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Cardiac Arrhythmogenic Sensitivity in a Rat Model of Neuroendocrine Tumor Metastasis

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BACKGROUND

Neuroendocrine tumor (NET) metastasis poses a significant risk to cardiovascular health. Patients with NET metastases exhibit hemodynamic instability, characterized by tachycardia, syncope, and cardiac arrythmias. These events may be attributed to the vasoactive hormones secreted by NETs, but the specific physiologic mechanisms are not known. Therefore, accurate animal models are needed to investigate the impact of NETs on cardiovascular function.

Our NET mouse model with identifiable liver metastases demonstrates baseline electrocardiographic (ECG) abnormalities, lower thresholds for epinephrine-induced arrhythmias, and altered vascular function. Building on these findings, this pilot study sought to develop a novel rat model of NET liver metastasis to evaluate mechanisms underlying altered hemodynamic responsiveness. We hypothesized that similar to our mouse model, this rat model would exhibit liver NET metastases and a sensitized risk for cardiac arrhythmic events.

METHODS

Anesthetized (3-5% isoflurane in 100% O_2) male NIH-nude rats received intrasplenic injections of 5-15x10^6 BON-1 NET cells (BON-1, n=4) or Dulbecco's Phosphate Buffered Saline (VEH, n=2) and monitored for 14 weeks. Resting 10-minute ECG tracings were recorded every two weeks to assess for ECG irregularities. At the14-week timepoint, intraperitoneal injections of epinephrine (0.01-2mg/kg) were given to induce cardiac arrhythmias in all NIH-nude rats (n=6) and an additional cohort of age-matched male Sprague Dawley rats (SD, n=3). The VEH and SD rats were combined into the control (CON) group. Cardiac arrhythmias were identified as abnormal deviations in the P wave, QRS complex, and/or T waves relative to normal sinus rhythm. Liver samples from BON-1 and VEH rats were sectioned and assessed for tumor presence by hematoxylin & eosin (H&E) staining. Percent occurrence of arrhythmias were compared by Chi-squared test, with significance set at $p<0.05$.

RESULTS

Liver tumor metastases were present in all BON-1 rats, and absent in VEH rats. Spontaneous baseline cardiac arrhythmias were not present in VEH or BON-1 rats during tumor development. However, the overall occurrence of epinephrine-induced arrhythmias was higher in BON-1 (60%) compared to CON (29%, $p<0.01$). Lower doses of epinephrine (0.01-0.1mg/kg) triggered arrhythmias in 75% of BON-1 rats ($p=0.18$). CON rats developed comparable arrhythmias starting at 0.2mg/kg epinephrine.

CONCLUSIONS

These data confirm the successful development of a NET rat model characterized by the presence of liver NET metastases and a sensitized induced arrhythmia threshold. This model parallels key cardiac abnormalities observed in our NET mouse model, providing a viable rodent model to investigate the influence of NET metastasis on cardiovascular function.

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