Bradykinin B2 Receptor Blockade Restores The Cardiopulmonary Baroreflex Control Of Renal Sympathetic Nerve Activity In Cisplatin-Induced Renal Failure Rats

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Renal failure and renal injury are associated with an increase of pro-inflammatory peptides within the kidney, such as bradykinin which activates B2 receptors on renal afferent nerves. The aim of this study was to investigate whether bradykinin B2 receptor activation contributed to the low-pressure baroreceptor regulation of renal sympathetic nerve activity (RSNA) in a rat model of acute renal failure.

Twelve male Wistar rats (290-390g) received either cisplatin (5mg/kg IP, n=6) three days before the acute study to induce renal failure, or saline as a control (n=6). Rats were anaesthetised with 1-1.3 ml of a chloralose:urethane mixture (16.5:250 mg/ml IP). The right femoral artery and vein were cannulated to measure mean arterial pressure (MAP) and heart rate (HR) or to administer saline (0.9% NaCl, 3ml/h), respectively. A renal nerve bundle of the left kidney was isolated and sealed onto recording electrodes. Rats were subjected twice to a 30 min period of acute volume expansion (VEP) by infusing saline IV at 0.25% body weight/min to induce a renal sympatho-inhibitory reflex (Abdulla & Johns, 2013). A 2h recovery period was allowed between the first and second VEP. Bradyzide, a bradykinin B2 receptor antagonist (10µg/ml), or saline, was infused IV for 20 min before, and during the volume expansions at 1ml/h. At the end of the experiment, the animal was euthanized to enable background noise recording. Data, mean±SEM were compared using repeated measures two-way ANOVA with significance at P<0.05. In control, the MAP, HR and RSNA values during bradyzide infusion (76±4 mmHg, 342±16 bpm, 1.05±0.21 µV.s respectively) were not different from their respective values before bradyzide (82±5 mmHg, 334±17 bpm, 1.25±0.06 µV.s respectively). In acute renal failure, MAP and HR were similar to their respective values before bradyzide, but RSNA was depressed (1.45±0.04 vs. 0.70±0.17 µV.s, P<0.05) by the antagonist infusion. Volume expansion decreased RSNA from the baseline value in the control group but not in the RF group (control: 69±14%; renal failure: 7±16%; P<0.05). The infusion of bradyzide had no effect on the magnitude of the renal sympatho-inhibition in the control group. In contrast, in the renal failure group, the reduction in RSNA during bradyzide infusion was 51±9% compared to 7±16% during the saline infusion (P<0.05). These data suggest that bradykinin B2 receptors seem to have little influence on the cardiopulmonary baroreceptor control of RSNA normally. However, in renal failure there is an attenuation of the sensitivity of the baroreflex which is in part mediated via bradykinin. These results may indicate that during a renal failure associated inflammatory response involving bradykinin, there is inappropriate activation of renal afferent nerves which blunts the cardiopulmonary baroreflex control of sympathetic outflow. This implies that B2 receptor antagonism may be a possible alternative to renal denervation for the treatment of renal failure associated hypertension, and should therefore be investigated.

Key words: renal sympathetic nerve; bradykinin; bradyzide; volume expansion; baroreceptors; renal failure.

References: