The Autophagy Inducing Drug Carbamazepine is a Radiation Protector and Mitigator


**Purpose:** To evaluate Carbamazepine (CBZ) as a radiation protector or mitigator in vitro and in vivo.

**Materials and Methods:** We hypothesized that the drug CBZ, currently used to treat mood disorders, epilepsy and trigeminal neuralgia, would be radioprotective in vitro and in vivo by upregulating autophagy and reducing apoptosis in cultured cells and in tissue. In vitro radiation dose modification by CBZ was assessed by clonogenic assay of murine hematopoietic progenitor cell line (32D cl 3) using 1, 10 or 100 uM CBZ treatment for 1 hour prior to or immediately after irradiation (0 - 8 Gy). The effect of CBZ on apoptosis was evaluated by JC1 stain and TUNEL assay. To determine the effect of CBZ on autophagy, 32D cl 3 cells were irradiated to 5 or 10 Gy, incubated with 50 uM CBZ for 24 hours and then collected and assayed by immunoblot with anti-LC3 antibody. C57BL/6NHsd mice received intraperitoneal injections (IP) of CBZ (10 mg/kg) at several intervals before or after 9.25 Gy total body, Cesium y-irradiation (80 cGy/min). Other mice received 10 mg/kg CBZ immediately before 9.25, 10.5, 11.0 or 11.5 Gy TBI (N = 15-30 / group).

**Results:** CBZ concentrations of 1, 10 and 100 uM for 1 hour before irradiation increased the Do from 1.5 ± 0.1 to 2.1 ± 0.1 (p = 0.012), 2.3 ± 0.1 (p = 0.010), and 3.6 ± 0.7 (p = 0.003), respectively. CBZ after irradiation increased the shoulder (ñ) on the survival curve from 1.5 ± 0.3 to 10.1 ± 4.2 (p = 0.011), 5.5 ± 1.7 (p = 0.019), or 3.6 ± 0.8 (p = 0.014), respectively. JC1 stain and TUNEL assay revealed that CBZ had no effect on mitochondrial membrane potential or apoptosis, respectively, following 5 or 10 Gy. Immunoblot for LC3 in 32D cl 3 cells 24 hours after irradiation revealed a 3.3x (5 Gy) and 6.2x (10 Gy) increase in LC3II/LC3I when cells were incubated in 50 uM CBZ. Cells irradiated in the absence of CBZ exhibited a 1.3x (5 Gy) and 1.8x (10 Gy) LC3II/LC3I increase, respectively. Mice receiving IP injections of 10 mg/kg CBZ immediately before or after 9.25 Gy irradiation demonstrated increased survival (p = 0.014 and 0.006, respectively). Mice receiving 10 mg/kg CBZ 10 min or 24 hrs before irradiation, or 10 min or 12 hrs after irradiation demonstrated increased survival (p = 0.012, 0.011, 0.0002, and 0.017, respectively). The dose-modifying factor was 1.1.

**Conclusion:** CBZ may be a valuable radiation protector and mitigator.

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