Novel Repurposing of Propranolol as an Anti-Tumor Agent in Glioblastoma

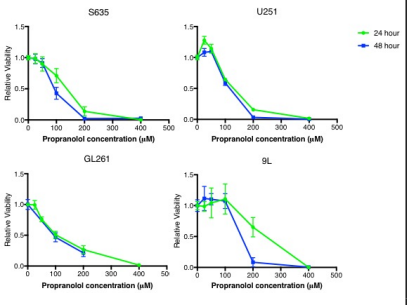
Matthew Shepard MD; Alejandro Bugarini BS; Qi Zhang MD; Zhengping Zhuang MD, PhD; Prashant Chittiboina MD MPH
Surgical Neurology Branch, NINDS, National Institutes of Health, Bethesda, MD
Department of Neurologic Surgery, University of Virginia, Charlottesville, VA

CNS 2017 ANNUAL MEETING
BOSTON, MASSACHUSETTS
OCTOBER 7–11, 2017

Introduction

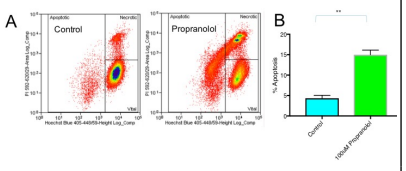
Glioblastoma (GBM) remains a uniformly fatal disease. Despite improvements in image-guided surgery, chemotherapy, and radiation, the prognosis for patients with GBM remains poor with a median overall survival of 14-months. Thus, investigation of novel anti-tumor therapies is imperative. Propranolol is a non-selective beta-1 and beta-2 adrenergic receptor (bAR1, bAR2) antagonist used for treatment of hypertension and arrhythmias. Propranolol was serendipitously discovered to harbor anti-tumor effects in infantile hemangiomas, thought to be due to inverse agonism of bARs leading to decreased intracellular levels of cAMP. Preclinical studies suggest that propranolol harbors broad anti-tumor activity against other solid tumors such as melanoma, breast and prostate cancer. We therefore investigated whether propranolol may have a role in the treatment of GBM.

Figure 1



Propranolol reduces glioma viability at 24 hours for S635, U251 and GL261 glioma cell lines with an IC50 of 100μM.

Figure 2



Propranolol exposure (100μM) to S635 and U251 glioma cell lines induces apoptosis as determined by flow cytometry (Hoechst-PI assay). Representative flow cytometry data (A) and results of biologic triplicates (B) are shown. ** $p < 0.001$

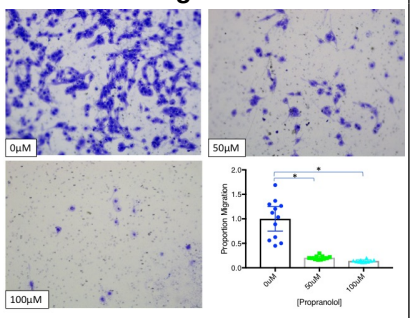
Conclusions

Propranolol induces apoptosis and decreases glioma viability in vitro. This result appears to be specific to propranolol and is not observed with other beta antagonists such as metoprolol. Consistent with previous findings in infantile hemangioma, VEGF transcription is increased in the setting of decreased intracellular VEGF protein levels. Preliminary data suggest that propranolol may exert its anti-tumor effects independent of AR expression. These results lay the framework for further pre-clinical animal studies and perhaps eventual clinical trials. Strengthened by the well-documented safety profile of propranolol and its low cost of administration, these findings encourage further investigation into the potential use of propranolol for treatment of GBM.

Methods

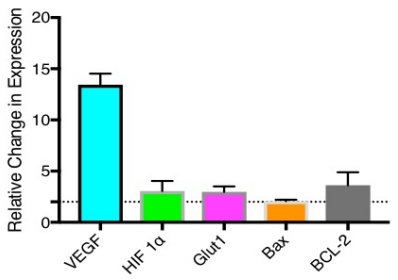
Four GBM cell lines (U251, S635, GL261 and 9L) were cultured and treated with propranolol or metoprolol (another AR antagonist). Cell viability, quantitative RT-PCR, flow cytometry, immunofluorescence, migration assay analysis were performed using clinically relevant concentrations of propranolol.

Figure 3



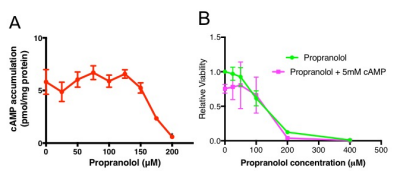
Results of a trans-well migration assay exhibit reduced migratory potential of S635 and U251 glioma cell lines treated with 50μM and 100μM propranolol for 48 hours. Representative photomicrographs (10x) and summarized results of biologic triplicates are shown. Treatment with sublethal doses of propranolol (50μM) still demonstrate diminished glioma migration. * $p < 0.001$

Figure 4



Similar to results seen in IHs, propranolol drives the expression of VEGF-A in cultured glioma cell lines. Results of QT-PCR experiments (24 hour exposure to 100μM propranolol) with -Actin as internal control.

Figure 5



Propranolol acts as an inverse agonist on the beta-receptor leading to decreased intracellular cAMP levels in target tissue. In glioma, however, cAMP levels did not change with propranolol treatment up to 150μM (A). Addition of cAMP to cultured glioma cells did not redcuse propranolol treated cells (B). siRNA directed against AR1 and AR2 did not affect cultured glioma response to treatment (data not shown).

Learning Objectives

1)Describe the current treatment strategies and prognosis for GBM
2)Describe the anti-tumor effects of propranolol for GBM in-vitro
3)Detail potential mechanisms by which propranolol exerts anti-proliferative effects on GBM and other solid tumors

References:

Zou, H. X., et al. (2013). "Propranolol inhibits endothelial progenitor cell homing: a possible treatment mechanism of infantile hemangioma." Cardiovasc Pathol 22(3): 203-210.

Leaute-Labreze, C., et al. (2015). "A randomized, controlled trial of oral propranolol in infantile hemangioma." N Engl J Med 372(8): 735-746.

Zhang, L., et al. (2014). "Propranolol inhibits angiogenesis via down-regulating the expression of vascular endothelial growth factor in hemangioma derived stem cell." Int J Clin Exp Pathol 7(1): 48-55.

Chang, P. Y., et al. (2015). "Propranolol Reduces Cancer Risk: A Population-Based Cohort Study." Medicine (Baltimore) 94(27): e1097.