATED CORPUS CAVERNOSUM DYSFUNCTION IN THE SPONTANEOUSLY HYPERTENSIVE RAT

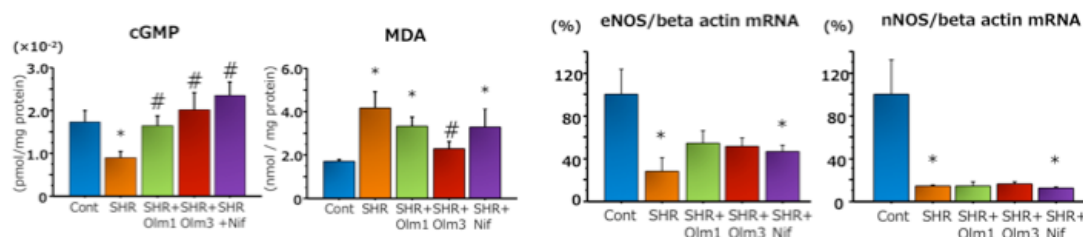
### Hypothesis / aims of study

Hypertension induces vascular remodeling, pathological changes in the penis, and then diminished blood flow supply to the penile tissue<sup>1,2</sup>. It also consists one of the risk factors for the development of vasculogenic erectile dysfunction (ED)<sup>3</sup>. In this study, we investigated the effect of olmesartan, an angiotensin II receptor blocker, or nifedipine, an L-type calcium channel blocker, on corpus cavernosum smooth muscle dysfunction in the spontaneously hypertensive rat (SHR).

### Study design, materials and methods

Twelve-week-old male SHRs, and Wistar rats were used as aged-matched controls. The treatment SHR groups were administered olmesartan (1 or 3 mg/kg, per orally (p.o.), respectively) or nifedipine (30 mg/kg, p.o.). The SHR and Wistar rat groups were treated with vehicle. The treatment lasted six weeks daily. At the age of 18 weeks old, penile cGMP and MDA, a marker of oxidative stress, concentrations and mRNA levels of endothelial and neuronal nitric oxide synthase (eNOS and nNOS, respectively) were investigated. Penile function was evaluated by organ bath studies with norepinephrine-induced contractions and acetylcholine-induced relaxations.

### Results



Data are shown as mean  $\pm$  SEM of six to eight separate determinations in each group.

Cont: 18-week-old Wistar rats (control) treated with vehicle p.o. once a day for 6 weeks;

SHR: 18-week-old spontaneously hypertensive rats treated with vehicle p.o. once a day for 6 weeks;

SHR+Olm1: 18-week-old SHRs treated with olmesartan 1 mg/kg, p.o. once a day for 6 weeks;

SHR+Olm3: 18-week-old SHRs treated with olmesartan 3 mg/kg, p.o. once a day for 6 weeks;

SHR+Nif: 18-week-old SHRs treated with nifedipine 30 mg/kg, p.o. once a day for 6 weeks.

\* Significantly different from the Cont group. ( $P < 0.05$ )

# Significantly different from the SHR group. ( $P < 0.05$ )

Data from functional studies in the penile tissue

Group	Contraction (norepinephrine)		Relaxation (acetylcholine)
	$E_{max}$	$EC_{50}$	Maximum relaxation
	(mg / mm <sup>2</sup> × 10 <sup>-1</sup> )	(× 10 <sup>-6</sup> M)	(%)
Cont	0.72 $\pm$ 0.10	1.11 $\pm$ 0.27	76.86 $\pm$ 5.90
SHR	1.17 $\pm$ 0.17*	1.66 $\pm$ 0.69	58.39 $\pm$ 4.31*
SHR+Olm1	0.91 $\pm$ 0.11	1.98 $\pm$ 0.63	66.55 $\pm$ 3.85
SHR+Olm3	0.71 $\pm$ 0.06 <sup>†</sup>	1.58 $\pm$ 0.61	75.50 $\pm$ 5.08 <sup>†</sup>
SHR+Nif	0.74 $\pm$ 0.10 <sup>†</sup>	1.68 $\pm$ 0.49	76.86 $\pm$ 5.90 <sup>†</sup>

Cont: 18 week-old Wistar rats (control) treated with vehicle p.o. once a day for 6 weeks; SHR: 18 week-old spontaneously hypertensive

rats treated with vehicle p.o. once a day for 6 weeks; SHR+Olm1: 18 week-old SHRs treated with olmesartan 1 mg/kg, p.o. once a day

for 6 weeks; SHR+Olm3: 18 week-old SHRs treated with olmesartan 3 mg/kg, p.o. once a day for 6 weeks; SHR+Nif: 18 week-old

SHRs treated with nifedipine 30 mg/kg, p.o. once a day for 6 weeks.

Data are shown as means  $\pm$  S.E.M. of eight separate determinations in each group. \*: Significantly different from the Cont group

( $P < 0.05$  is level of significance). #: Significantly different from the SHR ( $P < 0.05$  is level of significance).

The SHR showed significantly increased blood pressure (BP), decreased cGMP concentrations, decreased eNOS and nNOS mRNA levels, norepinephrine-induced hyper-contractions, and acetylcholine-induced hypo-relaxations in the penile tissue compared to the Wistar rat. Treatment with the high dose of olmesartan significantly decreased BP, increased the penile cGMP

concentrations, decreased oxidative stress, normalized the expressions of eNOS and nNOS mRNA, decreased the norepinephrine-induced contractions, and normalized the acetylcholine-induced relaxation compared to the control SHR. Although nifedipine significantly decreased BP and increased cGMP, and normalized the hyper-contractions and hypo-relaxations observed in the SHR group, the mRNA levels of eNOS and nNOS were significantly lower compared to the controls.

#### Interpretation of results

The present study is the first report, which investigated the effect of olmesartan on in the hypertension-associated erectile damage. The present data showed that olmesartan and nifedipine significantly ameliorated the BP, norepinephrine-induced hyper-contractions and acetylcholine-induced hypo-relaxations of the corpus cavernosum, and the penile cGMP level in the SHR. However, olmesartan but not nifedipine decreased MDA concentrations, and increased the expressions of eNOS and nNOS mRNAs in the SHR. These evidences suggest that olmesartan could ameliorate hypertension-related erectile damage via reducing oxidative stress.

#### Concluding message

Although nifedipine significantly decreased BP and increased cGMP, and normalized the hyper-contractions and hypo-relaxations observed in the SHR group, the mRNA levels of eNOS and nNOS were significantly lower compared to the controls. Our results indicate that the penile dysfunction can be better reversed by olmesartan treatment and to a slightly lesser extent by nifedipine treatment in the SHR.

#### References

1. J. Sex. Med. 5, 544-51.
2. Curr. Med. Res. Opin. 20, 607–17.
3. J. Clin. Hypertens. 8, 269–74.

#### Disclosures

**Funding:** Grants in aid from the Japan Society for the Promotion of Science (#24592431, 20591880). **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Tottori University Committee for Animal Experimentation and the experiments