RENAL NERVE STIMULATION AS A POTENTIAL ELECTROCEUTICAL THERAPY FOR OBSTRUCTIVE SLEEP APNEA

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Introduction

- Obstructive sleep apnea (OSA) is a prevalent sleep-related breathing disorder (**Fig. 1**) marked by recurrent upper airway collapse during sleep, resulting in sleep disruption, reduced oxygen saturation and an increased risk of mortality and cardiovascular events [1].
- The role of the renal nerves (**Fig. 2**) in blood pressure control is well-established [2]. However, their role in modulating respiration remains largely unexplored.
- Our recent data in spontaneously hypertensive rats (SHRs) suggest that low-intensity renal nerve stimulation (RNS) can enhance respiratory functions [3].
- Neuromodulation of the renal nerves may therefore offer a therapeutic alternative for OSA or other breathing abnormalities.
- This study aimed to investigate ventilatory responses to RNS in a genetic model of obesity-driven OSA (**Fig. 3**), the Zucker fat rat (ZFR).

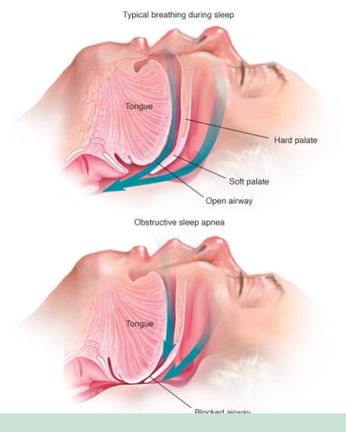


Fig. 1: An illustration of obstructive sleep apnea.

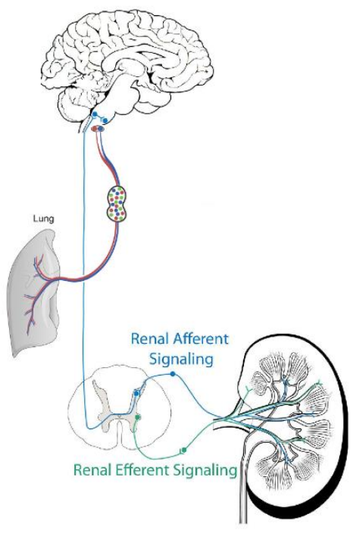


Fig. 2: Renal afferent and efferent signaling pathways.

Fig. 3: The Zucker fat rat (ZFR) model of obesity and obstructive sleep apnea.

Methods

- **Animals:** Male ZFRs (*n* = 12, weight = 914 ± 24 g).
- **Anaesthesia:** Sodium pentobarbital (induction dose: 50 mg.kg^{-1} i.p. and maintenance dose: 10 mg.kg.h^{-1} i.v. delivered at 2 ml.h^{-1}).
- **RSN protocol:** Bipolar monophasic stimulation of the intact left renal nerve (5 Hz, 0.5 mA, 0.5 ms, 30s; Fig. 4–6) was repeated 5 times, averaged, and performed at 5-min intervals.
- **Recorded output responses:** Mean arterial pressure (MAP), upper airway pressure (UAP), airway pressure (AP), tidal air flow (AF), and diaphragmatic EMG (dEMG).
- **Calculations:** Respiration rate (RR) was derived from integrated dEMG signal, and airway resistance (AR) was calculated by dividing AP values by corresponding AF measurements.

Fig. 4: Grass instruments S88 dual output square pulse stimulator.

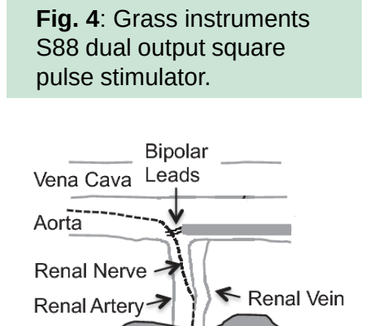


Fig. 5: Bipolar stimulation of the left renal nerve.

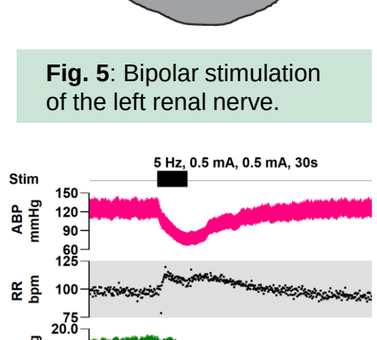


Fig. 6: Raw data Spike trace showing recorded physiological parameters.

Results

- Hemodynamically, RNS evoked an immediate but reversible 33 ± 4 mmHg (27 ± 3%) reduction in MAP (**Fig. 7**).

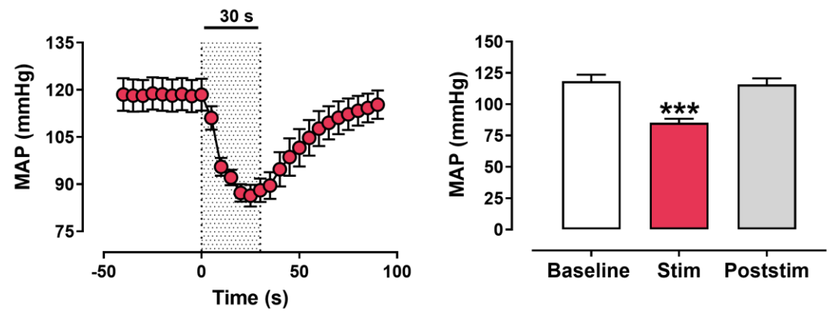


Fig. 7: Effect of renal nerve stimulation (RNS) on mean arterial pressure (MAP) in Zucker fat rats (ZFRs). Data were mean ± SEM. ****P*<0.001 vs. baseline.

- RNS increased RR by 7 ± 2 breaths.min^{-1} (7 ± 2%), with effects persisting temporarily beyond stimulation (**Fig. 8**).

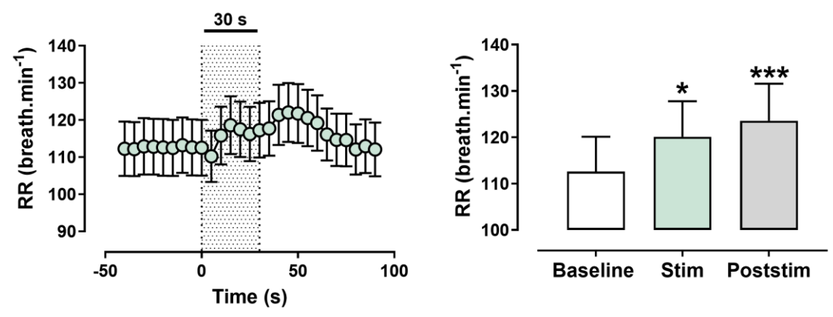


Fig. 8: Effect of renal nerve stimulation (RNS) on respiration rate (RR) in Zucker fat rats (ZFRs). Data were mean ± SEM. **P*<0.05, ****P*<0.001 vs. baseline.

- RNS did not alter overall AP. However, UAP dropped by 0.6 ± 0.2 mmHg (3 ± 1%) during stimulation and remained relatively low after stimulation (**Fig. 9**).

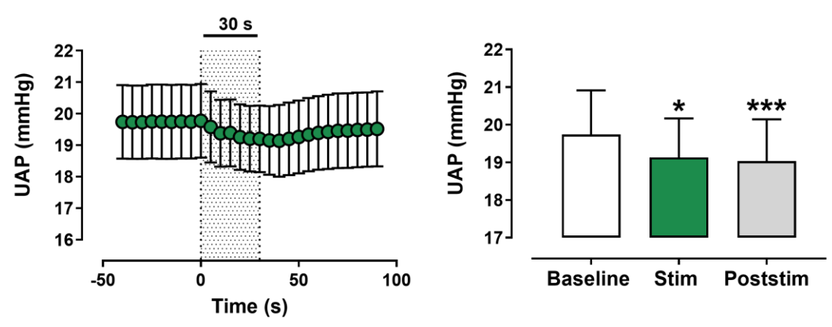
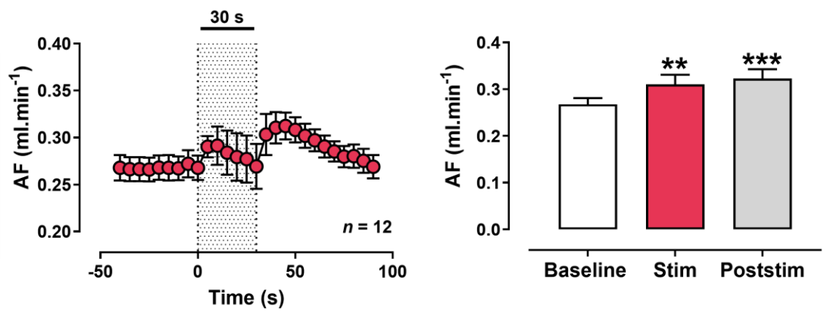


Fig. 9: Effect of renal nerve stimulation (RNS) on upper airway pressure (UAP) in Zucker fat rats (ZFRs). Data were mean ± SEM. **P*<0.05, ****P*<0.001 vs. baseline.

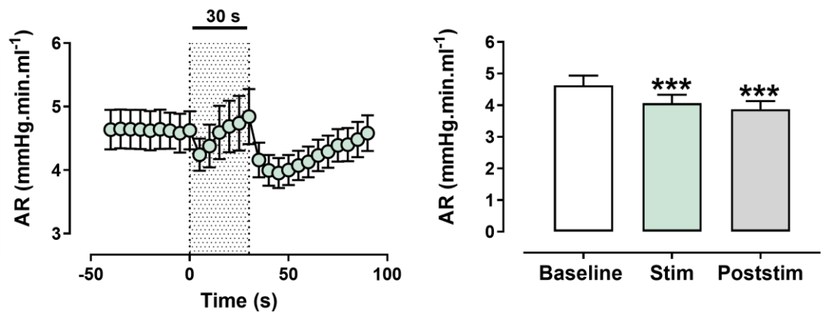
- RNS increased tidal AF by 0.04 ± 0.01 ml.min^{-1} (16 ± 3%) during stimulation, with increases not instantly returning to baseline after stimulation (**Fig. 10**).

Fig. 10: Effect of renal nerve stimulation (RNS) on tidal airway flow (AF) in Zucker fat rats (ZFRs). Data were mean ± SEM. ***P*<0.01, ****P*<0.001 vs. baseline.



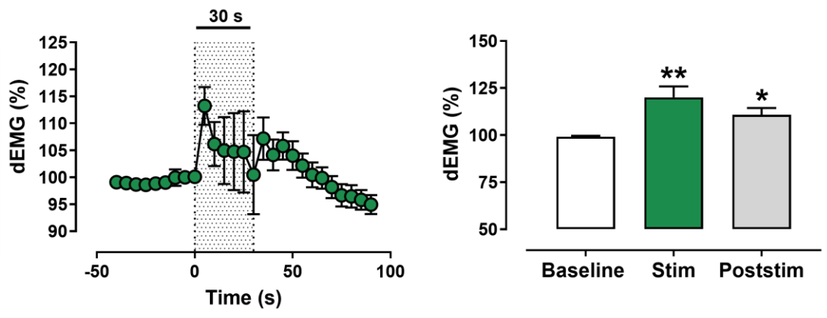
- RNS lowered AR by 0.6 ± 0.1 mmHg.min.ml^{-1} (12 ± 2%) when the stimulus was on, with the peak reduction briefly maintained when the stimulation was off (**Fig. 11**).

Fig. 11: Effect of renal nerve stimulation (RNS) on airway resistance (AR) in Zucker fat rats (ZFRs). Data were mean ± SEM. ****P*<0.001 vs. baseline.



- RNS induced a marked increase of 21 ± 6% in dEMG, with the increase temporarily persisting at 12 ± 3% post-stimulation (**Fig. 12**).

Fig. 12: Effect of renal nerve stimulation (RNS) on diaphragmatic EMG (dEMG) in Zucker fat rats (ZFRs). Data were mean ± SEM. **P*<0.05, ***P*<0.01 vs. baseline.



Conclusions

- Our data suggest that the renal nerves are not only involved in the modulation of cardiovascular function, but their role also extends to central regulation of respiration.
- Neurostimulation of the renal nerves effectively enhances ventilatory responses in the ZFR model of obesity-associated OSA.
- Clinically, neuromodulation of the renal nerves may offer an alternative novel therapy for patients with OSA.

References

1. Strollo PJ Jr, Rogers RM (1996). Obstructive sleep apnea. *N Engl J Med.*, 334(2), 99-104.
2. Nishi EE, Bergamaschi CT, Campos RR (2015). The crosstalk between the kidney and the central nervous system: the role of renal nerves in blood pressure regulation. *Exp Physiol.*, 100(5), 479-484.
3. Salman IM , Ameer OZ, Hassan SF, McMurray S, Sridhar A, Hsieh YH, Lewis SJ (2021). Neuromodulation of the renal nerves In spontaneously hypertensive rats. *Circulation*, 144 (Suppl_1), A12867.

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