B-4

Cardiac autonomic dysfunction in a mouse model of carcinoid disease

Sydney Kuehn, BS[1], Sofia Penrose, BS[1], Rodney F. Pommier, MD[2], Belinda H. McCully, PhD[3].

[1]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR; [2]Division of Surgical Oncology, Department of Surgery, Oregon Health & Science University, Portland, OR; [3]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR.

BACKGROUND

Patients with metastatic carcinoid disease confer a risk for carcinoid syndrome, characterized by hemodynamic instability and syncope. While the physiologic mechanisms linking carcinoid tumor metastases to impaired blood pressure regulation are not well understood, this may be attributed to changes in autonomic function, which is a key regulator of blood pressure. We hypothesize that metastatic carcinoid disease induces autonomic dysfunction. To test this, we longitudinally assessed autonomic function during tumor development in a mouse model of carcinoid disease.

METHODS

Anesthetized J:Nu nude mice (25-30g, Jackson Laboratories) received an intrasplenic injection of vehicle (VEH, n=5) or 1-2x107 neuroendocrine tumor BON1 cells (BON1, n=15). Mice were monitored for 8 weeks to develop carcinoid liver metastasis. Stable 10-minute electrocardiogram (ECG) tracings were recorded in anesthetized animals, with a baseline tracing recorded prior to injection, and every two weeks following injection. To assess autonomic function, ECG tracings were analyzed offline (Acknowledge, Goleta, CA) for indices of heart rate variability. Specifically, the low frequency and high frequency bands were assessed to provide ratios of sympathetic (SNS) and parasympathetic (PNS) tone, respectively. A rise in the SNS ratio accompanied by a decrease in the PNS ratio represents autonomic dysfunction. Data are presented as mean ± SE. $P<0.05$ indicates significance.

RESULTS

Prior to injection, VEH and BON1 mice had similar baseline SNS (VEH: 0.33±0.09; BON1: 0.30±0.07, p=0.57) and PNS (VEH: 0.67±0.09; BON1: 0.69±0.07, p=0.57) ratios. Over time, VEH-treated mice did not show changes in SNS (p=0.82) or PNS (p=0.82) ratios. In contrast, BON1 mice exhibited a rise in the SNS ratio over time (main effect, p=0.018), with a significant increase in the SNS ratio specifically at week 6 (0.40±0.04, p=0.009 versus baseline). This was accompanied by a decrease in the PNS ratio over time (main effect, p=0.020), with a significant decrease at week 6 (0.58±0.04, p=0.009 versus baseline). Postmortem gross examination and hematoxylin-eosin staining of liver samples verified the presence of metastases in BON1 mice and its absence in VEH mice.

CONCLUSIONS

In agreement with our hypothesis, our findings show that BON1 cell-induced liver metastases confers autonomic dysfunction, characterized by increased sympathetic drive and a concurrent decrease in parasympathetic tone. Future studies are needed to determine whether autonomic dysfunction is also present in patients with carcinoid disease, and if this contributes to the development of hemodynamic instability and risk for carcinoid crisis.

ABSTRACT ID 23458