Effects of Nitrones in Rodent Glioma Models assessed by 1H MR Spectroscopy

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Introduction

Gliomas are the most common and lethal primary brain tumors in the adult, with a median survival time of 12 to 15 months for grade IV gliomas, glioblastoma multiforme [1]. PBN and OKN007 are nitrones which have demonstrated beneficial effects in many aging diseases [2,3]. In this study, we evaluated the anti-tumor effects of PBN or OKN007 in several rodent glioma models (C6, RG2, and GL261) by assessing metabolite alterations with magnetic resonance spectroscopy (MRS).

Methods

PBN or OKN007 was administered in drinking water prior to or post tumor formation. MRI and short echo time, single-voxel point-resolved spectroscopy (PRESS) were obtained to assess tumor morphology and metabolites, respectively, following therapy. MRS data were processed using the "Bruker TopSpin" tool in the Paravision software and major metabolite ratios (Choline, N-acetyl aspartate (NAA), Lipid (methylene), and Lipid (methyl), all compared to Creatine) were calculated using a Mathematica program. Angiogenesis factors and apoptosis markers were detected in the tissues by immunohistochemistry.

Results

Nitrones, such as OKN007, decreased tumor volumes (Fig. 1) and induced tumor metabolism changes that resulted in restoring major metabolite ratios close to their normal levels, in the glioma regression phase. Nitrones (e.g. OKN007) treatment decreased the Lipid (methylene) to Creatine ratio significantly (Fig. 2), which can be a useful marker for evaluation of the efficacy of the treatments, and was found to be related with the reduction of necrosis. OKN007 was more effective than PBN when administered post-tumor formation in the C6 glioma model. OKN007 was able to inhibit angiogenic factors (VEGF, bFGF and HGF) and induce apoptosis (indicated by increase of the apoptosis marker m30 (Fig. 3)) in C6 gliomas, which might be potential mechanisms that are involved in the anti-glioma effects.

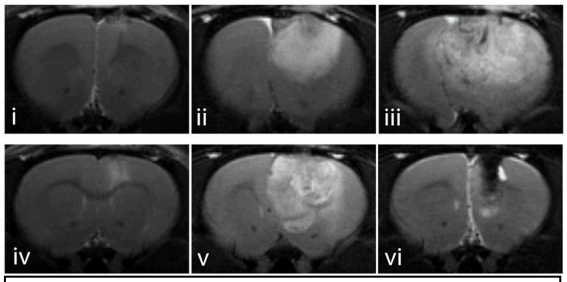

Figure 1: Effect of OKN007 on tumor growth in C6-glioma bearing rats. Representative morphological T_2-weighted images were obtained from Non-treated glioma at day 7 (i), 18 (ii) and 24 (iii, last time point), and OKN007 post-treated glioma at day 7 (iv), 27 (v), and 36 (vi). OKN007 was given on day 15.

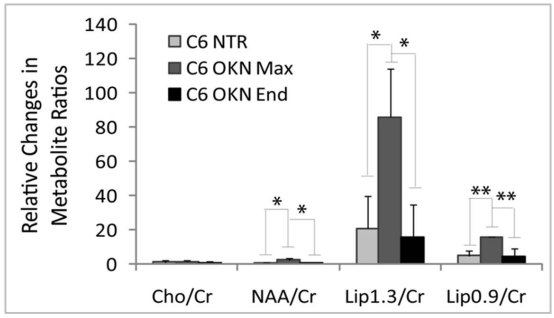

Figure 2: Effects of OKN007 on metabolite ratio changes in C6 rats. Using a one way ANOVA with Bonferroni's multiple comparison test, *p<0.05 or ** p<0.01 indicates significant differences between comparison groups.

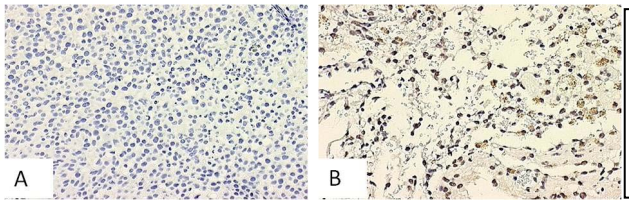

Figure 3: Effects of OKN007 on apoptotic marker m30. (A) non-treated C6 gliomas; (B) OKN-treated C6 gliomas.

Conclusion

In conclusion, OKN007 and PBN are effective in inhibiting the growth of C6 gliomas and may be considered as potential therapeutics for a clinical trial in human gliomas.

References

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