Sensitized serotonin-mediated vasodilation in a mouse model of carcinoid disease

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INTRODUCTION

Carcinoid tumors secrete vasoactive hormones such as serotonin that can impact cardiovascular function. In consequence, patients with metastatic carcinoid disease are at risk for carcinoid syndrome, characterized by profound cutaneous flushing, hypotension and syncope. This may be attributed to the vasodilatory effects of serotonin. Our recent work shows that in patients with carcinoid disease, higher serotonin levels are associated with lower vascular resistance. Whether the vasculature is sensitized to serotonin is not known.

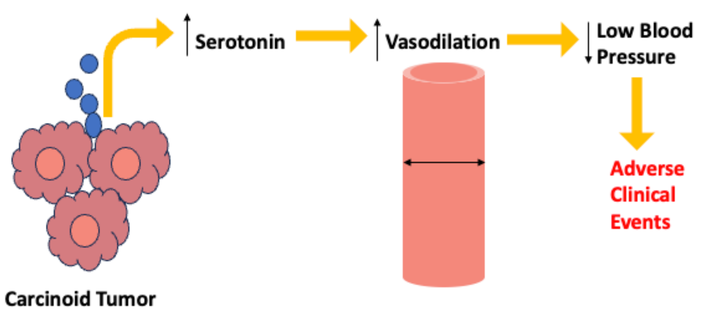


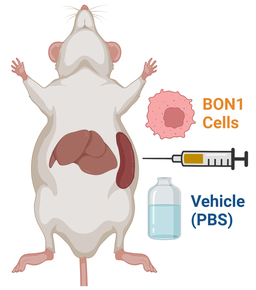
Figure 1: *Carcinoid Tumor Proposed Mechanism. It is believed that an increase in serotonin secretion from carcinoid tumor will induce serotonin-mediated vasodilation, resulting in hypotension and adverse clinical outcomes.*

HYPOTHESIS

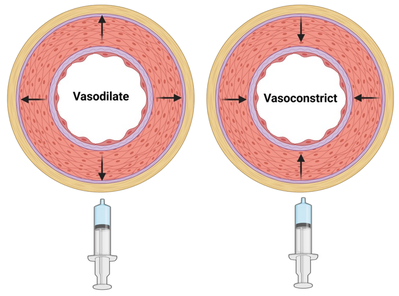
We hypothesized that serotonin-mediated vasodilation is increased by carcinoid metastases.

METHODS

Animal Model: Anesthetized (3-5% isoflurane in 100% O_2), J:Nu nude mice (25-30g) received intrasplenic injection of $2x10^7$ BON1 neuroendocrine tumor cells (BON1, n=5) or PBS-vehicle (VEH, n=5), and monitored for 10 weeks for the development of liver carcinoid metastases.



Ex vivo vascular function: Mesentery arteries were cannulated onto glass pipette tips, pressurized, and incubated in a physiological salt solution at 37°C in an organ chamber bath. After equilibration, vessels were pre-constricted with phenylephrine, and dose response curves were generated to assess serotonin-mediated vasodilation.



RESULTS

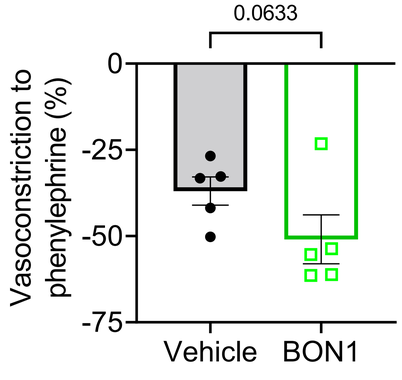


Figure 2: *For the same dose of phenylephrine, there was a higher vasoconstrictor response in BON1 mice (51 ± 7%), compared to VEH mice (37 ± 9%, p =0.06).*

RESULTS

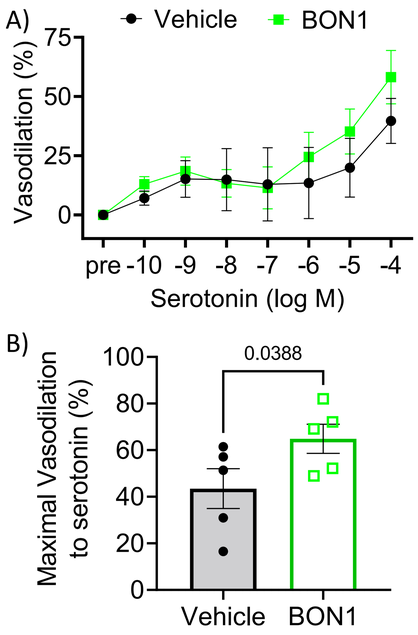


Figure 3: (A) *VEH and BON1 mice exhibited a dose-dependent increase in serotonin-mediated vasodilation. (B) The maximal vasodilatory response to serotonin was significantly higher in BON1 mice (65 ± 6%) compared to VEH (44 ± 8%, p<0.05).*

CONCLUSIONS

1) Serotonin-mediated vasodilation is sensitized in a mouse model of carcinoid disease.

2) Serotonin-mediated vasodilation is accompanied by enhanced α-adrenergic-mediated vasoconstriction, which may be a compensatory mechanism in response to sensitized vasodilatory mechanisms.

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