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The Impact of Acute Dynamic Exercise on Intraocular Pressure: Role of the β_2-adrenergic Receptor Polymorphism

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Effects of mutations in the β_2-adrenergic receptor (β_2AR) gene on intraocular pressure (IOP), in response to acute dynamic exercise, were investigated in 19 healthy males (age 22.6 ± 2.8 years). Intraocular pressures were measured pre- and post-exercise. Weight, height, body mass index, and maximal oxygen (VO_{2max}) uptake were recorded and subjects were genotyped for Arg16Gly, Gln27Glu and Thr164Ile mutations of the β_2AR gene. Post-exercise, reductions in mean IOP values were found in 16 subjects with the Gly16Gly and Arg16Gly genotypes, but these values remained low in the eight patients with the Gly16Gly genotype 3 h post-exercise, whereas they returned to baseline within 1 h in the eight subjects with the Arg16Gly genotype. β_2AR stimulation during exercise could be an important regulator of IOP response and determining β_2AR polymorphisms may improve understanding of pathogenesis and treatment selection in ophthalmic diseases, e.g. glaucoma.

KEY WORDS: Glaucoma; Intraocular pressure; β_2-adrenergic receptor; Polymorphism; Exercise

Introduction

The impact of dynamic exercise conditioning on intraocular pressure (IOP) is not fully understood, although transient reductions in IOP produced by acute dynamic exercise are well documented.[1,2] Some experimental and clinical studies imply that combining exercise conditioning with medical therapy may decrease IOP in glaucoma patients.[1 – 5] Numerous mechanisms of action have been postulated to explain the IOP-drop associated with acute, dynamic exercise, including changes in episcleral venous pressure, plasma lactate levels, blood pH, plasma osmolarity and hormone levels.[5 – 11] Activation of the sympathetic nervous system during exercise has already been shown to cause a seven-fold increase in circulating catecholamines in plasma.[12,13] β_2-adrenergic receptor (β_2AR) sites have been demonstrated in non-pigmented ciliary epithelial cells, human trabecular meshwork cells, and retinal vessels, and most of these

receptor sites are of the β_2AR type.[14 – 16]

The β_2ARs belong to the superfamily of G-protein-coupled receptors, with amino terminus localized extracellularly, seven transmembrane-spanning domains, and an intracellular carboxyl-terminus.[17] The coding region of the β_2AR was first investigated by Kobilka *et al.*[18] and is located on chromosome 5q31. Three polymorphic β_2ARs have been studied in some detail and display altered receptor function *in vitro*.[19] Wild-type β_2ARs contain Arg16, Gln27, and Thr164. Compared to their wild types, mutant β_2ARs display different receptor–effector interactions, namely Gly versus Arg at codon 16, Glu versus Gln at codon 27, and Ile versus Thr at codon 164.[20,21] All three polymorphisms appear to alter receptor function, and the airways of individuals with these receptors are likely to behave differently when exposed to circulating catecholamines or exogenous drugs.[19] The Gly16 form of the receptor down-regulates following exposure to an agonist, to a much greater extent than the Arg16 form, in both transfected cell systems and in primary cultured human airway smooth-muscle cells.[22] The Glu27 form exhibits a protective effect against down-regulation, in both transfected and non-transfected cell systems.[22,23]

No previous study has investigated the impact of dynamic exercise on IOP regarding the β_2AR gene polymorphism. As a result, we explored whether a relationship exists between these gene mutations and the IOP response to acute dynamic exercise.

Materials and methods

PARTICIPANTS

Nineteen healthy male adult students (mean age, 22.6 ± 2.8 years) volunteered to participate in this study. Before enrolment, each underwent a preliminary examination, including slit-lamp, gonioscopic, ophthalmoscopic and refractive error evaluation. No ocular pathology was seen. The subjects also had no history of systemic or ocular diseases and were not using topical or systemic medications.

PROCEDURE

Volunteers performed exercise testing in the form of a 20 m Shuttle Run Test (Endurance Shuttle Run Test). They ate ≥ 2 h before the test, ambient temperature was 21°C, no warm-up exercises were allowed and each participant had a 10-min rest in the supine position before testing started at 09.00. Testing began at walking pace, with subjects moving between lines 20 m apart. A sound signal dictated changes of direction and pace, which gradually got faster: each subject scored a successful lap when they crossed the end line with at least one foot when, or shortly before, the signal sounded. Failure to reach the end line more than once in succession before the sound indicated that the subject could not maintain the required pace. The individual score was then taken as the lap number at which the second successive failure occurred, or as the number of the last completed lap if a subject stopped. The maximal oxygen uptake (VO_{2max}) value of each subject was estimated as an indicator of individual cardio-respiratory endurance, using a table prepared for this test.

For each subject, IOPs were measured with a Perkins hand applanation tonometer (Clement Clarke International Ltd, Harlow, UK) pre- and immediately post-exercise, at 10.00, 12.00 and 16.00, after instilling one drop of benoxinate hydrochloride 0.2%, and fluorescein sodium 0.25% in each eye. All IOP measurements were performed by the same person, beginning with the right eye. Body weight (kg), height (cm), body mass index (kg/m^2), and VO_{2max} were recorded for each subject.

GENOTYPING

The mutation sites of the β_2AR gene were identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis.[24] The PCR reactions were undertaken in a total volume of 25 µl, containing specified amounts of DNA as template, 0.2 µmol/l of each primer (all primers were synthesized by TIB Molbiol, Berlin, Germany), 0.5 U Taq-DNA polymerase (Gibco, New Zealand), 0.2 mmol/L of each dNTP (Boehringer-Mannheim, Germany), 10 mmol/l Tris–HCl (pH 8.8), 50 mmol/l KCl, and 1.5 mmol/l $MgCl_2$. A 242 base pair (bp) fragment, including both the polymorphic sites at codon 16 and 27, was amplified using primers 5′-GAACGGCAGCGCCTTCTTGCTGGCACC-C<u>C</u>AT (sense, AB3) and 5′-CTGCCAGG CCCATGACCAGATCAG (anti-sense, AB2). Compared with the natural sequence of the β_2AR, the underlined C was changed from A to C, to generate a polymorphism-specific restriction site. Conditions for PCR were as follows: 2 min initial denaturation at 94 °C, 35 cycles of amplification (denaturation 94 °C, 30 s; primer annealing 64 °C, 45 s; polymerization 72 °C, 1 min) followed by final elongation (7 min, 72 °C), undertaken using a thermal cycler (9700 PCR-thermocycler, Perkin Elmer, USA). The PCR products were separated into two tubes, each containing 10 µl aliquots. To detect the Arg16Gly polymorphism, overnight digestion at 37 °C with 10 U *Eco130*I (Fermentas, St Leon-Rot, Germany) was performed in one tube of the PCR product, whereas presence of the Gln27Glu polymorphism was identified in the second tube using 10 U *Fnu4HI* (New England BioLabs, Frankfurt, Germany). To evaluate the mutation at codon 164, a second PCR procedure was performed, generating a 280 bp fragment with primers 5′-GTGATCGCAGTGGA-TCGCTACT (sense, AB4) and 5′-AGACGAAGACCATGATCACCAG (anti-sense, AB5) under the conditions described above, except primer annealing was at 58 °C. Again, 10 µl of the PCR product was digested by 10 U *Mn1*I (New England BioLabs). All RFLP fragments were separated on a 3% 3:1 NuSieve-agarose gel and documented with a still video system (Vilber Lourmat, Torcy, France).

STATISTICAL ANALYSIS

Statistical analyses were undertaken using Wilcoxon matched-pair signed-rank test for dependent groups and one-way ANOVA test for independent groups, with $P < 0.05$ regarded as statistically significant. All computations were made using SPSS software (SPSS Inc., Illinois, USA).

Results

Results of the 20 m Shuttle Run Test showed that all participants had good VO_{2max} values and were designated physically fit subjects.

Table 1 shows the β_2AR genotype distribution among subjects according to results of the PCR-RFLP. Polymorphisms of

TABLE 1:
β_2-adrenergic receptor genotype distribution of subjects (n = 19)

	Arg16Gly	Gln27Glu	Thr164Ile
0 (wild type)	3	11	19
1 (heterozygote mutant)	8	5	–
2 (homozygote mutant)	8	3	–

Gln27Glu and Thr164Ile were studied, but appropriate genotype distribution could not be provided, therefore statistical analyses of these polymorphisms were not performed.

Results of the PCR-RFLP identified three subjects with Arg16Arg, eight with Arg16Gly, and eight with Gly16Gly genotypes. Tables 2 and 3 show physical features and IOP pressures among subjects according to Arg16Gly mutations. The limited number of subjects with Arg16Arg genotype (n = 3) meant that statistical analyses could not be applied to this group.

No statistical difference was found for weight, height, body mass index or VO_{2max} between subjects with the Arg16Gly and Gly16Gly (Table 2) genotypes. Subjects with the Arg16Gly genotype demonstrated a statistically significant reduction in IOP in both eyes immediately post-exercise ($P < 0.02$), although by 10.00, mean IOP values were returning to pre-exercise levels. Subjects with Gly16Gly also demonstrated a statistically significant reduction ($P < 0.02$) in mean IOP in both eyes after exercise, but recovery of IOP to pre-exercise levels took

TABLE 2:
Distribution of the Arg16Gly polymorphism and physical and metabolic characteristics of subjects

Physical and metabolic characteristics	Arg16Arg n = 3	Arg16Gly n = 8	Gly16Gly n = 8	P-value
Height (cm)	175.33 ± 7.51	181.13 ± 4.22	180.25 ± 8.03	NS
Body weight (kg)	71.00 ± 14.73	73.00 ± 5.71	74.88 ± 8.98	NS
Mean age (years)	24.00 ± 3.61	21.88 ± 2.47	22.75 ± 3.01	NS
BMI (kg/m^2)	22.91 ± 2.78	22.23 ± 1.25	22.99 ± 1.71	NS
VO_{2max} (ml/kg per min)	50.67 ± 4.80	49.89 ± 3.41	47.68 ± 2.48	NS

All data are mean ± SD.
NS, not significant.
$P > 0.05$; one-way ANOVA test.

TABLE 3:
Intraocular pressures recorded in subjects pre- and post-exercise, according to genotype

		Intraocular pressure (mmHg)				
Genotype	Eyes	Before exercise (09.00)	Immediately post-exercise	10.00	12.00	16.00
Arg16Arg (n = 3)	Right	12.33 ± 1.53	6.00 ± 1.00	9.67 ± 0.58	10.67 ± 2.08	11.67 ± 0.58
	Left	11.67 ± 2.08	8.67 ± 3.06	9.00 ± 1.00	10.33 ± 2.08	11.67 ± 0.58
Arg16Gly (n = 8)	Right	11.75 ± 2.71	8.38 ± 1.69**	11.13 ± 2.47	12.13 ± 1.73	12.50 ± 0.76
	Left	11.75 ± 2.43	9.13 ± 3.04**	11.13 ± 2.10	12.63 ± 1.60	13.13 ± 0.83
Gly16Gly (n = 8)	Right	13.13 ± 2.03	7.63 ± 2.33**	11.25 ± 2.12**	10.38 ± 2.13*	12.88 ± 1.81
	Left	13.63 ± 1.30	7.50 ± 2.39**	11.00 ± 1.77**	11.25 ± 2.05*	12.38 ± 2.13

All data are mean ± SD.
*$P < 0.05$; **$P < 0.02$ (Wilcoxon matched-pair signed-rank test).

> 2.5 h ($P < 0.05$, Table 3) and there was a greater decrease in IOP immediately post-exercise (Table 3).

Discussion

Compared to individuals with the Arg16Gly genotype, our study showed that it took at least 2.5 h for IOP to return to baseline values in subjects with the Gly16Gly genotype after acute dynamic exercise, therefore an association between post-exercise IOP levels and Gly16Gly β_2AR gene polymorphism is postulated. The β_2ARs are membrane-bound G protein-coupled receptors, which transmit signals after binding of their ligands, epinephrine or norepinephrine.

Green *et al.*[23] found that the polymorphism of the human β_2AR gene alters agonist-promoted down-regulation: polymorphisms created by site-directed mutagenesis of cloned human β_2AR cDNA were expressed in Chinese hamster fibroblasts. They also proposed that these polymorphisms may be responsible for inter-individual variations in expression, regulation, and functional properties of β_2ARs.

The present study is the first to evaluate the mechanism of post-exercise decreases in IOP in terms of β_2AR gene polymorphism expression, which also implies that variations exist in response to circulating catecholamines. Endogenous catecholamines may induce down-regulation phenotypes,[22] therefore receptor function could be altered by amino-terminal receptor polymorphism.[22,25] The β_2-AR gene polymorphism influences physical activity and antropometric variables,[26] and studies that demonstrate how gene–exercise relations regulate the treatment of chronic ophthalmic disease are warranted: β_2AR polymorphism may be disease-modifying (treatment for conditions such as asthma,[17,20,27,28] diabetes mellitus,[29,30] hypertension,[31] myasthenia gravis,[32] congestive heart disease,[33] and obesity[30] can be affected).

Many reports demonstrate that exercise lowers IOP in healthy subjects and people with glaucoma,[4,23,34–39] although the exact mechanism of exercise-induced ocular hypotension remains unclear. Several concepts have been proposed: increases in blood lactate levels, plasma osmolarity and reductions in blood pH are associated with decreasing IOP after short-term exercise in humans and rabbits,[6,8,11] although a study comparing aerobic and anaerobic exercise found no statistically significant IOP decrease, despite significant differences in blood pH and lactate levels between the study groups.[8] This paper concluded that parameters other than decreasing blood pH and increasing blood lactate levels are responsible for much of the decrease in IOP that is associated with dynamic exercise.[8] The effect of continuous and increasingly difficult periods of standardized, sub-maximal workload on IOP were evaluated in another paper, reporting that two opposing mechanisms affect IOP changes during exertion: a fall in IOP secondary to physiological changes produced during exercise, and a negative feedback response causing a compensatory rise in decreased IOP.[2]

Acute, dynamic exercise may reduce IOP by three possible mechanisms:[11] first, increased blood colloid osmotic pressure may dehydrate the eye through the retinal and uveal vascular structure; secondly, an increase in colloid osmotic pressure may decrease aqueous formation through reduced ultrafiltration; thirdly, colloid osmotic pressure may affect the hypothalamus, with IOP changes caused by reflex responses.[11] One could hypothesize that acute exercise may decrease IOP by

increasing the plasma colloid osmotic pressure, which is associated with changes in iso-osmotic extracellular volume.

Another study focused on the outflow facility of aqueous humour or episcleral venous pressure to explain decreases in IOP after acute, dynamic exercise.[40] An association between IOP and episcleral venous pressure has also been reported,[41] although another study found no significant association between IOP and episcleral venous pressure or outflow facility.[40]

Exercise conditioning, together with glaucoma medication, has also been shown to decrease IOP: Era *et al.*[4] concluded that physical activity may lower IOP, particularly in subjects with high pre-exercise values, although no association between changes in IOP and blood lactate levels was identified in this study. The authors demonstrated this effect among subjects in whom glaucoma had not been diagnosed, as well as patients receiving hypotensive glaucoma medication.[4]

Many clinical and experimental studies have tried to explain the mechanism of IOP decrease during and after exercise, but no single mechanism has been proposed as the primary cause. Our finding suggests that subjects with Gly16Gly genotype show significantly longer periods of decreased IOP than subjects with the Arg16Gly variant, which supports the receptor down-regulation properties of Gly16Gly. This finding may provide additional support in investigations implying a role of circulating catecholamines on IOP drop after dynamic exercise, in addition to other parameters studied.

Gene expression may also be influenced by changes caused by exercise that moderate nuclear-protein binding or relocation of transcription factors to the nucleus.[42] Investigations on the cellular and molecular basis of gene–exercise interactions will explore the mechanism and treatment of glaucoma coupled with exercise conditioning. β_2AR is acknowledged as an important target of drugs and endogenous substances, therefore polymorphisms in this receptor may explain differences in treatment response and disease-modifying conditions.[24,43]

In conclusion, we believe that investigations on the cellular and molecular basis of gene–exercise interactions will help to explore the mechanism and treatment of glaucoma in the light of exercise conditioning. These observations reinforce the concept that β_2AR stimulation during exercise may be an important regulatory factor in daily IOP variations. As a result, β_2AR polymorphism may provide a useful contribution to understanding the treatment of certain ophthalmic diseases, such as glaucoma.

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