Experimental Studies

Neopterin level in the anterior segment of the eye in induced uveitis with ocular hypertension when treated by dipeptide carnosine

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Background: *We have previously demonstrated that the course of inflammatory process was significantly more severe in eyes with anterior uveitis with ocular hypertension (OHT) than in those with anterior uveitis with normal intraocular pressure (IOP), which was largely due to a more marked activation of enzymes producing active oxygen as well as peroxidative processes in uveal structures of experimental animals. Aside from oxidative stress characteristics, our attention has been drawn to neopterin as a potential marker of inflammation severity and the efficacy of inflammation control. Because there is a paucity of reports focused on the potential for using this characteristic as a diagnostic criterion in ocular disorders, especially in uveitis with raised IOP, studies on this subject are important.*
Purpose: *To assess the impact of dipeptide carnosine on the level of neopterin in the rabbit's anterior eye segment in anterior uveitis with ocular hypertension.*
Material and Methods: *Forty-four Chinchilla rabbits (88 eyes) were divided into 4 experimental groups (group 1, 10 animals with induced OHT only; group 2, 10 animals with induced experimental non-infectious uveitis only; group 3, 12 animals with OHT induced prior to experimental non-infectious uveitis; group 4, 12 animals treated with carnosine for experimental uveitis with OHT). Rabbits of group 4 received 5% carnosine solution into the conjunctival sac, twice daily for the four weeks. The control group comprised 9 intact rabbits. Neopterin enzyme-linked immunosorbent assay kit was used to determine neopterin levels in uveal tract tissue, aqueous humor and tear samples according to the manufacturer's instructions. Statistica 5.5 (StatSoft, Tulsa, OK, USA) software and parametric statistical tests were used for statistical analysis.*
Results: *Neopterin levels in uveal tract tissue, aqueous humor and tear samples taken from rabbit's eyes with induced OHT only were increased compared to controls but lower than those in non-infectious uveitis only. Neopterin levels in uveal tract tissue, aqueous humor and tear samples from rabbit's eyes with induced both anterior uveitis and OHT (group 3) were 5.2-, 3.7- and 2.4 times higher, respectively, than in controls, and 42.5% ($p < 0.05$), 28.5% ($p < 0.05$) and 23.6% ($p < 0.05$) higher, respectively, than in samples taken from rabbit's eyes of group 2. The carnosine treatment of induced both anterior uveitis and OHT (group 4) contributed to reduced levels of neopterin is samples under study, with neopterin levels in uveal tract tissue, aqueous humor and tear fluid being 39.4%, 38.9% and 30.2% lower, respectively, than in samples taken from rabbit's eyes of group 3 (anterior uveitis plus OHT without treatment) ($p < 0.01$), and 3.2-, 2.2- and 1.7 times higher, respectively, than in controls ($p < 0.001$).*
Conclusion: *High neopterin levels in the uveal tract tissues and anterior chamber aqueous fluid indicated its impact on the course of inflammation in animals with induced uveitis only and especially in those with induced both uveitis and OHT. A high neopterin level in the tear fluid in anterior uveitis can be considered a diagnostic marker of the severity of inflammation in the anterior segment of the eye. The carnosine treatment statistically significantly reduced neopterin levels in the uveal tract tissues, anterior chamber aqueous fluid and tear fluid in rabbit's eyes with induced both uveitis and OHT. The changes in neopterin levels were caused by a reduction in the severity of inflammation in the anterior segment of the eye.*

Keywords:
non-infectious uveitis, ocular hypertension, neopterin, carnosine, rabbits

Introduction

An increase in the prevalence of inflammatory anterior eye disease provides a significant medical and social challenge to our society [1, 2]. The disease most commonly occurs in young people and working-age adults, and some of its complications can cause a significantly impaired quality of life including blindness [3, 4].

Epidemiological studies have found that anterior uveitis is the most common type of intraocular inflammation and most commonly of noninfectious origin [5-7]. Raised intraocular pressure (IOP) has been attributed a major role in the development complications in degenerative and inflammatory processes in numerous publications on uveitis-associated conditions [8-10].

Oxidative stress characteristic particularly of glaucoma but also of uveitis, and significant oxidative balance disturbances contribute to the development of inflammatory processes in the presence of ocular hypertension (OHT) [11-14].

We have previously demonstrated that the course of inflammatory process was significantly more severe in eyes with anterior uveitis with OHT than in eyes with uveitis with normal IOP [15], which was largely due to a more marked activation of enzymes producing active oxygen as well as peroxidative processes in uveal structures of experimental animals [16].

Identification of characteristic biomarkers is essential for diagnostic procedures. Although a variety of characteristic biomarkers of inflammatory processes are already known, not all of them provide enough information. Excessive levels of oxidative stress components are pathogenic and contribute to an increase in inflammation, and not only they, but also significant changes in the cytokine and chemokine profile have been detected in the ocular tissues and biological fluids in uveitis [17, 18]. They, however, may not always be a reliable marker of inflammation in biological fluids (e.g., tear fluid) due to their short life span and paracrine effects [19, 20]. That is why our attention has been drawn to neopterin as a potential marker of inflammation severity and the efficacy of inflammation control.

This compound is a stable low-molecular-weight heterocyclic product of monocytes, macrophages and other cells [20, 21], and regarded as a marker of activation of cellular immunity in a number of disorders. Given the role of immune mechanisms in the pathogenesis of uveitis, and that neopterin levels correlate with intraocular inflammatory response in an uveitis model [22, 23], neopterin level is a potential important marker of the severity of inflammation in uveitis [20, 24]. Because there is a paucity of reports focused on the potential for using this characteristic as a diagnostic criterion in ocular disorders, especially in uveitis with raised IOP, studies on this subject are important. It has been reported on increased levels of neopterin in uveitis of various etiologies and that these levels could correlate with the course of the disease [20, 25].

Presently available medications for the treatment of uveitis have significant side effects as well as a low efficacy to prevent complications of ocular inflammation, including ocular inflammation with ocular hypertension (OHT). The pathogenetic mechanisms of these conditions and a potential for an increase in efficacy-to–side effect ratio [26, 27] should be taken into account in order to reduce the rate and amount of the phenomenon. Because of this, in our studies we used the naturally occurring dipeptide carnosine (beta-alanyl-L-histidine), an anti-oxidant that has been shown to exhibit biological effects on the ocular structures in the treatment of various inflammatory and degenerative disorders [28], to assess its effect on the level of neopterin as a marker of the degree of inflammation.

The purpose of this study was to assess the effect of dipeptide carnosine on the level of neopterin in the rabbit's anterior eye segment in induced anterior uveitis with ocular hypertension.

Material and Methods

Forty-four Chinchilla rabbits (88 eyes) weighting 3.0 to 3.5 kg, maintained under normal vivarium conditions and fed and watered ad libitum, were used for all experiments. All animal experiments were performed in compliance with the General Ethical Principles of Animal Experiments (approved by Third National Congress on Bioethics, Ukraine, Kyiv, 2007) and European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes from the European Treaty Series (Strasbourg, 1986). Forty-four rabbits were divided into 4 experimental groups (group 1, 10 animals with induced OHT only; group 2, 10 animals with induced experimental non-infectious uveitis only; group 3, 12 animals with OHT induced prior to experimental non-infectious uveitis; group 4, 12 animals treated with carnosine for experimental uveitis with OHT). The control group comprised 9 intact rabbits.

Non-infectious uveitis was induced by introducing bovine serum albumin at a dose of 5 mg into the conjunctival cavity only after the animal was sensitized [29]. OHT was induced by a single 0.1-mL injection of 0.3% carbomer into the anterior chamber of the rabbit. Carnosine was introduced by instilling 5% solution into the conjunctival sac of each eye in animals of group 4, twice daily for the four weeks.

General anesthesia was administered by intramuscular injection of ketamine hydrochloride (50 mg/kg), and topical anesthesia was performed by instillation of 0.5% proparacaine hydrochloride into the conjunctival sac one minute before injection. Animals underwent biomicroscopy, ophthalmoscopy and tonometry. We used a Maklakoff tonometer with a 7.5-g plunger load to perform IOP measurements after topical anesthesia was performed by instillation of 0.5% proparacaine hydrochloride into the conjunctival sac.

Uveal tract tissue, anterior chamber aqueous humor, and tear samples were harvested 4 weeks after completing

the induction of non-infectious uveitis and OHT to determine neopterin levels.

A 5 mm x 40 mm filter paper (Filtrak, Niederschlag Bärenstein, Germany) strip was folded and placed between the eyelid and the cornea and left for 1 minute. Thereafter, strip samples were eluted in physiological solution. The eluate was centrifuged (3,000 rev/min, 10 min) and the supernatant was collected for biochemical analysis. Animals were deeply anesthetized with thiopental sodium 10% (1.0 mL/kg, intramuscularly) and euthanized by air embolism.

Eyes were enucleated and immediately placed on ice at 0 to 4 degrees C. A syringe with needle was used to harvest aqueous humor, and uveal tract tissue was separated from the sclera and optic nerve to prepare the homogenate. Neopterin levels were determined in the centrifuged supernatants using the neopterin enzyme-linked immunosorbent assay kit according to the manufacturer's instructions.

Statistica 5.5 (StatSoft, Tulsa, OK, USA) software and parametric statistical tests were used for statistical analysis.

Results

Groups of animals with induced non-infectious uveitis only, induced OHT only, and induced both non-infectious uveitis and OHT varied in the degree of increase in the levels of neopterin, an inflammation marker. Neopterin levels in uveal tract tissue, aqueous humor and tear fluid from rabbit's eyes with induced OHT only (group 1) were 29.4%, 23.8% and 18.7% higher, respectively, than in controls (Table 1).

The induction of anterior uveitis only resulted in a significant increase in neopterin levels in uveal tract tissue, aqueous humor and tear samples taken from rabbit's eyes of group 2, by 265.0%, 184.1% and 96.3%, respectively, compared to controls ($p < 0.001$).

Neopterin levels in uveal tract tissue, aqueous humor and tear fluid from rabbit's eyes with induced both anterior uveitis and OHT (group 3) were 5.2-, 3.7- and 2.4 times higher, respectively, than in controls, and 42.5% ($p < 0.05$), 28.5% ($p < 0.05$) and 23.6% ($p < 0.05$) higher, respectively, than in samples taken from rabbit's eyes of group 2.

The carnosine treatment of induced both anterior uveitis and OHT (group 4) contributed to reduced levels of neopterin is samples under study, with neopterin levels in uveal tract tissue, aqueous humor and tear fluid being 39.4%, 38.9% and 30.2% lower, respectively, than in samples taken from rabbit's eyes of group 3 (anterior uveitis plus OHT without treatment) ($p < 0.01$). In addition, although neopterin levels in uveal tract tissue, aqueous humor and tear fluid in eyes treated with carnosine for induced both anterior uveitis and OHT were significantly lower than in untreated eyes with induced both anterior uveitis and OHT, they were 3.2-, 2.2- and 1.7 times higher, respectively, than in controls ($p < 0.001$).

Discussion

We found increased neopterin levels in uveal tract tissue, aqueous humor and tear fluid of rabbit's eyes with induced non-infectious uveitis. In addition, raised IOP contributed to an increase in inflammation marker levels.

We have previously found an activating effect of OHT on oxidative stress [16] in the presence of an exhausted enzyme antioxidant system [30]. Oxidative stress activates an increased level of neopterin. A recent study [31] found that, compared with controls, neopterin concentration was increased in patients with pulmonary arterial hypertension, with an increase in the cytotoxic potential of activated macrophages and dendritic cells due to promotion of oxidative stress.

Another recent study [32] found that serum interferon gamma, protein carbonyl, malondialdehyde and Neopterin levels were increased in infectious uveitis, and inflammation severity correlated with these markers. The authors noted that biomarkers in the aqueous humor could be a potential alternative for diagnosing a condition that may otherwise be thought to be idiopathic in uveitis.

In the current study, we demonstrated increased neopterin levels in biological fluids of animal eyes with induced anterior uveitis. This may facilitate the development of potential diagnostic approaches and contribute to improved treatment efficacy. In addition, in the current study, neopterin levels were especially increased in animal's uveal tract tissue.

It has been demonstrated previously that periodontal diseases are characterized by enhanced macrophage infiltration to the periodontal lesion, so neopterin being a macrophage activation marker may be seen in higher levels [33]. A similar pattern could be observed in our data. Uveal tract tissues showed higher content of the inflammation marker than biological fluids, tear fluid and anterior chamber aqueous humor.

However, somewhat increased neopterin levels were also seen in the group with induced OHT only. We believe this fact can be explained by the following mechanisms. Raised IOP facilitates the activation of oxidative stress processes and thus can induce inflammation, with a marker of the latter, neopterin, being increased in OHT. We noted these mild changes in the inflammatory status of the anterior eye segment in the group with induced OHT only. However, inflammation is accompanied by the activation of free radical oxidation that plays a major role in the pathogenesis of inflammation [34,35]. We have demonstrated previously [15,16,30] that ocular hypertension exacerbated the course of uveal tissue inflammation and worsened oxidative stress characteristics in uveitis.

Our data on the use of dipeptide carnosine in rabbit's eyes with induced uveitis and OHT demonstrate a significant anti-inflammatory effect of this substance in the anterior eye under conditions of induced comorbidities. We have reported previously [15] that carnosine facilitated significantly reduced pathological changes in ocular

tissues in rabbit's eyes with induced both non-infectious uveitis and OHT. A study on the anti-inflammatory effect of carnosine concluded that it is an effective adjunct in the treatment of keratitis and facilitated prompt re-epithelization [38]. Carnosine has been reported [36] to positively affect some age- and diabetes-related ocular diseases due to its metal-ion chelation and antioxidant capacity as well as the capacity to protect against formation of advanced glycation and lipoxidation end-products.

Dipeptide carnosine, being an antioxidant, protects tissue cells from the pathogenic effect of oxidative stress and improves their resistance to increased functional loads caused by aging or pathological changes [37].

A positive effect of carnosine on healing of wounds of the cornea [39], lung tissue [40], and periodontium [41] has been demonstrated previously.

In our experimental study, there was evidence of increased neopterin levels in the anterior chamber aqueous fluid, tear fluid and uveal tract tissues of animals with induced non-infectious anterior uveitis. Raised IOP facilitated increased levels of this inflammation marker in studies samples. High neopterin levels in the uveal tract tissues and anterior chamber aqueous fluid indicated the presence of a substantial oxidative stress as well as its impact on the course of inflammation in animals with induced uveitis only and especially in those with induced both uveitis and OHT. A high neopterin level in the tear fluid in anterior uveitis can be considered an effective diagnostic marker of the severity of inflammation in the anterior segment of the eye.

Antioxidant carnosine treatment courses resulted in significant reductions in neopterin levels in the uveal tract tissues, anterior chamber aqueous fluid and tear fluid in rabbit's eyes with induced both uveitis and OHT. The changes in neopterin levels in our experimental studies were caused by a reduction in the severity of inflammation in the anterior segment of the eye.

We believe it reasonable to use the tear fluid neopterin level as a stable biomarker of the degree of inflammation in the anterior segment of the eye which permits for monitoring of the course of anterior uveitis and assessing the efficacy of therapy for the disease. The naturally occurring dipeptide carnosine, an anti-oxidant, can be recommended as an effective anti-inflammatory treatment option in anterior uveitis with OHT which reduces the level of neopterine, an inflammatory marker, in the uveal tract.

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Conflict of Interest:
Authors declare that there are no conflicts of interest that might influence their opinion on the subject matter or materials described or discussed in this manuscript.

Table 1. Impact of carnosine on neopterine levels in the uveal tract tissue, anterior chamber aqueous humor and tear samples taken from rabbit's eyes with both anterior uveitis and ocular hypertension (OHT)

Statistical characteristics	Controls n = 9	OHT n = 10	Uveitis only n = 10	Uveitis plus OHT n = 12	Carnosine plus uveitis plus OHT, n = 12
Uveal tract tissue, nmol/g					
M	226.72	293.48	827.46	1179.13	714.52
m	17.14	25.53	72.54	104.32	70.23
p	-	<0.05	<0.001	<0.001	<0.001
%	100.0	129.4	365.0	520.1	325.7
p_1	-	-	-	<0.05	>0.05
$\%_1$	-	-	100.0	142.5	86.4
p_2			-	-	<0.01
$\%_2$			-	100.0	60.6
Anterior chamber aqueous humor, nmol/L					
M	4.78	5.92	13.58	17.45	10.67
m	0.34	0.40	1.13	1.42	1.03
p	-	<0.05	<0.001	<0.001	<0.001
%	100.0	123.8	284.1	365.1	223.2
p_1	-	-	-	<0.05	>0.05
$\%_1$	-	-	100.0	128.5	78.6
p_2	-	-	-	-	<0.01
$\%_2$	-	-	-	100.0	61.1
Tear fluid, nmol/L					
M	1.34	1.59	2.63	3.25	2.27
m	0.10	0.14	0.23	0.29	0.18
p	-	<0.05	<0.001	<0.001	<0.001
%	100.0	118.7	196.3	242.5	169.4
p_1	-	-	-	<0.05	>0.05
$\%_1$	-	-	100.0	123.6	86.3
p_2	-	-	-	-	<0.01
$\%_2$	-	-	-	100.0	69.8

Note: n, number of animals; p, significance of difference compared to control; p1, significance of difference compared to uveitis only; p2, significance of difference compared to uveitis plus OHT