UK Journal of Pharmaceutical and Biosciences
Available at www.ukjpb.com
ISSN: 2347-9442

Protective Role of Oral Bupropion in Prevention of Cataract Induced Experimentally in Rabbits

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Article Information
Received 26 October 2017
Received in revised form 13 June 2018
Accepted 14 June 2018

Keywords:
Cataract,
Oral bupropion,
Rabbits,
Malondialdehyde,
Reduced glutathione,
Lens opacity

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Abstract

Cataract is one of the chief causes of blindness and visual impairment in the elderly people throughout the developing world. The aim of the study was to investigate the possible protective role of oral bupropion against selenite induced cataract in rabbits. Adult rabbits were used in the present study. Groups of study were: Apparently normal group, Cataract group and oral bupropion group. Cataract induction was done by a single intravitreal injection of 0.1 ml (0.01% w/v) of sodium selenite solution in the right eyes. Bupropion (50 mg/kg two times daily) was given for five days before intravitreal injection sodium selenite solution and 21 days after. The parameters were: Lens opacity, pupil diameter, light reflex, corneal sensation, conjunctival redness, the level of malondialdehyde (MDA) and reduced glutathione (GSH) in aqueous humor of rabbit eyes. Oral bupropion resulted in high significant protection from cataract development and there was no change in pupil diameter, positive light reflex, positive corneal sensation, no conjunctival redness, decreased level of MDA and increased level of GSH.

1 Introduction

Cataract is one of the chief causes of blindness and visual impairment in the elderly people throughout the developing world[1]. Presently, the existing treatment for the cataract is the surgical extraction of the cataractous lens and followed by substitution with a synthetic implant[2,3]. Attempts to avoid cataract formation, or at least considerably retard the onset of the cataract formation would be of great value[4]. This is the reason for greatly required biochemical solutions or pharmacological intervention which will maintain the transparency of the lens; it is found that a delay in cataract development of about 10 years would decrease the incidence of cataract by about 45%.

Many factors, such as genetics, cigarette smoking and sunlight exposure are found to be implicated in the progression of lens opacity[5,6]. Specifically, oxidative stress is established to have a major role in the etiology of age-related cataract[7]. Bupropion was categorized as an “atypical” antidepressant since its neurotransmitter effects were indeterminate but known to be different from those of classical antidepressants which are monoamine oxidase inhibitors [MAOIs], tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors (SSRIs). Behr and co-workers[8] found that bupropion had antioxidant effect in animal models and several researches supported that some antidepressants are capable to modulate nitric oxide (NO) synthesis and nitrosative stress-related signalling cascades[9]. The aim of the study was to investigate the possible protective role of oral bupropion against selenite induced cataract in rabbits.

2 Materials and Methods

2.1 Experimental animals

Adult rabbits with no ocular inflammation were included in this study. The rabbits were housed in animal house of The High Institute for Infertility Diagnosis and Assisted Reproductive Technologies / Al-Nahrain University.

The study was done in the period between (June 2014 and December 2014). All rabbits were maintained during the study with appropriate temperature and good ventilation. Animals were kept on fresh diet and allowed for free access to water. The experiments were approved by Animal Ethical Committee, College of Medicine / Al-Nahrain University, Baghdad, Iraq. Rabbits were divided into three groups: Apparently normal, Cataract and Oral bupropion groups.

2.2 Induction of cataract

The rabbits were anesthetized by an intramuscular injection of 0.5 ml of Ketamin (50 mg/ml). In addition Lidocaine solution in concentration of (2%) was applied locally to the eyes to obtain additional anesthesia. The induction of cataract in the right eyes was done by single intravitreal injection of 0.1ml from of sodium selenite solution (0.01% w/v). After injection, the rabbits were monitored every day for caractogenesis[10].

2.3 Parameters of the present study

2.3.1 Lens opacity

The score of lens opacity (by the use of ophthalmoscope grading criteria) was done in accordance with the classification of Kador[11] and Chylack[12].

2.3.2 Pupil diameter

By using the pupil gauge, measuring of pupil diameter was done and the results would be presented in millimeter units[13].

2.3.3 Light reflex

It was examined by swinging flashlight to investigate a relative afferent papillary defect. The obtained results would be expressed as either it was intact or absent[14,15].

2.3.4 Corneal sensation

Could be examined with wisp of cotton wool which applied and moved from side to side. The results was presented as either the corneal sensation was intact or absent[13].

2.3.5 Conjunctival redness

It could be detected by examination of conjunctiva of both eyes and the results would be either present or not[15].

2.3.6 Intraocular pressure (IOP measurement)

IOP measurement were done by anesthetization of the cornea with a local anesthetic (2% lidocaine hydrochloride), and "the foot plate of the tonometer is placed on the cornea (90^o on the pupil), a small force (weight) is applied to a central plunger, readings from the tonometer is converted to the corresponding mmHg of tension by referring to a standard chart"[16,17].

2.3.7 Measurement of glutathione (GSH) and MDA level in aqueous humor of rabbit eyes

Glutathione was measured in accordance with the method of Godin regarding to the reaction of glutathione with 5,5-Dithiobis (2-nitrobenzoic acid) (DTNB) at PH of 8, the result was a colored complex which absorbed light at 412 nm and this was directly proportional to the concentration of GSH. The technique to find out the MDA level is based on the reality that, in acid medium, MDA reacts with thiobarbituric acid (TBA) to form a pink-colored MDA-TBA complex that exhibits an absorption maximum at 532 nm[18,19].

2.3.8 Histopathology study

The rabbit eye lens samples fixed by Gluteraldehyde (3%) solution for 48 hours. Subsequent washing, treatment with osmium tetra oxide (1%) for 20 minute, washing, dehydration at 4 °C and embedding, the tissues capsules sectioned at (1micron), these sections stained with solution A (0.4% basic fucshin in 25% methanol) and B (Prepared by mixing the same volumes of (azure II, methylene blue, Na_2CO_3, absolute methyl alcohol) and examined microscopically[20].

2.4 Statistical methods

By using SPSS version 16, the obtained quantitative data was introduced as mean ± Standard error of mean (S.E.M.). In graphic presentation, only the means of these data (i.e. without S.E.M.) were presented. The significance of the differences between mean values was estimated by using paired and unpaired student's *t*- test accordingly. The obtained difference was considered to be not significant if p value > 0.05, significant if ($0.05 \geq p > 0.01$) and highly significant if ($p \leq 0.01$).

3 Results

3.1 Lens opacity

Oral bupropion in a dose of 50mg/kg twice times daily for five days before cataract induction and continued for 21 days after cataract induction resulted in high significant difference between the cataract maturity of right eyes of oral bupropion group and right eyes of cataract group (P= 0.0001) after two weeks of cataract induction and high significant difference (P= 0.0001) after three weeks of cataract induction, i.e. at the end of the study, only two rabbits had lens opacity one of them of score one and the other of score two lens opacity and other rabbits completely protected from cataract by oral bupropion. These results referred that bupropion had beneficial prophylactic anticataract effect (Fig 1 and associated table).

3.2 Pupil diameter

Along trial period, there was no alteration in pupil diameter and the mean was (8.75± 0.36 mm) for both eyes.

3.3 Light reflex

The pupillary response to light of both eyes was positive along the trial period.

3.4 Corneal sensation

Both eyes had positive corneal sensation before and after administration of oral bupropion and until the end of study.

3.5 Conjunctival redness

There was no conjunctival redness in rabbits' eyes after administration of oral bupropion.

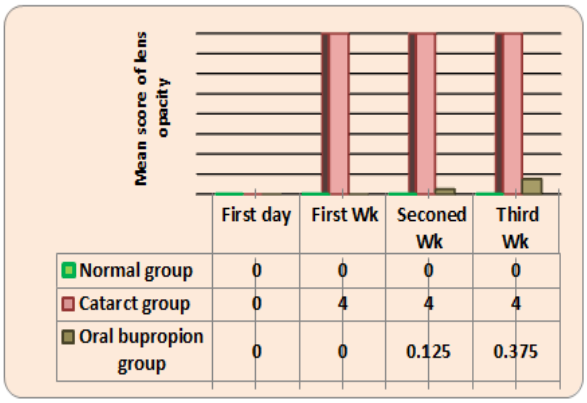

Fig 1: Mean score of lens opacity in rabbits' right eyes of oral bupropion group compared to apparently normal group and cataract group

3.6 Intraocular pressure

The mean± SEM of intraocular pressure (IOP) of rabbits eyes was represented in figure 2 and associated table. In the present study, the IOP of right and left eyes where measured to exclude if that bupropion might cause an increase in the IOP as one of its side effects, but the results showed that bupropion resulted in a decrease in the IOP in normotensive rabbit eyes significantly (but still within normal values) and these results could be a benefit to the use of bupropion.

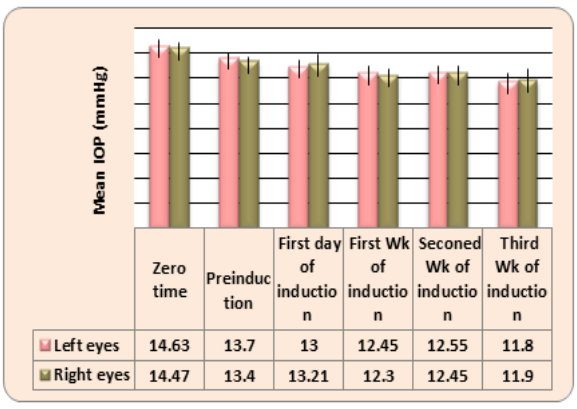

Fig 2: Mean IOP of rabbits' eyes of oral bupropion group

3.7 The GSH and MDA levels

The levels of GSH and MDA were measured at the end of the study in the aqueous humor of apparently normal, cataract and oral bupropion groups, (Fig 3 and Fig 4 and associated tables). Bupropion administration orally resulted in high significant increase in GSH and high significant decrease in MDA levels in aqueous humor compared to cataract group.

3.8 Histopathology study of rabbit lens

The cytoplasm of normal eye was uniform, featureless, and it was stained homogenously as shown in figure (5A). In the lens of cataract group, there was thick darkly stained collectives inside the fiber which extended along the lens fiber, these aggregations characterize the insoluble proteins that build up and aggregate in the lens fiber which caused by the oxidative and sclerotic outcome of selenite on the lens proteins. These aggregations are surrounded by plain or lighter areas produced as a resultof losing the cytoplasm its homogenous form as shown by figure (5B). As shown in figure (5C), oral bupropion administered twice daily prevented the aggregations of proteins

4 Discussions

These results showed that bupropion had good antioxidant effects and these result agreed with Guilherme and co-workers[21] who did preclinical study on animal model and showed positive antioxidant effect of bupropion and also agreed with Dhir and Kulkarni who demonstrated that acute treatment to male albino rats with bupropion resulted in "modulation of L-arginine-NO-cyclic GMP signalling pathway in rat brain". Howell and co-workers[22] provided evidence that bupropion action may include targeting TNF- α production which is secondary to neuroinflammatory processes. Kumari and co-workers[23] found that TNF- α level an approximate 12-fold increased in the lenses of rat that were received sodium selenite as inducing agent of cataract. TNF-α is an excitatory cytokine of the human lens epithelial cells which activates nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). Bupropion has complex pharmacological properties and the obvious inverse relation between bupropion use and open glaucoma may be an outcome of a more direct effect of bupropion on norepinephrine or dopamine metabolism.

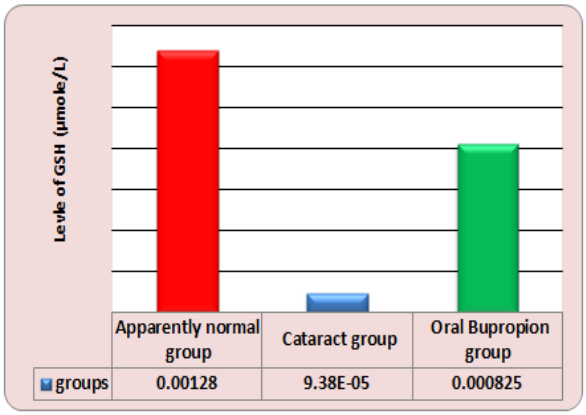

Fig 3: Levels of GSH (µmole/L) in aqueous humor of groups of study

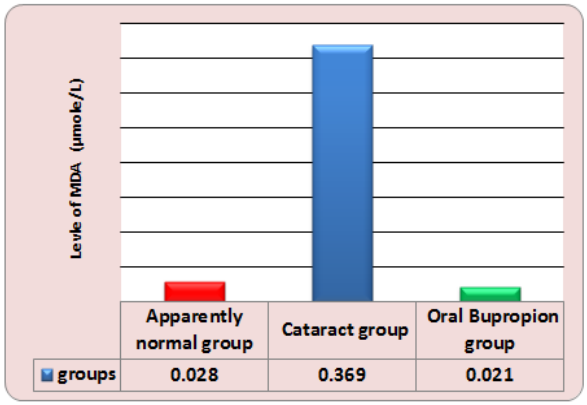

Fig 4: Levels of MDA (µmole/L) in aqueous humor of groups of study

In addition, "the subsequent secondary effect of increasing intracellular cAMP could be beneficial in glaucoma", since cAMP signaling is vital for both trabecular meshwork[24], and retinal ganglion cell function[25], nevertheless, other antidepressants such as selective serotonin reuptake inhibitors and tricyclic antidepressant drugs as well increase cAMP levels but these agents did not show to impact open angle glaucoma risk in researches[26].

The histopathological study showed the role of bupropion in the protection of the lens from opacification, because bupropion prevented the proteins aggregation and the cytoplasm approximately looked homogenous (Fig 5). These results gave indication to the beneficial prophylactic and anticataract effect of bupropion.

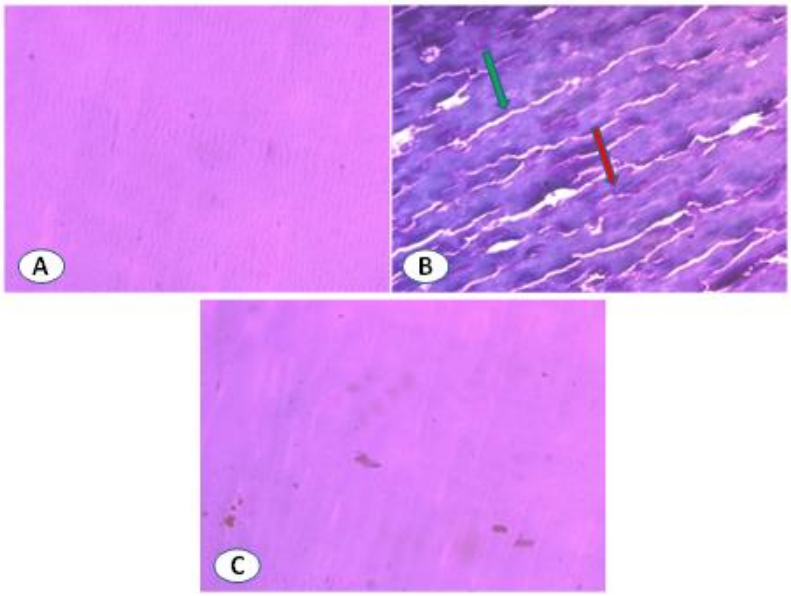

Fig 5: Longitudinal section of rabbits' lens stained with solution A and B for semithin section (40X). A: Normal group shown homogenous cytoplasm of the normal lens fibers. B: Cataract group shown darkly stained aggregation (red arrows), alternating with clear areas (green arrows) with loss of the homogenous architecture of the cytoplasm of lens fibers. C: Oral bupropion shown homogenous and clear cytoplasm of lens fibers

5 Conclusion

Administration of oral bupropion resulted in high significant protection against cataract induced by selenite.

6 Acknowledgements

The author would like to thank Al-Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad - Iraq, Al-nahrain University Baghdad. Iraq for their support in the present work and for providing necessary facilities.

7 Conflict of interest

The author declared non

8 Author's contributions

AAA, AMR and BAA brings the study design into its applicable state along with drafting the manuscript. The literature review, result discussion, lab work was carried out by DAAS (the corresponding author). All authers read and approved the final manuscript.

9 References

1. Thylefors B, Negrel AD, Pararajasegaram R, Dazie KY. Global data on blindness. Bull World Health Org. 1995; 73: 115–12.
2. Kyselova Z. Different experimental approaches in modeling cataractogenesis. Interdiscip Toxicol. 2010; 3(1): 3–14.
3. Porth CM. Essentials of Pathophysiology. 4th ed. Wolters Kluwer. 2015; 956-957.
4. Cornish KM, Williamson G, Sanderson J. Quercetin metabolism in the Lens. Role in inhibition of hydrogen peroxide induced cataract. Free Radic Biol Med. 2002; 33: 63–70.

5. McCarty C, Taylor HR. Light and risk for age-related eye diseases. In: Taylor A (ed). Nutritional and Environmental Influences on the Eye. 1999; 135–150.
6. Delcourt C, Cristol JP, Tessier F, Leger C, Michel F, Papoz L. The Pathologies Oculaires Lieers al'Age. Risk factors for cortical, nuclear, and posterior subcapsular cataracts: the POLA study. Am J Epidemiol . 2000; 151(5): 497-504.
7. Olmedilla B, Granado F, Blanco I, Vaquero M. Lutein, but not-tocopherol, supplementation improves visual function in patients with age-related cataracts: a 2-y double-blind, placebo-controlled pilot study. Nutrition. 2003; 19: 21–24.
8. Behr GA, Jos´e CF, Moreira, Benicio N. Preclinical and clinical evidence of antioxidant effects of antidepressant agents: implications for the pathophysiology of major depressive disorder. Oxidative Medicine and Cellular Longevity. 2012.
9. Dhir A, Kulkarni SK. Involvement of nitric oxide (NO) signaling pathway in the antidepressant action of bupropion, a dopamine reuptake inhibitor," European Journal of Pharmacology. 2007; 568(1): 177–185.
10. Abdul-Hussein BA, Alzubaidy AA, Radi HA. Effect of diltiazem on intraocular pressure in normal and ocular hypertensive rabbits. 2012; 8(13): 69-83.
11. Kador PF, Kinoshita JH. Diabetic and galactosaemic cataracts. Ciba Foundation Symposium. 1986; 106: 110– 131.
12. Chylack LT, Leske MC, McCarthy D. Lens opacities classification system II (LOCS II). Arch Ophthalmol. 1989; 107(7): 1991
13. Ahuja M.Ophthalmology Handbook. 1st ed. India Binding House. Delhi. 2003: 6-24 and 145-163.
14. Jaffe NS, Jaffe MS, Jaffe GF. Cataract surgery and its complications.5th ed. Mosby. ST. Louis. 1990: 6-18.
15. Macdonald M. The examination of the eye. In: Munro J. and Edwards C. Macleod's Clinical Examination.10th .ed. Churchill Livingstone. Edinburgh. 2000: 257-271.
16. Moses RA. Intraocular pressure. In: Moses R.A. and Hart W.M. Alder's Physiology of the eye Clinical Application. 9th ed. Mosby Company. St. Louis. 1997: 223-245.
17. Cacho I, Sanchez-Naves J, Batres L, Pintor J, Carracedo G. Comparison of Intraocular Pressure before and after Laser Situ Keratomileusis Refractive Surgery Measured with Perkins Tonometry, Noncontact Tonometry, and Transpalpebral Tonometry. Journal of Ophthalmology. 2015; 2015: 6.
18. Stocks J, Dormandy TL. The auto-oxidation of human red cell lipids induced by hydrogen peroxide. Br JHaematol. 1971: 20: 95-111.
19. Ohkawa H, Ohishi N, Yagi K. Assay of lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979; 95: 351-8.
20. Al-Habib MF. Effects of aflatoxin B on some skeletal muscle resident cells using a nuclear differentiating stain technique. Iraqi J. Med Sci. 2007; 5(2): 71-77.
21. Guilherme A. Behr Jos´e CF. Moreira, and Benicio N. Frey. Preclinical and clinical evidence of antioxidant effects of antidepressant agents: implications for the pathophysiology of major depressive disorder. Oxidative Medicine and Cellular Longevity. 2012: 2012
22. Howell GR, Soto I, Ryan M, Graham LC, Smith RS, John SW.Deficiency of complement component 5 ameliorates glaucoma in DBA/2J mice. J Neuroinflammation. 2013; 10: 76.
23. Kumari RP, Ramkumar S, Thankappan B, Natarajaseenivasan K, Balaji S, Anbarasu K. Transcriptional regulation of crystallin, redox, and apoptotic genes by C-Phycocyanin in the selenite-induced cataractogenic rat model. Molecular Vision. 2015; 21: 26-39.
24. Wu J, Li G, Luna C, Spasojevic I, Epstein DL, Gonzalez P. Endogenous production of extracellular adenosine by trabecular meshwork cells: potential role in outflow regulation. Invest Ophthalmol Vis Sci. 2012; 53: 7142–7148.
25. Wang DY, Ray A, Rodgers K, Ergorul C, Hyman BT, Huang W, Grosskreutz CL.Global gene expression changes in rat retinal ganglion cells in experimental glaucoma. Invest Ophthalmol Vis Sci. 2010; 51: 4084–4095
26. Jain R, Majunder P, Gupta T. Pharmacological intervention of nicotine dependence. Biomed Res Int. 2013.