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THE PROTECTIVE INFLUENCE OF CURCUMIN ON RETINA AND OPTIC NERVE IN NICOTINE AFFECTED RATS

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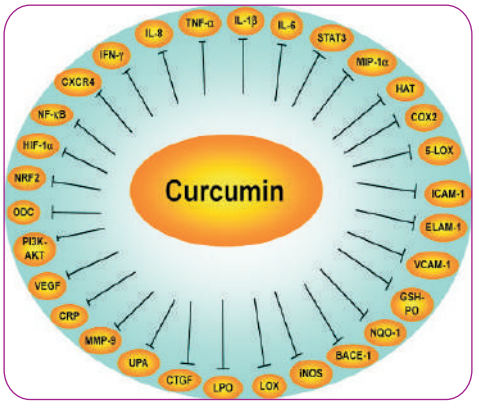
ABSTRACT: -

Background: *Active smoking is an accepted risk factor for several disorders including age-related macular degeneration, cataract, and anterior segment surface disorders. The present study was planned to analyze histopathologically effect of nicotine on retina and optic nerve and the possible protective effect of curcumin as an antioxidant.* ***Materials and Methods:*** *Twenty five rats were randomly divided into 3 groups as follows: l) control group, 2) nicotine injected group, 3) nicotine and curcumin treated group. Histopathological examination of all groups was carried out where their retinas and optic nerves were prepared for light microscope examination.* ***Results:*** *Results showed that the nicotine is toxic for the retina and optic nerve and the curcumin exerts its protective effect on it.* ***Conclusion:*** *Pilot clinical trials on curcumin are recommended to achieve its beneficial antioxidant effects, avoiding the toxicity of nicotine and other harmful environmental substances.*



KEYWORDS: *nicotine, smoking, curcumin, retina, optic nerve.*

INTRODUCTION :

Smoking, both active and passive, creates a plethora of health-related problems, which primarily affect the cardiovascular and respiratory systems. Tobacco consumption is one of the leading preventable causes of death and disease worldwide. Tobacco use kills more than five million people per year and is responsible for one in 10 adult deaths. Although lung cancer is strongly associated with smoking, tobacco use also increases the risk of heart disease and other vascular diseases and leads to malnutrition, which will eventually result in increased health-care costs and premature death (Omotoso et al., 2010). Nicotine, a major toxic component of tobacco, has been identified as an important risk factor for eye-related disease. The toxins associated with smoking decrease blood flow or aid in the formation of clots within ocular capillaries, thus cutting off vital nutrients that are essential for eye health. Free radicals that are produced because of smoking impair the normal functionality of the cells and have been reported to cause ocular diseases.

People who smoke cigarettes are at an increased risk of developing cataracts, age-related macular degeneration, diabetic retinopathy, glaucoma, Grave's ophthalmopathy, and optic neuritis. Heavy smokers are at higher risk of developing exudative or atrophic age-related macular degeneration. However, there is very little evidence on the effects of tobacco smoke on the eye, especially ocular related pathology. Increasing evidence demonstrated that oxidative stress plays a crucial etiological role in the development of eye-related disease (Jyothi et al., 2012). Curcumin, a constituent of turmeric is an effective antioxidant and is known to induce the enzymes of glutathione -linked detoxification pathways in rats; curcumin seems to prevent oxidative damage.

Curcumin, a plant polyphenol, possesses diverse antioxidant and anti-inflammatory properties. It significantly decreases lipid peroxidation, increases intracellular antioxidant, regulates antioxidant enzymes, and scavenges hyperglycaemia.

In addition, it could be considered a new natural agent against the Acanthamoeba cyst, which had a significant inhibitory effect on the multiplication of Acanthamoeba cysts as compared to the drug control (chlorhexidine) and non-treated control, and the inhibition was time and dose dependent (El-Sayed et al., 2012). Furthermore curcumin is shown to inhibit the pro-inflammatory transcriptional factor, NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), and prevent up-regulation of VEGF mRNA (vascular endothelial growth factor of messenger ribonucleic acid) and micro vascular angiogenesis. The antioxidant capacity, a measure of the total protective antioxidant mechanisms (both for preventing the production of free radicals and for repairing oxidative damage), of curcumin has been considered to be mediated via its beneficial effects on the antioxidant defence system, the scavenging of free radicals and/or via preventing lipid peroxidation and it is at least 10 times more active as an antioxidant than vitamin E (Pescosolido1et al., 2014).

The present study was carried out to determine the histopathological effects of nicotine on the retina and optic nerve and the ameliorative effect of curcumin on their possible damage

MATERIALS AND METHODS

Twenty five (25) albino rats with an average weight of 300-400 gms. were randomly divided into 3 groups. The rats were housed in stainless-steal cages and fed with standard rat chow and tap water and libitum in the animal house of the Research Institute of Ophthalmology. The animal experiment was carried out according to the internationally valid guidelines and the research protocol was approved by the local ethical committee of the Research Institute of Ophthalmology, Giza, Egypt.

Group 1: consisted of 5 rats and served as control.

Group 2: consisted of 10 rats and injected with 25mg/Kg. bodyweight nicotine (nicotine tartrate, ICN Biomedicals Inc., OH, USA) .,intraperitoneally for 8 weeks. The given doses and the route of nicotine administration are the regimens that produce plasma nicotine levels spanning the range of low, moderate, and heavy smokers in humans, respectively (Karam et al., 2014)

Group 3: Consisted of 10 rats and administrated with curcumin which was purchased from Sigma Company (Sigma Chemical Co., St. Louis, MO) as yellowish powder, dissolved in corn oil at a dose of 80 mg/Kg. bodyweight by stomach tube simultaneous with 25mg/Kg. bodyweight nicotine injection.

The rats of all groups were sacrificed after 8 weeks. The eyes were immediately enucleated ,bisected and placed in 2.5% glutaraldehyde fixative for 4-6 hours .After phosphate buffer wash, posterior segment sections from the retina and the intracanalicular part of the optic nerve were dissected into small pieces and postfixed in 1.33% buffered osmium tetroxide, dehydrated in ascending grades of ethanol and embedded in Araldite (resin embedded samples). Semi-thin sections, approximately 0.5um thick, were cut with a glass knife, stained with 1% toluidine blue and examined by light microscopy.

RESULTS

Retinas obtained from control group (group l) after 8 weeks show the normal nine layers and a supporting pigment epithelium layer (PE); 1) photoreceptor layer ,rods and cones (PRL), 2) outer limiting membrane (OLM), 3) outer nuclear layer (ONL), 4) outer plexiform layer (OPL), 5) inner nuclear layer(INL), 6) inner plexiform layer(IPL), 7) ganglion cell layer(GCL), 8) nerve fiber layer(NFL), and 9) inner limiting membrane (ILM) (Fig. l).

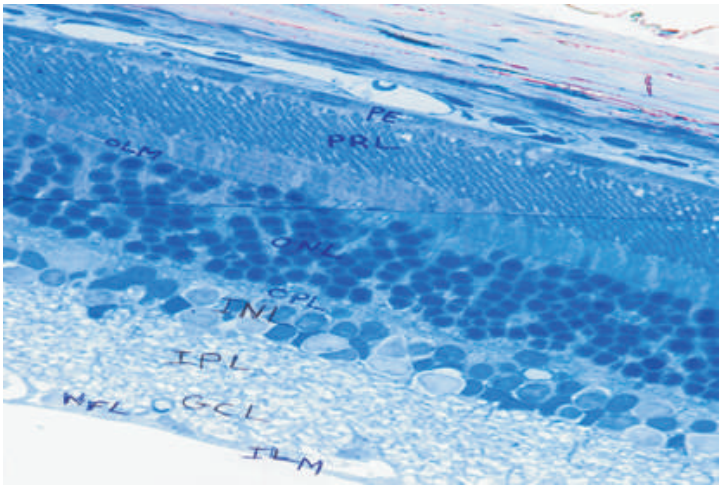


Fig. 1: Light micrograph of rat retina of the control group showing the normal nine layers and a supporting pigment epithelium layer (PE); 1) photoreceptr layer, rods and cones (PRL), 2) outer limiting membrane (OLM), 3) outer nuclear layer (ONL), 4) outer plexiform layer (OPL), 5) inner nuclear layer (INL), 6) inner plexiform layer(IPL), 7) ganglion cell layer (GCL), 8) nerve fiber layer (NFL) and 9) inner limiting membrane (ILM) (Montag, Toluidine bluex1250).

Administration of nicotine for 8 weeks resulted in evident pathological changes in retinal layers. In general, retina was edematous. The pigment epithelium nuclei appeared swollen, rounded and darkly stained. Rupture of pigment epithelial membrane and migration of nuclei was observed in some areas. The rods and cones of the photoreceptor layer and their cell bodies in the outer nuclear layer showed signs of karyolysis where the nuclei appeared blurred with lack of cellar details. The outer plexiform layer lost their reticular appearance (Fig. 2a). The ganglion cell layer showed slightly swelling of their nuclei with lucent cytoplasm. In addition, congestion of blood vessels was also observed, No significant changes in NFL (Fig. 2b).

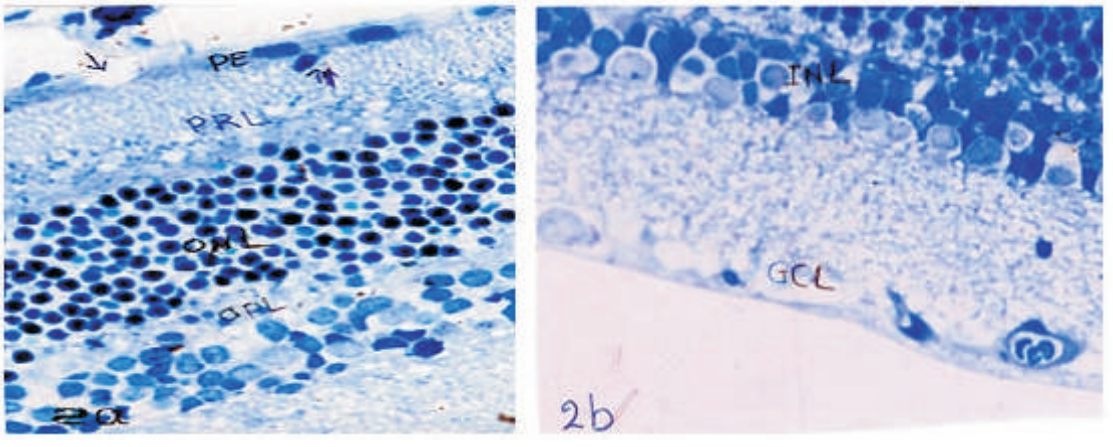


Fig. 2: Light micrograph of rat retina obtained from "group 2", after 8 weeks of nicotine injection showing edema in all retinal layers.
a) The pigment epithelium nuclei appeared swollen, rounded and darkly stained .Rupture of pigment epithelial membrane (arrow) and migration of nuclei (double arrow) was observed in some areas.
b) The ganglion cell layer showed slightly swollen of their nuclei with lucent cytoplasm .In addition, congestion of blood vessels was also observed, No significant changes in NFL(Toluidine blue x1250).

By curcumin treatment, light microscopic examination of retina showed well-presented cytoarchitecture of all retinal layers, with exception of thickening of the blood vessels wall in the ganglion cell layer. The orbital part of optic nerve in control group showed bundles of myelinated nerve fibers(axons) surrounded by abundant oligodendrocytes (Fig. 3).

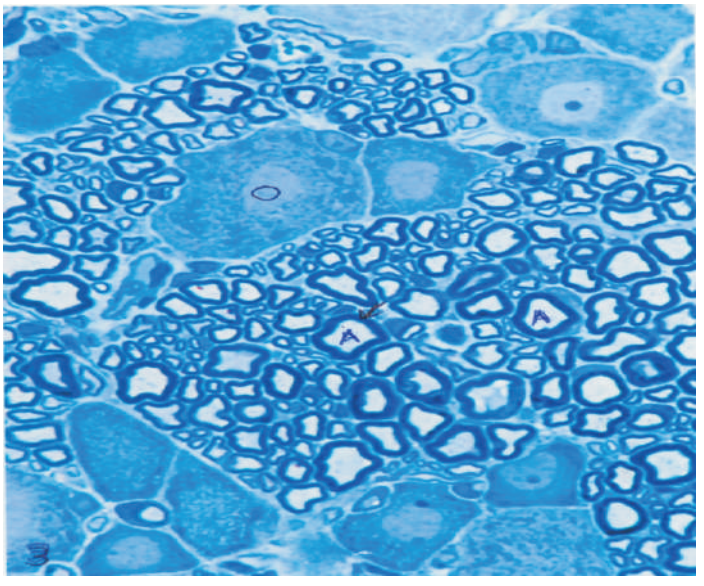


Fig. 3: Light micrograph of control rat optic nerve showing myelinated nerve axons, (A) with abundant oligodendrocytes are evident (O) (Toluidine blue X1250.

Meanwhile, the optic nerve of the nicotine-induced group displayed abnormally formed myelin sheaths of different thickness. Edema is also observed between the nerve axons (Fig. 4). However, with the use of curcumin, the myelin sheaths regained its normal thickness (Fig. 5).

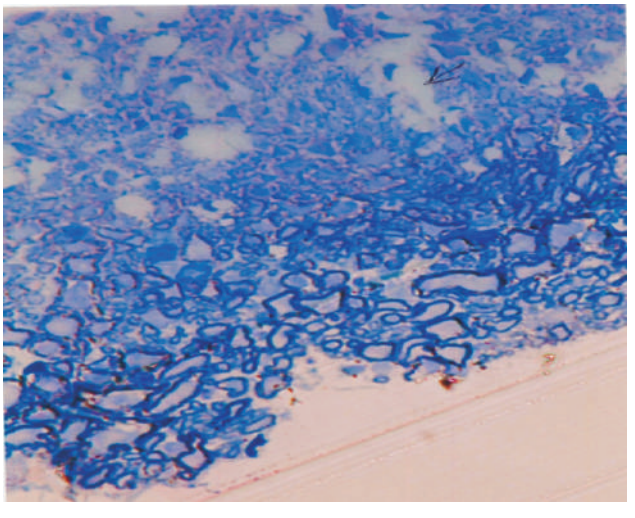


Fig. 4: Light micrograph of rat optic nerve obtained from "group 2", after 8 weeks of nicotine injection showing abnormally formed myelin sheaths of different thickness. Edema and vacuoles (arrow) is seen between the nerve axons. (Toluidine blue X500).

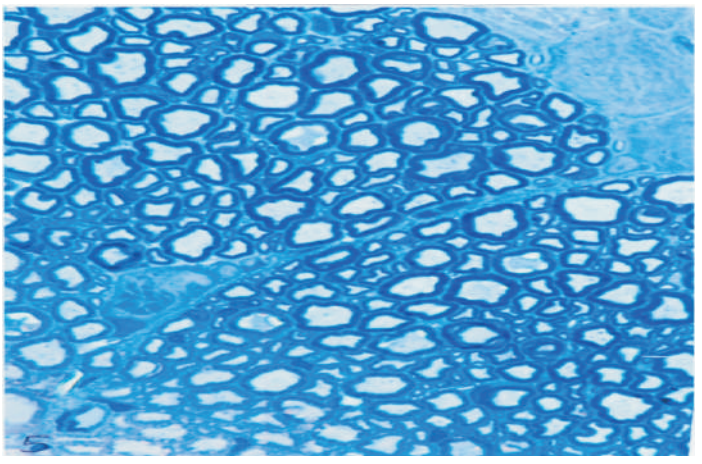


Fig. 5: Light micrograph of rat optic nerve obtained from "group 3", after 8 weeks of nicotine with curcumin injection showing normal thickness of myelin Sheath (Toluidine blue X1250).

DISCUSSION

Cigarette smoking is at present considered a health serious public problem around the world. Cigarette smoke is known to contain more than 4000 toxic substances that exist in the form of gas or particles. Many of the 4000 constituents of tobacco smoke are known to be toxic to the body, affecting many systems in the body: the brain, cardiovascular, lung, urinary bladder, ocular structures and others. The chief pharmacologically active ingredients are nicotine (acute effects) and tar (chronic effects). A completely burned cigarette stick usually; contains between 1-6 mg of nicotine, apart from the 1-5 % carbon monoxide present in the smoke .Tobacco smoke, as an exogenous source of reactive oxygen species, has a broad spectrum of oxidant-ionizing radiation which generates free radicals in exposed tissues, and causes hypoxia, vascular injury and ischemia.

On the other hand, curcumin has an outstanding safety profile and a number of pleiotropic actions with anti-inflammatory, antioxidant, and anti-protein-aggregate activities. These can be achieved in vitro, however might not be achievable in target tissues in vivo with oral dosing. However, despite concerns about poor oral bioavailability, dietary curcumin is a strong candidate for use in the prevention or treatment of major disabling age-related disease like Alzheimer's, cataract and stroke (Wang et al., 2013).

Tobacco smoking is also one of the preventable risk factors for age-related macular degeneration (AMD). Studies have shown that current smokers and ex-smokers are more likely to develop AMD than people who have never smoked. The optic nerve is also susceptible to damage from smoking. People with poor diets who smoke heavily and drink excessive amounts of alcohol run the risk of developing optic nerve-related vision loss (called tobacco-alcohol amblyopia) (Ahuja et al., 2016). To our knowledge this is the first study concerning the histopathological effects of nicotine and curcumin on the retina and optic nerve, we were unable to find data in the literature regarding this topic. This study has been conducted to study the histopathological toxic effects of nicotine, together with antitoxic protective effect of curcumin on both structures.

The present work showed that intraperitoneal injection with nicotine to the rats showed a histopathologically damaging effect to the retina and optic nerve in the form of edema, with of blurring of cellular details and disruption. These changes come in accordance with Patil et al. (2009) who found that the nicotine was toxic to retinal cells in cell cultures through an oxidant pathway that is non-caspase, non-calpain and also via necrosis. Understanding the mechanisms of cell death may have potential therapeutic implications in the treatment of cigarette smoking related retinal diseases such as age-related macular degeneration (AMD).
This study showed that retinal pigment epithelial injury disrupted the blood retinal barrier which probably interfere with the phagocytic, protective and nutritive function of the RPE cells. This destruction explains the retinal changes induced by nicotine. One study on cigarette smoking on the ocular structures concluded that the longer the number of days of the treated group was exposed to nicotine, the more the degree of architectural distortions and cellular degenerations (Jyothi et al., 2012).

This is consistent with our findings which showed edema and abnormally formed myelin sheaths of different thickness of optic nerve with eight weeks exposure to nicotine in our specimens. More exposure may lead to severe damaging effect with more loss of function and visual loss. Zhang et al., 2007), studied the effect of curcumin on human pterygium in culture, searching for a new method to prevent its recurrence. They concluded that curcumin at an oral dose ranging from 20-80 micromole/L for 24-72 hours could interfere with cell growth cycle of fibroblasts, induce apoptosis, thus suppressing proliferation of fibroblasts. Other studies showed also that curcumin at a time and a dose dependant manner can interrupt with the cell cycle, thus having a role in cytotoxicity, antiproliferation and inducing apoptosis (Wang et al., 2013). In a study made by Pandya et al. (2010), found that administration of naphthalene can induce cataract in rats through oxidative stress. They concluded that curcumin, a famous spice in Indian curry, has an effective antioxidant action through activating the glutathione detoxification pathways thus preventing the oxidative toxicity of naphthalene.

From this study, it could be concluded that nicotine has a damaging mainly oxidative stress activity effect on the retinal layers and optic nerve morphology, thus affecting the visual acuity. However, concomitant administration of curcumin can has a protective free radical scavenging activity on the retina and optic nerve from nicotine toxicity. In reference to these promising results, we recommend pilot clinical trials on curcumin to achieve its beneficial antioxidant effects, avoiding the toxicity of nicotine and other harmful environmental substances.

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