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RESEARCH ARTICLE

EFFECT OF ORAL ADMINISTRATION OF FORSKOLIN, HOMOTAURINE, RUTIN, L-CARNOSINE, MAGNESIUM, VITAMINS B1, B2, B6 AND FOLIC ACID ON PATTERN- ELECTRORETINOGRAM AND VISUAL FIELD PARAMETERS IN GLAUCOMATOUS PATIENTS

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ABSTRACT

This is a review article about the potential neuroprotective activity of forskolin, a receptor-independent activator of adenylate-cyclase, associated to homotaurine, rutin, L-carnosine, vitamins B1, B2, B6, magnesium and folic acid in a food supplementation to patients affected by open angle glaucoma. The combined action on IOP and neuron survival suggests a neuroprotective activity of this food supplement in glaucomatous neurodegenerative disease, in which elevated IOP is the main risk factor, but not the only determinant of the progressive death of retinal ganglion cells from campimetric and electrophysiological points of view.

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INTRODUCTION

Primary open angle glaucoma (POAG) is a progressive degenerative disease of the optic nerve (Kwon, 2009) and the second leading cause of blindness in the world, affecting roughly 67 million people globally (West, 2000). One of the main risk factors for glaucoma is high intraocular pressure (IOP), which may rise above statistically normal values. This increase can be ascribed, from a strictly physical point of view, to a defective efflux of the aqueous humor from the anterior chamber of the eye (Friedman, 2004). A common feature of POAG involves an excavation of the optic disk, which is extended to its margins, thus increasing the cup-to-disk ratio. Several studies indicate that early lesions occur in the optic nerve at the level of the lamina cribrosa (Morgan, 2000). Intraocular hypertension may cause significant over expression of caspase 3 in retinal ganglion cells (RGCs), which is a commonly accepted marker of programmed cell death (Ji, 2005; Calandrella, 2007), further supporting the neurodegenerative nature of POAG. In fact, decreasing IOP appears to be a necessary, although not sufficient, strategy to prevent glaucoma progression, which is due to the continuous deterioration of RGCs that evidently can occur and continue also in the presence of a normal or normalized IOP (Leskea, 2004; Miglior, 2005).

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Therefore, nowadays glaucoma is considered to be a neurological disease, an optic neuropathy for which ocular hypertension is the main risk factor, but not necessarily the primary causative agent (Coleman, 2009). This concept is further corroborated by the recent finding reported by Grieshaber and Flammer 2010. The Authors conclude against the dogma stating that "the greater the IOP reduction the better the visual field prognosis", suggesting that also the nature of the drug by which IOP reduction is achieved is important. In fact, betaxolol has also been shown to have neuroprotective activities, improving ocular blood flow (Turacli, 1998), and protecting RGCs from apoptosis (Cheon, 2002; Wood, 2001). Moreover, a very recent paper published by Krupin and colleagues, 2011 shows that in a group of patients with low tension POAG treated with either timolol or brimonidine, despite a similar response to the hypotensive activity of each drug, the patients treated with brimonidine (a supposed neuroprotective agent) progressed (by visual field analysis) at a much slower rate during 30 months of observation than those treated with timolol. These data confirm that IOP decrease and neuroprotection can be two different, albeit concurrent, events. Forskolin (7beta-acetoxy-8, 13-epoxy-1a, 6β, 9a-trihydroxy-labd-14-en-11- one) is a diterpenoid isolated from the plant *Coleus forskohlii* (Lamiaceae). In India, since ancient times, *Coleus forskohlii* has been used in traditional Hindu and Ayurvedic medicine (De Souza, 1983). *Coleus forskohlii* was used as a medicinal herb to treat hypertension, congestive heart

failure, eczema, colic, respiratory disorders, painful urination, insomnia, convulsions, asthma, angina, psoriasis and for prevention of cancer metastases (Valdez, 1987; Ammon 1982, 1985). Forskolin is a receptor-independent adenylate-cyclase activator, so that the concentration of the second-messenger cAMP rapidly increases in forskolin- stimulated cells (Seamon, 1981, Barber 1985). Of the 9 types of adenylate-cyclase in humans, forskolin can activate all but type IX, which is found in spermatozoa (Rojas, 1992). Human non pigmented ciliary epithelial cells have been shown to contain adenylate-cyclase (subtypes II, IV), and bovine trabecular meshwork cells contain subtype VII, the activity of which contributes to the regulation of aqueous humour dynamics (Zhang, 2000, Busch, 1993). Elevation of cAMP after forskolin treatment apparently activates a reverse flow of secretion in the ciliary body, from the posterior chamber into the stroma, which counteracts the normal flow of secretion, proceeding from the stroma into the posterior chamber. This results in a decreased net inflow of aqueous humour into the eye chambers (Caprioli, 1983, 1984). Moreover, it has been described that elevation of cAMP inhibits the activation of the Rho protein, thus causing a disorganization of the actin cytoskeleton, which in the trabecular meshwork has been shown to result in tissue relaxation, and an increase of AH outflow (Shen, 2008; Ramachandran, 2008). The combination of these two events may explain the hypotensive effect of topical administration of forskolin, as shown in experimental animals and humans (Hu, 2008, Honjo, 2001). Moreover, forskolin-mediated activation of cAMP contributes to neuronal cell survival and growth (Kilmer, 1984).Forskolin (a natural compound present in the extract of the plant Coleus Forskohlii), magnesium, homotaurine, L-carnosine, vitamins B1, B2, B6 and folic acid are ingredients of a food supplement commercially available. They can act in synergy with topical pharmacological treatment, and contribute to the control of intraocular pressure (IOP) (Pescosolido, 2010). It was also designed and evaluated as a thermoreversible in situ gelling system for ophthalmic drug delivery (Gupta, 2010).

Table1. Pattern-electroretinogram parameters as long as one year of therapy.

not treated PERG amplitude	100%+/-7,2	100,14+/-2,3	94,90+/-1,8	88,11+/-1,8	79,20+/-1,8
p value		NS	NS	<0,05	<0,05
treated PERG amplitude	100%+/-3,2	100,8%+/-3,1	114,51%+/-3,2	116,12%+/-2,6	103,22%+/-2,8
p value		NS	NS	<0,01	<0,05
not treated/ treated p	NS	NS	NS	<0,05	<0,05
T	T0	T1(3months)	T2(6months)	T3(9months)	T4(12months)
not treated foveal sensitivity	100%+/-7,9	106,82%+/-7,9	97,92%+/-9,9	101,04%+/-9,6	94,24%+/-10,5
p value		NS	NS	NS	NS
treated foveal sensitivity	100%+/-9,4	107,37+/-9,1	116,57+/-3,2	109,44+/-7,3	107,7+/-4,7
p value		<0,05	<0,05	<0,05	<0,01
T	T0	T1(3months)	T2(6months)	T3(9months)	T4(12months)
not treated/ treated p	NS	NS	NS	<0,05	<0,05

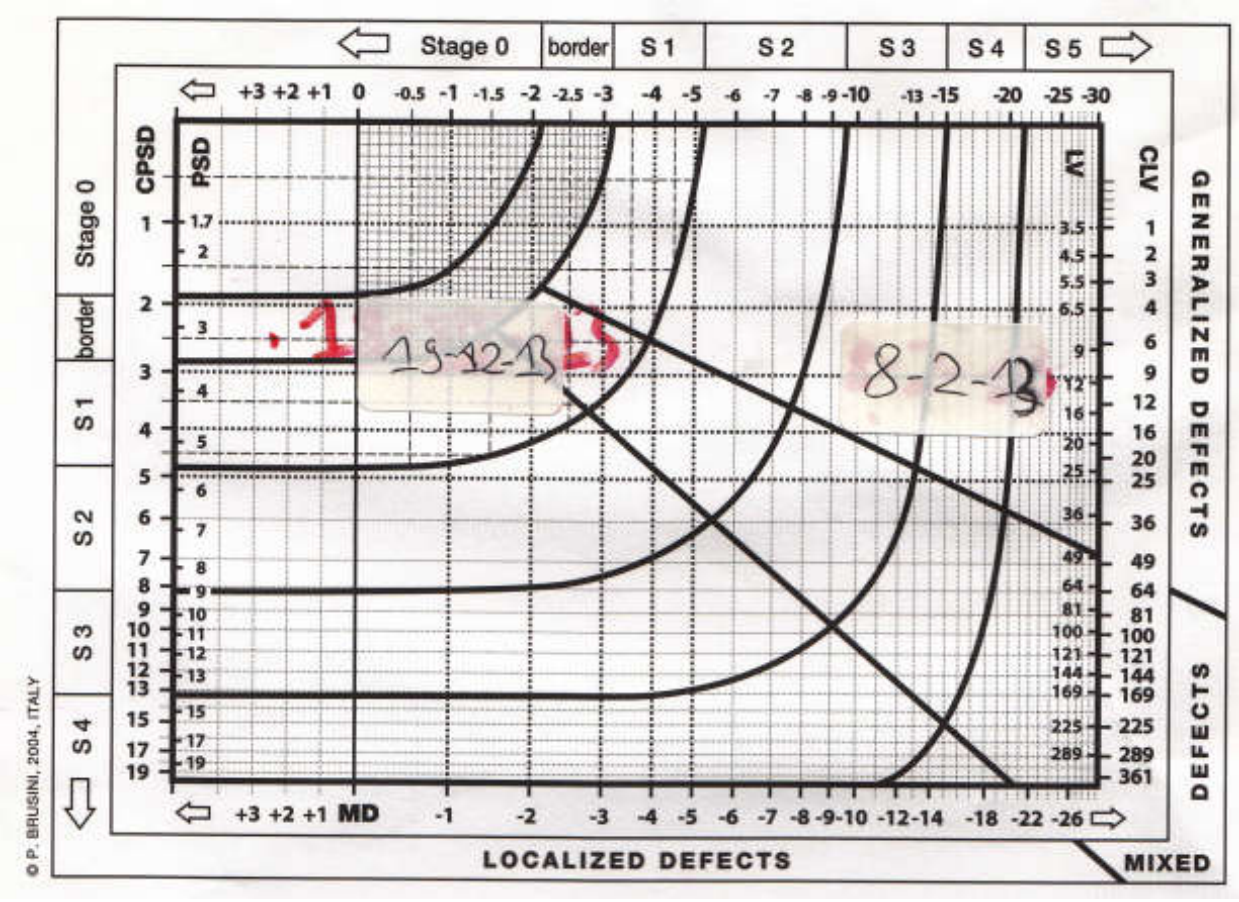

Fig. 1 Improvement of FDT parameters in RE of patient # 1

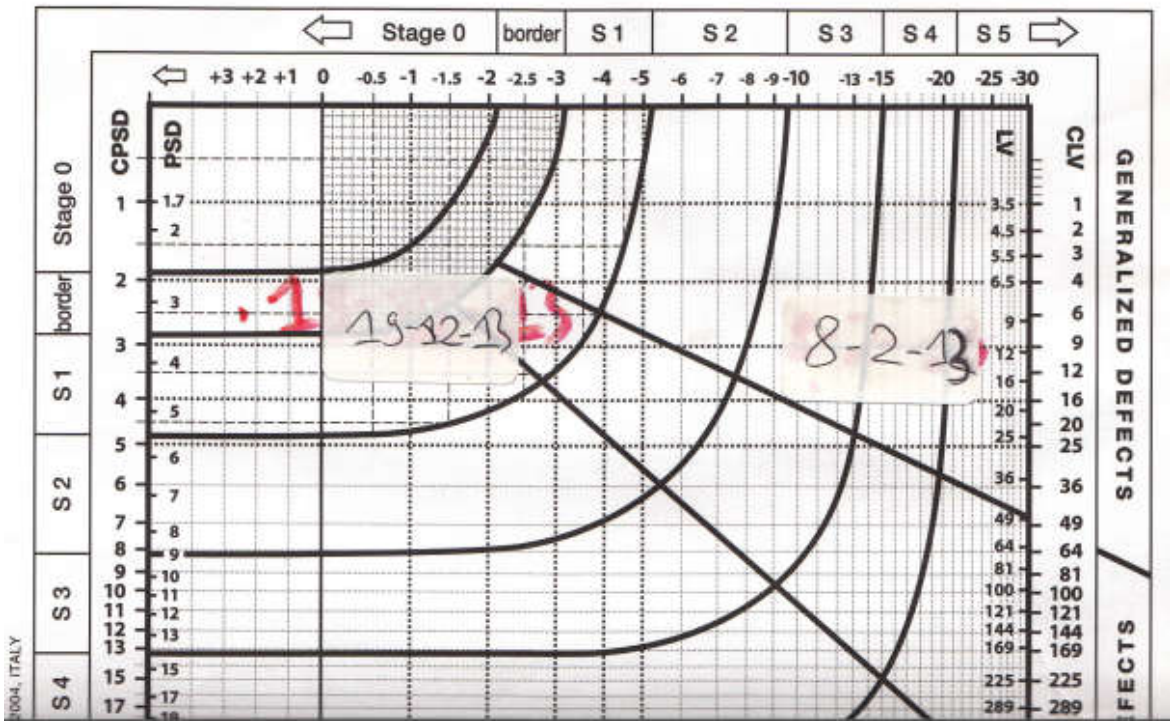

Fig. 2. Improvement of FDT parameters in LE of patient #1

They can contribute to a better control and a further small reduction of IOP in patients who are poorly responsive to multitherapy treatment (Vetrugno, 2012). Increased intracellular cAMP mediated by forskolin led to a significant increase in extracellular adenosine production. This pathway might play an important role in the homeostatic regulation of outflow resistance in the porcine trabecular meshwork (PTM) and in human non pigmented ciliary epithelial cells. These experimental data suggest a novel mechanism by which pathologic alteration of TM, such as tissue rigidity, could lead to abnormal elevation of IOP in glaucoma (Wu, 2012). Forskolin is a receptor-independent adenylate-cyclase activator. It has been described that elevation of cAMP inhibits the activation of the Rho protein. Forskolin-mediated activation of cAMP contributes to neuronal cell survival and growth (Nebbioso, 2013). Forskolin is actually commercialized alone or in association with homotaurine, L-carnosine, rutin, magnesium, vitamins B1, B2 and B6 and folic acid. Homotaurine is a derivative of taurine. It acts as GABA-A neurotransmitter. It inhibits NMDA receptor up regulation and it counteracts MAPK activation and it inhibits Aβ-amyloid deposits in Alzheimer disease. Carnosine is an antioxidant able to scaveng free radicals and binds heavy metal, such as iron, zinc and copper. Indeed, it protects from glutammate excitotoxicity. It binds soluble Aβ-amyloid in Alzheimer disease as homotaurine. At last but not least, this association appears to be protective for the ocular surface, contributing to restore a normal equilibrium of the tear film in glaucomatous patients in which toxic agents such as BAK had determined alterations of its homeostasis (Nebbioso, 2013; Mutolo 2016). In 2015 Russo and Co-Authors stressed that the intravitreal injection of this drug may be promising to achieve glaucoma neuroprotection. Instead, in mild to moderate Alzheimer disease tramiprosate showed only a trend towards slowing the decline of this neurodegenerative disease (Aisen, 2011). In Neurology and in Ophthalmology also nicergoline and citicoline can be used as neuroprotective drugs (Cheung, 2008; Chang, 2012).

In my experience (Giuffre', 2016) a pilot study clearly indicated that this oral supplement may have a neuroprotective effect on the main parameters of the visual field in patients affected by early-stage glaucoma after 12 months of therapy (Fig. 1-2). The PERG amplitude increased by the month 9 and the fovea sensitivity by month 6 from baseline in a statistically significant way ($p<0.05$) (Table I). From the psychological point of view, there is a small increase of points in the memory questionnaire as for the control group. Apart from the improvement of the iatrogenic ocular surface disease, this association may also contribute to increase patients compliance during their pharmacologic treatment. The strength of this study is that it is the first in the international Literature to prove a neuroprotective effect of this pharmacological association from a campimetric and PERG points of view. Its limitations are: the small number of patients enrolled and only one year follow-up. This is the reason why the Author considers it as a preliminary report.

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