BIOELECTRONIC NEUROMODULATION OF THE RENAL NERVES AS A NOVEL THERAPEUTIC MODALITY FOR HYPERTENSION TREATMENT

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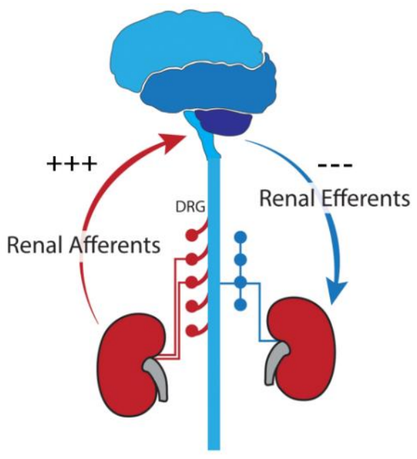
BACKGROUND

- Hypertension poses a global burden, placing patients at risk of cardiovascular complications [1].
- In patients with hypertension, activity in renal sympathetic nerves is commonly increased. Therefore, renal denervation has been touted as a possible therapeutic strategy for the treatment of resistant hypertension [2].



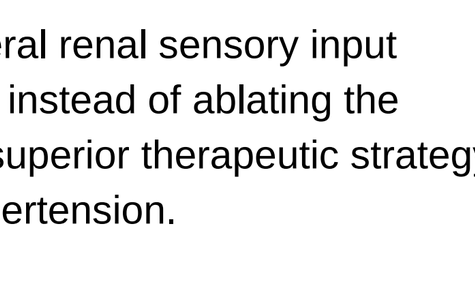
- Despite promising initial renal denervation results [3], subsequent studies have failed to demonstrate a meaningful reduction in blood pressure (BP) suitable for treating hypertension [4].
- In contrast to renal denervation, neuromodulation of renal nerve traffic in hypertension has not received similar attention. Specifically, the reno-renal reflex, a neural reflex mechanism where renal sensory receptors detect variations in renal perfusion and send an afferent signal to the central nervous system to reflexively reduce sympathetic outflow, peripheral vascular resistance, and systemic BP [5], represents a promising neuromodulation target.
- Bioelectronic amplification of ipsilateral renal sensory input using targeted electrical stimulation, instead of ablating the renal nerves, may therefore offer a superior therapeutic strategy for the management of resistant hypertension.

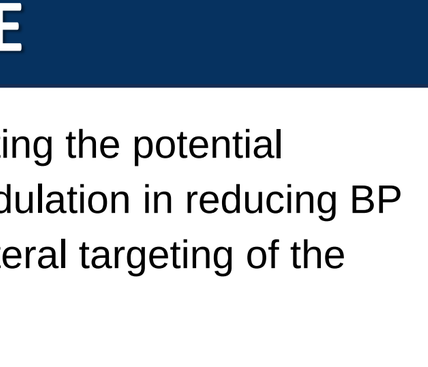
OBJECTIVE

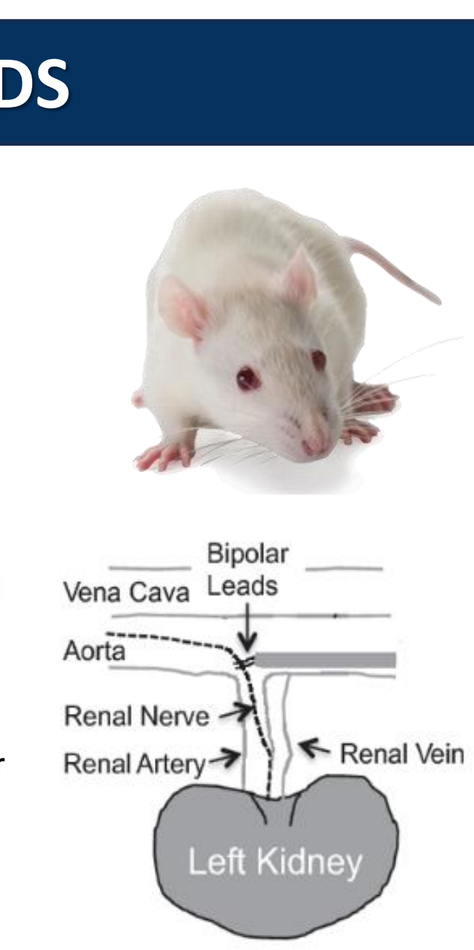
- To present preclinical evidence supporting the potential effectiveness of bioelectronic neuromodulation in reducing BP under hypertensive conditions by unilateral targeting of the renal nerves.

METHODS

- **Animals:** Male Spontaneously Hypertensive Rats (SHRs, *n* = 6–10, weight = 384±7 g, age = 32±2 weeks).
- **Anesthesia:** Sodium pentobarbital (induction: 50 mg.kg^{-1} i.p. and maintenance: 10 mg.kg.h^{-1} delivered in saline as 2 ml.h^{-1} i.v.).
- **Neurostimulation protocol:** Bipolar renal nerve stimulation (RSN) of the intact left renal nerve (see schematic) at 5 Hz, 0.5 mA and 0.5 ms, delivered continuously for 30s.
- **Recorded parameters:** Mean arterial pressure (MAP) via a femoral artery cannula, left renal cortical blood flow (CBF) using laser doppler, and aortic (hindquarter) blood flow (ABF) using a perivascular flowmeter.
- **Calculations:** Heart rate (HR) from pulsatile arterial BP and aortic vascular (AVR) and cortical vascular resistance (CVR) by dividing BP by corresponding flow measures [6].

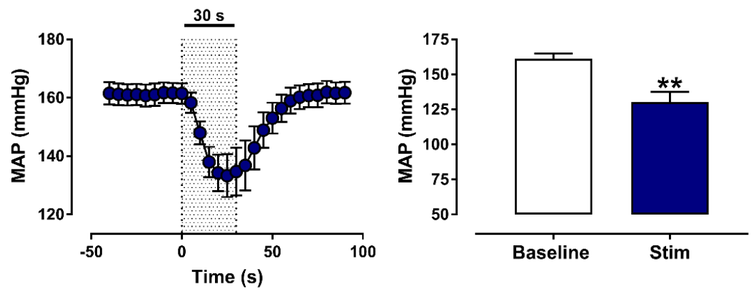




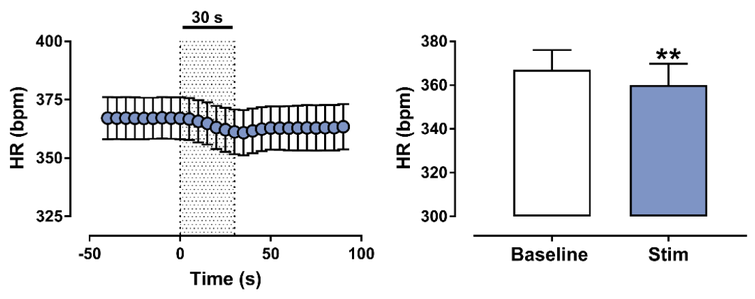


RESULTS

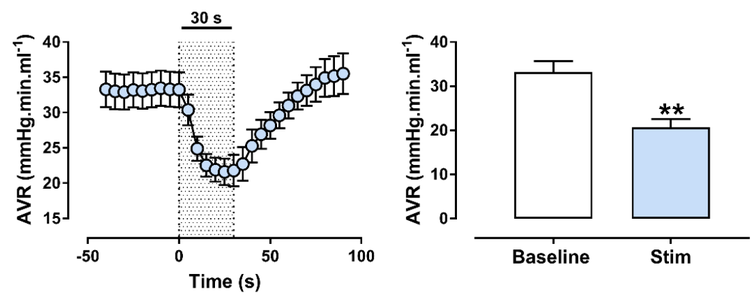
- RSN evoked an immediate drop of 31±7 mmHg (19±4%) in MAP.



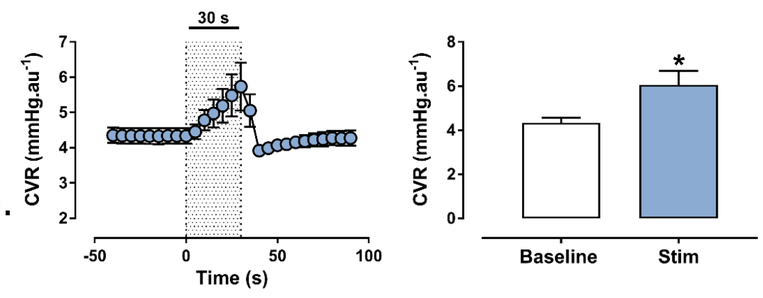
- RSN elicited minor reflex bradycardia of 7±2 bpm (2±1%).



- RSN significantly decreased AVR by 13±3 mmHg.min.ml^{-1} (35±6%).



- RSN induced a marked increase in CVR of 2±1 mmHg.au^{-1} (42±15%).



CONCLUSIONS

- Neuromodulation of the renal nerves appears to be a promising therapeutic alternative for hypertensive patients. However, a major drawback of stimulating "*intact*" renal nerves is the unavoidable engagement of renal sympathetic nerve traffic, which compromises ipsilateral renal hemodynamics.
- For clinical trials of renal nerve neuromodulation to be viable, further optimization of this neurostimulation approach is necessary. This may involve further reduction of stimulation parameters or the development of an electrode design that allows for unidirectional current, solely activating the sensory arm of the reflex.

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