Histamine H_3 receptor antagonists reduce intraocular pressure and retains neuroprotective effects in a rabbit model of glaucoma

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Elevated intraocular pressure (IOP) is the major risk factor for the development of glaucoma, therefore the reduction of IOP is considered the mainstream of glaucoma therapy. The present work is focalized to evaluate the effects of selective histamine H_3 drugs in reducing IOP, oxidative stress and improving ocular vascular perfusion in different models of glaucoma.
Elevated IOP was obtained by the injection of 50 ml of hypertonic saline (5%) into the vitreous or carbomer 100 ml (0.1%) in the anterior chamber of New Zealand albino rabbits'eyes. IOP measurements were performed prior to saline or carbomer injection (baseline), immediately before drug dosing (pre-treatment) and 1, 2, 3 and 4 hours after saline injection in acute model and every day for 2 weeks in chronic carbomer model 24 hours after each drug instillation (H_3R antagonists and timolol vs vehicle). All the animals underwent Ecocolor Doppler evaluation before and after drug treatment and Pourcelot Resistance Index (RI) was calculated. Morphological changes were assessed in retinal histological sections with hematoxylin and eosin staining to evaluate the number of retinal ganglion cells (RGC).Oxidative stress marker levels were measured in retinal tissues of H_3R antagonist and timolol treated animals vs vehicle. Western blot analyses of proteins derived from basal retinae and ciliary bodies and immunofluorescent staining of histological sections of these ocular structures were performed to localize the H_1 and H_3 receptors.
IOP rose from 13.4 ±2.7 mmHg at baseline to 36.6 ±8 mmHg after hypertonic saline and was significantly reduced by H_3R antagonists at 60 and 120 minutes, interestingly ciproxifan reduced IOP with $p<0.01$ at 120'. In the chronic model IOP rose from 12.2 ±2.1 to 34.4± 4.2 and remained stable for 2 weeks: DL-76 reduced IOP at day 10 and 11 with $p< 0.5$ vs vehicle, ciproxifan at day 5-7 and 12 with $p<0.5$, at day 8-10 with $p<0,01$; timolol at day 5,10,12 with $p<0.5$, at day 9 with $p<0,001$. After chronic treatment with DL-76, ciproxifan and GSK 189254 (1%) in glaucoma carbomer model, mean resistance index (RI) of retinic artery and oxidative stress markers were significantly decreased as well as retinal ganglion cells loss (p value <0.05). H_1 and H_3 receptors were expressed and localized in retinae and ciliary bodies in basal conditions. H_3 receptors represent an interesting new therapeutic target for the development of new drugs for glaucoma treatment.