

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Cross talk between brain and kidney for regulation and dysregulation of hypertension

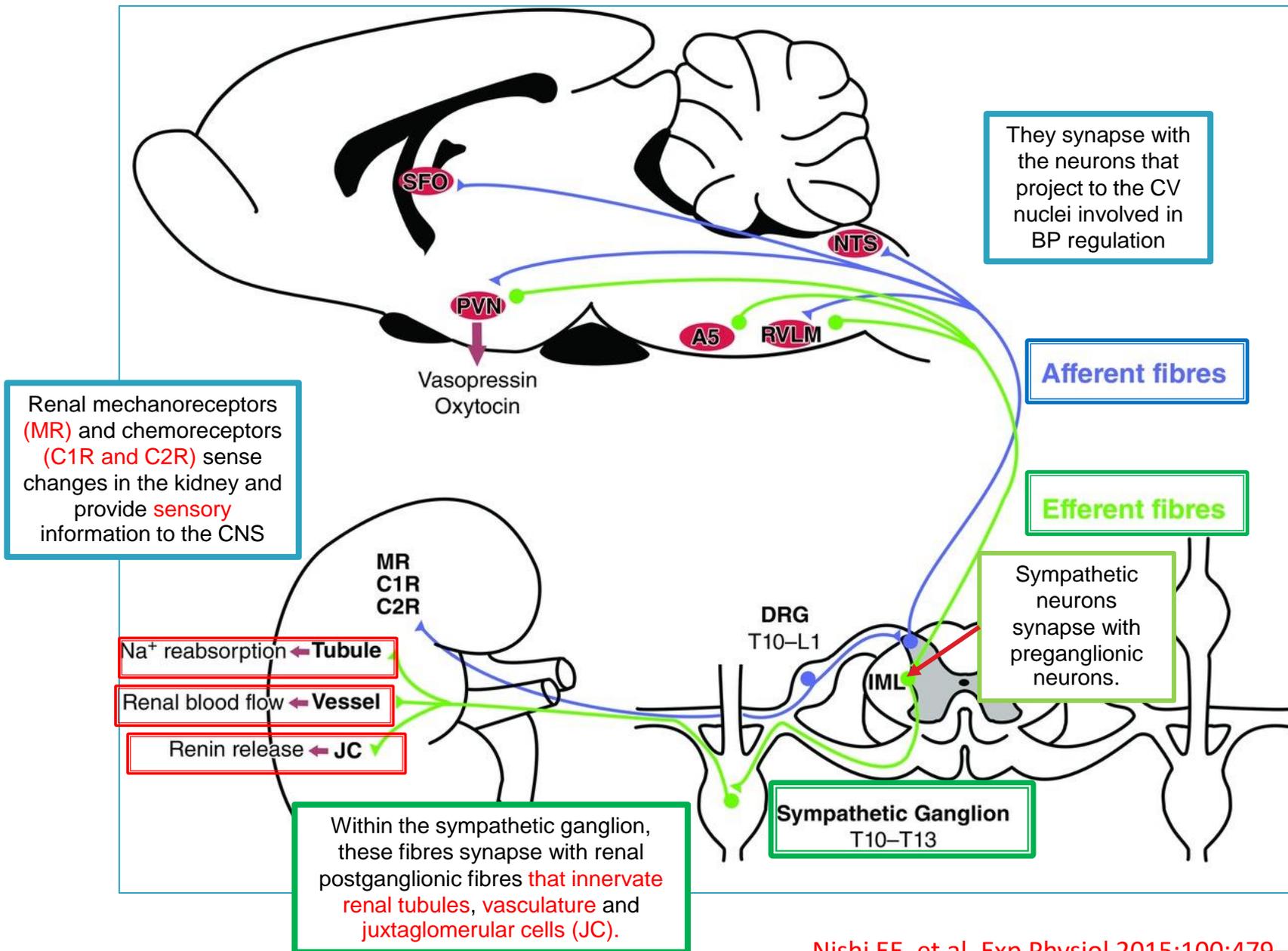
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Cross-Talk: Definition

- ▶ Cross-talk is generally defined as endogenous homeostatic signaling between vital organs such as kidneys and brain
- ▶ Under physiological states, the nervous system and the kidneys communicate with each other to maintain normal blood pressure (BP)

The role of renal nerves in BP regulation



Physiological cross-talk between the nervous system and the kidney

- ▶ Sympathetic nerves innervate the whole renal vasculature with the most dense innervation to the afferent arterioles
- ▶ Norepinephrine released from sympathetic nerve terminals can directly act on the renal vasculature and the tubular epithelial cells
- ▶ Increased efferent renal sympathetic nerve activity increases renin secretion (JC), decreases urinary sodium excretion (tubular epithelial cells), and decreases renal BF (VSMCs).

Normal blood pressure regulation

- ▶ Sympathetic nerves alter renal BF and GFR via renal vasoconstriction and alterations in the RAAS
- ▶ In the normal state, renal afferent sensory activity leads to a reflex decrease in sympathetic outflow, which is known as an inhibitory reno–renal reflex

Renal or autonomic dysfunction is the predominant contributor to systemic HTN

- ▶ The increased sympathetic nerve activity to the kidney and the renal afferent nerve activity to the CNS contribute to HTN

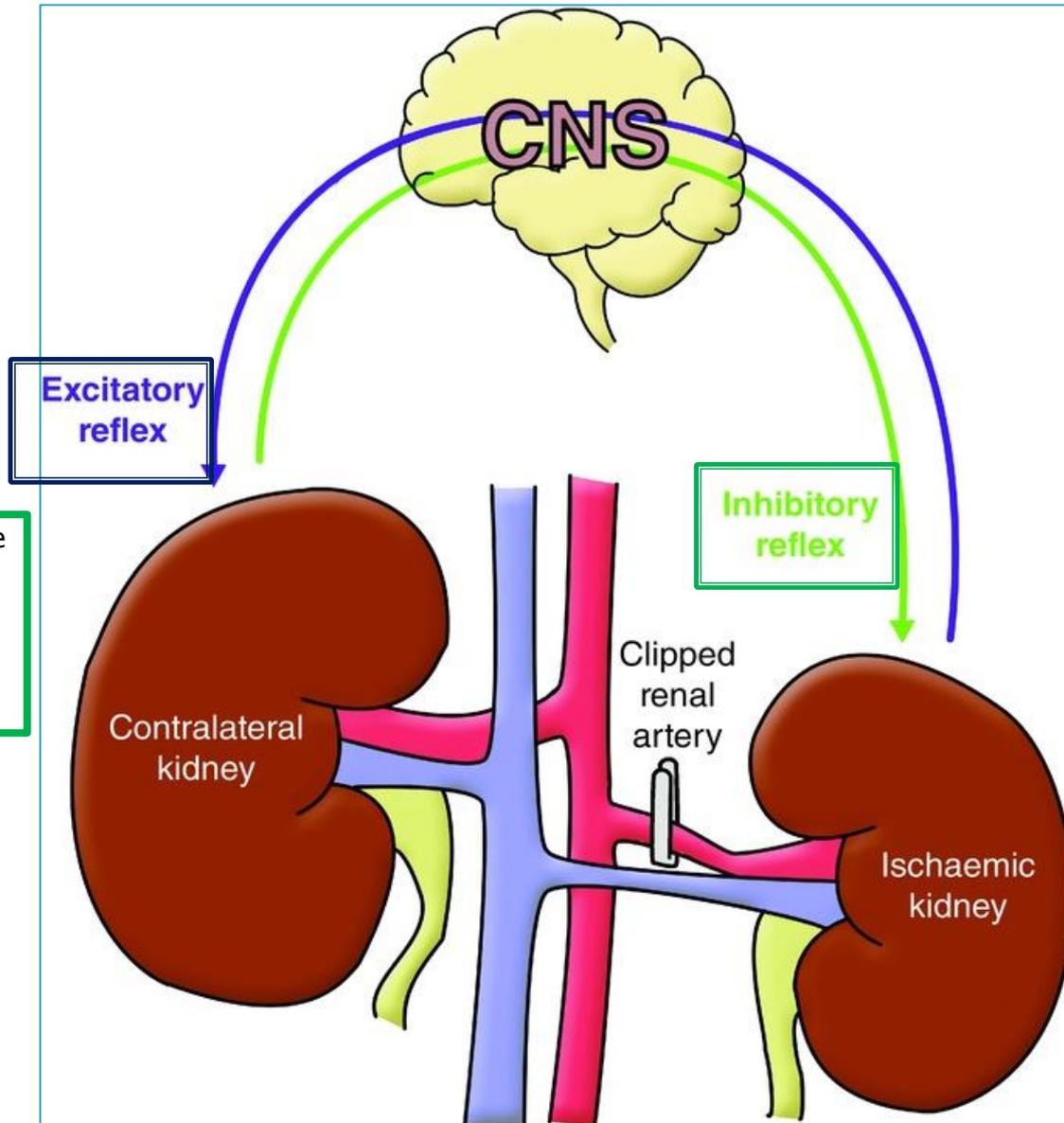
Nishi EE, Bergamaschi CT, Campos RR. Exp Physiol 2015;100:479-84

In Hypertension

- ▶ The reno-renal reflex is **impaired**, and an increase in renal afferent activity augments the sympathetic excitation to the kidney and aggravates HTN

B. Afsar et al. / European Journal of Internal Medicine xxx (2016) xxx-xxx

The renorenal reflex



Afferent activity from the contralateral kidney leads to inhibitory renorenal reflex to the ischaemic kidney as occurs in normal kidney

↑ afferent activity from the ischaemic kidney leads to an excitatory reflex that augments the sympathetic outflow in the contralateral kidney, contributing to HTN

The two-kidney, one-clip (2K1C) model of **renovascular HTN**

Clinical Relevance

- ▶ Renal denervation has been used as a novel therapy for resistant HTN
- ▶ Ablation of renal nerves was shown to produce a long-term reduction in BP in resistant HTN patients
- ▶ 15 randomized control trials showed **no significant benefit of renal denervation on BP control** in patients with resistant HT

E. E. Nishi and others *Exp Physiol* 100.5 (2015) pp 479–484

Agasthi, P. et al. *Scientific Reports* (2019) 9:6200

Sodium glucose co-transporter 2 (SGLT2) Inhibitor-Induced Sympathoinhibition

Herat, L.Y. et al. *J Am Coll Cardiol Basic Trans Science*. 2020;5(2):169-79

SGLT2 inhibitors improve cardiovascular outcomes

- ▶ Chemical denervation in neurogenic hypertensive mice reduces renal SGLT2 expression
- ▶ SGLT2 inhibition **lowered BP** and significantly reduced norepinephrine levels in the kidney of neurogenic **hypertensive mice**

Herat, L.Y. et al. J Am Coll Cardiol Basic Trans Science. 2020;5(2):169-79

SGLT2 inhibitors improve cardiovascular outcomes

- ▶ Crosstalk between the sympathetic nervous system and SGLT2 regulation appears as a key mechanism of the cardiorenal protective effects demonstrated with SGLT2 inhibition

Herat, L.Y. et al. *J Am Coll Cardiol Basic Trans Science*. 2020;5(2):169–79

Cooperative Oxygen Sensing by the Kidney and Carotid Body in BP Control

- ▶ Acute and chronic hypoxia is sensed by both kidney and carotid body that activates afferent nerve signaling promoting reflex increases in sympathetic nerve activity triggering HTN
- ▶ Hypoxia-mediated renal and carotid body afferent signaling triggers uncontrolled activation of the RAAS
- ▶ **In renovascular HTN:** Renal and carotid body mediated responses in arterial pressure appear to be synergistic as interruption of either afferent source has a collective effect of reducing BP

Conclusions

- ▶ Sympathetic nerves innervate the whole renal vasculature with the most dense innervation to the afferent arterioles
 - ▶ In the normal state, renal afferent sensory activity leads to a reflex decrease in sympathetic outflow
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Conclusions

- ▶ Renal or autonomic dysfunction is the predominant contributor to systemic HTN
 - ▶ In HTN the reno-renal reflex is impaired, and an increase in renal afferent activity augments the sympathetic excitation to the kidney and aggravates HTN
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Conclusions

- ▶ Hypoxia-mediated renal and carotid body afferent signaling triggers uncontrolled activation of the RAAS
- ▶ Sodium glucose co-transporter 2 (SGLT2) Inhibitor-Induced Sympathoinhibition

Thank You

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