Is the central sympathetic inhibition impaired

in primary open angle glaucoma?

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Objective: Primary open angle glaucoma (POAG) is an ophthalmologic disease of still unknown origin. Irene Loewenfeld hypothesized from observations in single cases that the central sympathetic inhibition was reduced in POAG. Such hypothesis was based on the shape or in other words the dynamics of the pupillary light reflex (PLR). Our aim was to investigate this hypothesis in a clinical trial in normals and POAG patients with standard pupillographic procedures regarding the PLR and spontaneous pupillary oscillations in darkness.

Methods:

Patients with POAG were recruited from the glaucoma clinic in Tübingen. The diagnosis of POAG was based on an intraocular pressure above 26 mmHg (measured twice) and typically excavated papilla. Main exclusion criteria for normal subjects were: any ocular pathology except refractive errors, no history of ocular disease and no family history of glaucoma. Pupil examinations took place in a dark room in the pupil lab of the eye hospital Tübingen.

CIP (AMTech, Germany) is an automated infrared video pupillograph with a CCD array, which enables a high temporal resolution of 0,004 seconds. We tested the PLR at four different stimulus intensities: 0.43, 1.36, 7.84 and 30.20 lux. Each condition was repeated four times and averaged. Parameters of evaluation for the PLR were: baseline pupil diameter, latency, amplitude (mm), constriction velocity, velocity of the early and late phase of redilation.

PST (AMTech, Germany) records spontaneous pupillary oscillations in darkness (duration 11 minutes) as an indirect measure of central inhibition. Primary parameter of analysis was the Pupillary Unrest Index (mm/min).

Results: 30 patients (16 m, 15 f; aged 37 to 76 y; median 64y) were compared to 31 normals (12m, 19 f; aged 38 to 76; median 63y). In the parameters of the PLR we found a number of trends in the expected direction of differences between both groups, the vast majority scarcely missing the mark of significance. The velocity (mm/sec) of the early redilation phase, which is regarded to represent the action of central inhibition, was significantly slower in POAG patients than in normals for the 1.36 (POAG 0.90+/-0.33; normals 1.02 +/- 0.27) and 7.84 (POAG 1.07+/-0.32; normals 1.21 +/- 0.31) lux condition. The PUI showed a tendency to be higher in patients than in normals; this difference was not significant (POAG mean 1.77 +/-0.467, median 1.75; normals mean 1.69 +/- 0.54, median 1.85). In comparison to a larger sample of normal subjects of the same age group from a former PST study (normative study, n=349, mean 1.50 +/- 0.389, median 1.49), the PUI of the POAG group was higher than in normal subjects (Wilcoxon Test p=0.003).

Conclusions:

In the majority of parameters – though not in all of them - our findings from this clinical trial gave hints at a confirmation of the hypothesis of Irene Loewenfeld: there are indeed signs of decreased central inhibition in patients with primary open angle glaucoma.

<u>Relative afferent pupillary defect with normal vision:</u> <u>Results of hemifield stimulation</u>

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Objectives: To demonstrate pupillographic results of a patient with a presumed lesion of the interconnection between the optic tract and the midbrain.

Methods: Clinical examination, CT-scan, pupillographic measurement of the relative afferent pupillary defect by a binocular pupillographic system (SWIFT), pupillary hemifield stimulation using a custom built pupil campimetry system covering 36x27 deg of the visual field on a CRT monitor.

Results: A 65 year old woman suffered from a basal ganglia bleeding which extended to the right posterior thalamus and the right posterior midbrain. On examination, a relative afferent pupillary defect (RAPD) was seen on the left side. Visual acuity was normal, visual field did not reveal any hemianopia or other defect explaining an RAPD, and optic discs were not atrophic one year after the haemorrhage.

The RAPD was quantified with 0.9 log units by neutral density filters and 1.33 by pupillography. In this patient we had the opportunity to do hemifield stimulation using one stimulus in each quadrant of varying size (3, 6, 12 deg) and luminance (8 and 16 cd/m² on a 1 cd/m² background). A typical left hemiakinesia resulted, i.e. the responses in the left hemifield were markedly reduced as compared to the right. However, there was also a reduction of both hemifields of the left eye as compared to the right.

Conclusions: Several similar cases have been published but no pupil perimetry has been demonstrated yet. Our finding of pupillary hemiakinesia indicates that this RAPD with normal visual function is a variant of the RAPD found in optic tract lesions. It is not yet sufficiently explained by present concepts of the pupillary pathways and of the differences in pupillomotor sensitivity between the temporal and nasal hemifield. In this case it could be demonstrated that the pupillary pathway connecting the optic tract and the dorsal midbrain is organized in a similar way as the optic tract.

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<u>Recovery of visual and pupil response deficits in</u> multiple sclerosis and optic neuritis

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Objectives: To examine whether achromatic and chromatic signals can yield useful and independent information about relapsing and remitting phases in demyelinating diseases using both visual psychophysics and pupillometric techniques

Methods: The recovery of visual performance and pupil responses were investigated in patients with demyelinating optic neuritis and multiple sclerosis. The response amplitude and time delay (latency) of the pupil response were measured in 14 patients with a previous history of unilateral optic neuritis (five of them were also diagnosed later with MS) in response to either achromatic (luminance) or chromatic (isoluminant) stimulus modulation. In addition, we measured detection thresholds for achromatic stimuli using standard visual field perimetry and chromatic thresholds using a new Colour Assessment and Diagnosis (CAD) test, which isolates the use of colour signals.

Results: Pupil light reflex and pupil colour responses were measured binocularly in repose to monocular stimulation of each eye. The use of sinusoidal modulation techniques made it possible to extract automatically the pupil response amplitude and latency (Barbur et al, 2004). Colour thresholds (red-green and yellow-blue) were measured in each eye using methods that isolate the use of colour signals <u>www.city.ac.uk/avrc/colourtest.html</u>

Conclusions: The results show that, despite significant improvements in visual function (visual acuity and fields) observed after the acute phase, important pupil response deficits can persist. The data also show that precise measurements of pupil responses and chromatic thresholds can reveal deficits that may remain undetected with more conventional techniques. We believe that these new techniques can provide useful information about remitting and relapsing demyelinating phases that are often observed during MS and ON.

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Absence of pupil response components in small scotomas caused by cortical lesions

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Objectives: To investigate the integrity of pupil response components within a small, bilateral scotoma (~ 3°H by 5°V), straddling the vertical meridian and just below the horizontal meridian, caused by occipital head injury. To assess and compare the effectiveness of visual psychophysics and pupil-based perimetric techniques in patients with small scotomas.

Methods: The patient investigated had an unusual visual field defect caused by damage to the occipital lobes, both sides of the calcarine fissure, slightly more extensive above. The lesion is small and passed unnoticed in the first MRI scan. Perimetry testing was carried out using a customised Advanced Perimetry Program (APP), pupil perimetry and Humphrey VFA. The dynamic component of the Pupil Light Reflex (PLR) and Pupil Colour Responses (Barbur, 2004) were also measured with small stimuli located within the centre of the scotoma.

Results: The perimetry maps show very localised loss of visual sensitivity that affects all stimulus attributes. The increased resolution of the APP reveals fine detail within the scotoma that remains undetected in VFA. Pupil measurements show complete absence of both PLR and PCR components.

Conclusions: Advanced perimetry techniques can be used to reveal islands of visual field loss that remains undetected using clinical perimetric methods. Damage to the occipital pole causing very localised loss of visual field sensitivity also eliminates the dynamic pupil light reflex and the colour response components.

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<u>Pupillometry detects different degrees of involvement of</u> the autonomic neuromuscular junction in myasthenia gravis

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Objective: We had previously reported that myasthenia gravis (MG) affects the pupil. Parasympathetic pupillometric parameters are mostly affected, pointing to a defect of the iris autonomic neuromuscular junction. In this study, we analyzed the degree of pupillometric changes in MG in relationship to the severity of the disease.

Methods: We performed infrared dynamic pupillometry (IDP) on 42 patients diagnosed with MG and on 93 healthy controls. We subdivided the patients into subgroups of 2 categories each: generalized versus ocular MG, no thymectomy versus status-post thymectomy, symptoms present versus absent at the time of testing. We compared pupillometric parameters between patients and controls, between the categories within each subgroup and between each subgroup category and controls.

Results:

- 1) **Patients versus Controls;** Reflex Amplitude (RA) was lower, Constriction Velocity (CV) slower and Latency longer in patients (p<0.001) than in controls. Maximal Redilation Velocity (MRV) was also slower in patients (p=0.029).
- 2) **Generalized versus ocular MG;** Latency was longer in generalized than in ocular MG (p=0.013)
- 3) **No thymectomy versus thymectomy;** CV was slower (p=0.047) and RA lower (p=0.024) in non-thymectomized than in thymectomized patients.
- 4) Symptomatic versus asymptomatic; Mean CV was slower and mean RA lower in symptomatic patients than in asymptomatic patients, but this difference was not statistically significant.
- 5) Generalized MG, non-thymectomized and symptomatic patients showed more significant differences with controls in RA, CV and Latency (p<0.001) than did ocular MG, thymectomized and asymptomatic patients (p varied from 0.005 to 0.88 for the above parameters).

Conclusions:

1. The autonomic neuromuscular junction is affected in MG at the iris sphincter and dilator, more severely at the sphincter.

2. IDP detected different degrees of pupillary abnormalities in MG, corresponding to different degrees of disease severity. It is a precise test of pupillary autonomic function that deserves further exploration.

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Photophobia in myasthenia gravis patients; questionnaire and intraocular muscle assessment with Iriscorder

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Objective: To make it clear that photophobia is one symptom of myasthenia gravis (MG).

Methods: We studied clinical frequency of photophobia complaints in 19MG patients and 18 healthy volunteers with questionnaires, and evaluated their pupillary light response with Iriscorder (Hamamatsu Photonics, Japan).

Results: Over 40 percent of MG patients experienced photophobia. Group of MG patients with photophobia showed changes of pupillary light response.

Conclusions: Photophobia is one symptom to discuss in MG patients, and intraocular muscles might be involved in MG.

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<u>Combined sympathetic and parasympathetic denervation of the pupil:</u> <u>a retrospective case series</u>

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Objective: To describe the pupil and clinical findings in patients who have both Horner's syndrome (H) and a tonic pupil (T)

Methods: A retrospective case-note review of all patients on our database with both pupil abnormalities (H+T)

Results: Of 688 patients on our database listed as having Horner's syndrome and/or a tonic pupil, only 20 (3%) had both (H+T). The records were available in 18 of these cases. The majority of these patients (12/18) had generalised autonomic failure throughout the body caused by diabetes (3), pure autonomic failure (PAF, 2), autoimmune/paraneoplastic processes (2) or unknown aetiology (5), and as expected in these patients both pupils usually showed signs of both sympathetic and parasympathetic denervation (9/12). Of the remaining cases, one patient with longstanding Holmes-Adie syndrome (HAS) later developed a coincidental Horner's syndrome caused by a Pancoast tumour. However there were 5 other patients who seemed to have tonic pupils and tendon areflexia typical of HAS but who were also found to have an idiopathic Horner's syndrome. 4/5 of these cases were female (median age 50) and all were in excellent general health. In all cases the Horner's syndrome was unilateral and in 4/5 cases associated with ipsilateral harlequin syndrome (which was not found in any of the other patients). Autonomic function tests showed mild disturbances in sweating and in cardiovascular control in some of these patients but none seemed to have a generalised dysautonomia or peripheral neuropathy and no cause could be found for the Horner's syndrome.

Conclusions: Combined sympathetic and parasympathetic lesions are rarely found in the same patient, and usually occur in the context of widespread dysautonomia. Occasionally both lesions may arise by coincidence as a result of unrelated conditions. However we have identified a small group of patients with idiopathic unilateral Horner's syndrome in the context of Holmes-Adie syndrome: we hypothesise that these patients may have a limited form of autonomic ganglionopathy which is distinct from more widespread peripheral neuropathies, progresses slowly (over decades) and carries a good overall prognosis.

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<u>Three cases of acetamiprid intoxication suspected from</u> <u>clinical symptoms, and their objective findings of electrocardiography,</u> <u>auditory brainstem responses and pupillary functions</u>

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Purpose: Recently, the use of neonicotinoid insecticide as an alternative of organophosphate is increasing in agricultural/forest regions in USA and Japan, which act mainly as insect nicotinic acetylcholine receptor¹⁾. Acetamiprid, a neonicotinoid insecticide, was developed in Japan. The chronic toxicity of acetamiprid is rather strong, no-observed-adverse-effect-level for chronic toxicity (NOAEL) in rats is 7.1mg/kg/day. However, the report on the human health effect is lacking except our study²⁾. In 2006, we reported the cardiac symptoms and ECG abnormality of the 63 patients after acetamiprid spray to the pine trees. In June 2007, we reported more than 100 patients had been visited with the complaints of autonomic nervous system. They are almost identical ECG abnormalities with the abnormal heart rate, ST-T changes e.g. chest pain, muscle weakness, finger tremor and/or memory disturbance²⁾.

Methods: Three cases visited clinic A (Maebashi, Gunma Prefecture) between March 1st till August 31st, 2007. The authors are studying sequel of the inhabitant where a massive spray of mainly organophosphates and carbamates, and a spray of acetamiprid 40 m into the air with insect sprayer have been repeatedly performed. By detailed interviews with the patients, it was considered that oral intake of acetamiprid via certain foods; especially vegetables, fruits, green tea (over 400-500ml per days) and/or insecticide spray in the nearby field are most likely factor to produce those clinical manifestations.

Clinical symptoms and the findings of Electrocardiography (ECG), Auditory Brainstem Response (ABR) and the Pupil function followed by photic stimulation examined by infrared pupillography (Iriscorder C7364, Hamamatsu, Japan) were made.

Results: Mild neutrophilia (8200/ μ I) and CRP increase (0.97mg/dI) were shown in Case 1. Other routine laboratory examinations were within normal limits. The residue of acetamprid in the patient's blood and urine was not made. Clinical summary of the results are shown in the Table below. Tachycardia and ST-T change in ECG, V wave shortening in ABR, as well as abnormal function of the autonomic nervous system was seen by pupillographical test.

Discussion: Neonicotinoid insecticide acts as an agonist at $\alpha 4\beta 2$ subtypes of nicotinic acetylcholine receptor, which exist at the brain of human¹⁾. A metabolite of neonicotinoid insecticide, for example, imidacloprid acts as stronger agonist on the $\alpha 3$ subtype, which exist at the autonomic ganglia of human³⁾.

Environmental exposure of pesticides is hard to diagnose when a suspected patient visits the physician with unidentified complaints. We need objective tests to discriminate from psychosomatic syndrome. As introduced here objective tests of ECG, ABR and Pupillography may help to establish the diagnosis. Although clear route of entry and the dosage dependency of acetamiprid has not been established, present three cases may give us important clinical suggestion to find out the subacute or chronic toxicity of neonicotinoid which is considered as a major pesticide all over the world in the future.

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	Case 1	Case 2	Case 3
	(28 y.o. female)	(31 y.o. male)	(51 y.o female)
Suspicious Source	green tea	green tea insecticide use	Insecticide use
Clinical Symptoms	headache palpitation myalgia throatpain constipation fever (38.5°C) memory disturbance	headache chest pain muscle weakness depression insomnia memory disturbance finger tremor	muscle weakness dyspnea palpitation myalgia finger tremor
ECG	Tachycardia ST depression	ST elevation RV conduction delay	Tachycardia T wave flattening
ABR	V wave shortening	V wave shortening	V wave shortening
Pupillography 4)	D1↓, A1↓, CR↓ ,	D1↓, A1↓, CR↓ ,	D1 ↑ , A1 ↑ , CR ↓ ,
In the darkroom	t1 \uparrow , t2 \uparrow , t3 \uparrow , t5 \downarrow	t1 \uparrow , t2 \uparrow , t3 \uparrow , t5 \downarrow	t3 ↑ , t5 ↑
findings	Parasympathetic?	Parasympathetic?	Sympathetic?

Table 1: Clinical manifestations of 3 cases.

Sick building/house syndrome due to organophosphorus pesticide and volatile organic compounds examined by pupil response to the light

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Purpose: During the past 10 years, sick building/house syndrome (SBS) has become a critical health problem, especially due to the use of chemicals and air-tight structure in a newly built house. A major factor that generates the syndrome is anti-termite pesticides and volatile organic compounds including formaldehyde. Physicians are visited by the patients with unidentified complaints. In Japan, a person who is extremely sensitive to the environmental chemicals is referred to as "chemical sensitive or environmental sensitive patients" and presumably about 700,000 patients exist domestically. However, it is quite difficult to exclude the patients due to the other etiology such as psychological problem in origin. ---A careful analysis of the environmental history in regard to the toxic chemical is necessary together with the gas analysis inside the room is needed. ---A combination with clinical manifestation, in particular, objective findings e.g. positron CT and the loading of suspected gas are important but is costly. Neuro-sensory test give us significant information to establish the diagnosis. In this presentation, we will introduce the results of pupil tests in patients with SBS.

Methods: The subjects were 31 patients (16 males and 15 females) with the age ranging 21-43 years selected from the patients at Kitasato Hospital. They were diagnosed as SBS according to the diagnostic criteria issued from the Japanese Government Research Team in 1999. They had no history of diabetes mellitus, hypertension, or no other serious general complications. No medicine was taken during 1 month prior to the examination. They were tentatively classified into two groups according to their environmental study: an etiology due to anti-termite organophosphorus pesticide (group I) and to volatile organic compounds (VOC) including formaldehyde (group II), respectively.

Pupil test was performed in both groups using infrared pupillography (Iriscorder:C7364) with 15-minute pre-dark adaptation, with one second photic stimulation. From one pupillogram within the time of 5.25 seconds, particularly the pupil size was determined. The rate of constriction in percent and the pupil size in percent at 5.25 second after the photic stimulation (tentatively we call the rate of dilatation in percent) were studied. Time sequence of the pupil size in a continuous recording during 1 minute with 4 stimuli of every 10-second interval was measured.

Results: In the group I, the pupil size was smaller and the dilation in percent was less than the group II. The time sequence of the pupil size tended to constrict against time in Group I.

Discussion: Anti-termites e.g. ethyl-chlorpyrifos was banned followed by the outbreak of environmentally sensitive patients. However, other organo-phosphtes DDVP, Diazinon, and Fenitrothion etc. are still in use in the market. Since these compounds produce neuro-toxic effects based on inhibitions of cholinesterase, fatty amid-hydrolase, neurotoxic esterase and other esterases, they should not be used inside the houses and buildings. Pupil response followed by the light stimulus gave us important information.

Conclusion: The analysis of pupillography may be helpful to differentiate the SBS syndrome from anti-cholinesterase and from VOC in origin. The technique is simple, economical and non-invasive than the other neurological tests, therefore, a routine application can be expected.

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Evaluation of driver's sleepiness by pupillary fluctuation and anti-saccade reaction time

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Objective: Prediction of drowsiness based on an objective measure is demanded in machine and vehicle operations in which human errors may cause fatal accidents. The pupil of the eye is innervated by the autonomic nervous system whose activity is known to change in parallel with drowsiness. It is a unique organ that is non-invasively and visually observable from outside the body. We have focused on the pupil and evaluated it as a possible premonitor of drowsiness.

Methods: We employed uneventful driving simulation (monotonous driving simulation experiment) to induce drowsiness of human subjects, and an anti-saccade task to evaluate their cognitive and motor performance (anti-saccade driving experiment). A total of 25 healthy subjects participated in the experiment. During the experiment, we measured horizontal eye position, heart rate, respiratory abdominal motion together with pupil diameters. In anti-saccade driving experiment, a visual target was randomly presented for 200 ms on either shoulder of the road every 20 s. Subjects were asked to make a saccade in the opposite direction to the presented visual target (anti-saccade) during the same driving simulation. The simulation time for both monotonous and anti-saccade driving was usually 10 minutes.

Results: Of 25 subjects who participated in the monotonous driving simulation experiment, 16 reported sleepiness. First we confirmed that pupil diameter fluctuated with large amplitude at low frequencies when these subjects were aware of his/her drowsiness as reported previously. During this large pupil fluctuation period, the latency of anti-saccade initiation was elongated and varied. We then found that prior to this fluctuation, pupil diameter decreased gradually in most subjects, and they were not aware of sleepiness during this period.

Conclusions: It has been known that the pupil fluctuation with large amplitude at low frequencies appears when people perceive sleepiness [1], [2]. Our new findings are 1) prior to the large low frequency fluctuation, a gradual miosis occurs in approx. 80 % of the subjects, 2) during this gradual miosis period, the subjects did not perceive their own sleepiness, and 3) the latency of anti-saccade initiation during the gradual miosis is not necessarily longer than that of control whereas it was elongated and varied during the large low frequency fluctuation period. These findings suggest that we can predict a person is going to be drowsy well before he/she perceives sleepiness by observing the gradual miosis. We conclude that this monotonic gradual miosis can be a reliable predictor of drowsiness.

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Is an NMDA glutamate receptor involved in the afferent arm of the human pupillary light reflex?

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Introduction: The transmitters involved in the afferent arm of the pupillary light reflex are unknown. Previous studies have shown that nitrous oxide, a known antagonist at the NMDA glutamate receptor depresses the light reflex. We asked whether another NMDA antagonist, ketamine, also depresses the light reflex in humans. We tested the hypothesis that the NMDA receptor noncompetitive antagonists nitrous oxide and ketamine diminish the human pupillary light reflex.

Methods: Following approval from the Committee on Human Research, we studied 40 consenting adults. General anesthesia was induced with 1.5-2 mg/kg propofol and 2 mcg/kg fentanyl. Following muscle relaxation and tracheal intubation, desflurane in oxygen, fentanyl (2 mcg/kg/hr), and vecuronium bromide were administered to maintain anesthesia. Ketamine (1 mg/kg, n=11), ketamine 0.5 mg/kg, n=9), nitrous oxide 60% (n=8), or saline (n=12) was administered after a stable level of anesthesia had been achieved. The following parameters were recorded every two min as possible indicators of ketamine or nitrous oxide effect: systolic and diastolic blood pressure, heart rate, processed EEG (BIS), pupil size, and percent pupillary light reflex. An infrared hand-held pupillometer (Neuroptics, Irvine, CA) was used for pupillary measurements. Repeated measures ANOVA were used to compare maximal changes in the measured parameters following drug administrations.

Results: Ketamine increased the BIS score and depressed the light reflex at both doses. Nitrous oxide had variable effects on the BIS score and depressed the light reflex. Maximal changes in the light reflex were: Saline $+29 \pm 37\%$, nitrous oxide – $54 \pm 18\%$, ketamine 1 mg/kg – $58 \pm 10\%$ and ketamine 0.5 mg/kg – $48 \pm 9\%$. Both doses of ketamine and nitrous oxide were significantly different from the saline control group (p < .0001). Blood pressure, heart rate, and pupil size did not change significantly after ketamine but blood pressure was decreased following nitrous oxide.

Conclusions: The NMDA antagonists ketamine and nitrous oxide consistently depressed the pupillary light reflex with minimal changes in pupil size. Although the excitatory transmitters at the pretectal nucleus and the pupilloconstrictor nucleus are unknown, this study provides preliminary evidence that an NMDA glutamate receptor is involved in the afferent limb of the human pupillary light reflex.

Molecular affinity and efficacy at alpha adrenoceptor of the iris

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Objective: Mydriasis is produced by exogenous sympathomimetic drugs or the endogenous transmitter *l*-norepinephrine which activates α_1 -adrenoceptor of the iris dilator muscle. The activation of the neuronal prejunctional α_2 -adrenoceptor by the agonist reduces the release of the transmitter. The affinities and efficacies of the sympathomimetic drugs for the prejunctional and postjunctional adrenoceptor vary greatly (1, 2). The molecular nature of the initial activations by these drugs with the G-protein coupled α -adrenoceptors are not known. Hence, three dimensional amino acids homology modeling of receptors based on the low resolution crystal structure of bovine rhodopsin (PDBID: IF88) was used to understand the affinity and efficacy of agonists.

Methods: In vitro procedure for recording contractions of iris dilator muscle reported before (1, 2). The protein model for the α_{1A} and α_{2A} adrenoceptor were generated via MODELLER 9v2. The backbone trace of the α_{1A} and α_{2A} models were kept with similar conformation to the rhodopsin template, whereas the arrangement of side chains of binding site residue were predominantly determined by the published data. AutoDock 4.0 was used for flexible docking of ligands in which three dimensional induced-fit conformational changes were simulated (3).

Results: For the catecholamine two binding modes with α_{1A} adrenoceptor were observed. First charged amine interacted with Asp¹²⁵ at TM3 and at least one of hydrogen bonds with both Ser¹⁸⁸ and Ser¹⁹² of TM5. The phenyl ring, of the ligand showed aromatic interaction with Phe³⁹¹. Only the chiral hydroxyl group of ℓ -epinephrine shows hydrogen bond formation with ASP¹²⁵. The imidazoline ring of oxymetazoline showed strong electrostatic and hydrogen bonding interactions with ASP¹²⁵. α_{2A} -Adrenoceptor shows similar interactions with catecholamines and oxymetazoline but the binding energy is lower. Interactions of ℓ -phenylephrine, ℓ and ∂ -norepinephrine, P-aminoclonidine and other drugs will be presented.

Conclusion: (1) Using this model, the selective interaction of the chiral hydroxyl group of the active enantiomer with ASP¹²⁵ was recognized. (2) The pharmacological affinity and efficacy of agonists closely parallels the dynamics of the ligand receptor interactions.

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Effect of various neuropeptides on rabbit iris sphincter and dilator muscles

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Purpose: Various neuropeptides, such as Calcitonin gene-related peptide (CGRP), Substance P (SP), Somatostatin, galanin, Pituitary adenylate cyclaseactivating peptide (PACAP) are known as sensory neuropeptide in the eye that is released by noxious stimuli and considered to be a mediator of the neurogenic ocular injury response including miosis. The purpose of this study is to clarify the functional role of these peptides on iris sphincter and dilator muscles.

Methods: Iris sphincter and dilator muscles were isolated from rabbit eyes, and the effect of various neuropeptides on mechanical responses of these muscles were investigated using isometric tension recording methods.

Results: Substance P dose-dependently contracted the rabbit iris sphincter, however, this agent had no effect on the dilator. CGRP had no effect on either the resting muscle tone or the amplitude of contraction evoked by field stimulation of the sphincter. On the other hand, CGRP relaxed dilator muscle which had been pre-contracted by phenylephrine and reduced the amplitude of contraction evoked by field stimulation. Both somatostatin and galanin attenuated the amplitude of contraction evoked by field stimulation of the sphincter. Galanin was more effective compared with somatostatin. The dilator muscle response to field stimulation was not changed by either peptide. Both PACAP 27 and PACAP 38 enhanced the amplitude of contraction evoked by field stimulation of the sphincter. For the iris dilator muscle, PACAP 27 inhibited the contractions induced by field stimulation or phenylephrine while PACAP 38 had no effect.

Conclusions: Various neuropeptides had different effect on iris sphincter or dilator muscles. However, we conclude that these peptides may induce miosis by contracting sphincter, attenuating cholinergic neurotransmitter release, relaxing dilator or inhibiting adrenergic neurotransmitter release.

<u>The most appropriate reflex factors expressing artificial afferent defects in</u> <u>pupillary light reflex as measured by infrared video-pupillogram</u>

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Objective: To determine the most appropriate reflex factors which express artificial afferent defects in the pupillary light reflex.

Methods: The attenuation of the pupillary light reflex resulting from reduction of the visual input, afferent pupillary defect, was analyzed by using reflex factors including our originally developed relative factors as follows:

L; latency time (msec) %A; (A-0.2/PA) x100 (%) A= amplitude of constriction (mm²) PA= pupil area before constriction (mm²) %VCmax; (VCmax-12.9/A) x100 (%/sec) VCmax= maximum constriction velocity (mm²/sec)

The subjects were 11 young healthy volunteers and their randomly selected unilateral eyes were examined. Pupillary light reflexes under open-loop condition (Maxwellian view) were measured by infrared video-pupillography. Fifteen levels of the light stimulus changing by neutral density filters (NDFs) of -4.2 to 0 log were irradiated, and artificial afferent pupillary defect was made. Before examination, we confirmed that the pupillary light reflexes factors in these subjects were within the normal range of their respective age.

Results: Due to application of NDFs, the light reflexes became sluggish and shallow, the latency time (L) prolonged, and % amplitude of constriction (%A) decreased. However, % maximum velocity of constriction (%VCmax) was constant regardless of the afferent pupillary defect. A comparative study of the alternations in L and %A revealed that %A was a suitable factor to imply the effect of afferent defect on the pupillary light reflex because of its less variation.

Conclusions: %A should be applied in the objective and quantitative analysis of the afferent pupillary defect in the light reflex.

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Effect of the pupil size on contrast sensitivity

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Purpose: To investigate the effect of pupil size on contrast sensitivity with the higher-order aberrations.

Methods: In 10 right eyes of 10 emmetropic subjects. We measured the contrast sensitivity with a VCTS6500 (VISTECH Consultants, Inc.) using an artificial pupil from 1 mm to 5 mm each 1 mm step size. The contrast sensitivity data were calculated AULCSF (the area under the log contrast sensitivity function). Ocular higher-order aberrations were measured with an iTrace (Tracey Technologies, LLC.) from 2 mm to 5 mm pupil size.

Results: The AULCSF was the best at a 3 mm pupil size, and declined in the order of 2 mm, 4 mm, 5 mm, 1 mm, respectively (p<0.01). A higher-order aberration has reduced as the pupil size decreased (p<0.01).

Conclusions: The pupil size affects the contrast sensitivity in connection with the higher-order aberration and the retinal illuminance. We should pay attention to the pupil size in clinical evaluation of the contrast sensitivity.

Age-Related changes in pupil size

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Purpose: It is essential that the pupil size be above $3 \sim 3.5$ mm in a bright room in order to obtain satisfactory near visual function after refractive multifocal intraocular lens implantation. The age-related changes in pupil size and the maximum suitable age for implantation of refractive multifocal intraocular lenses were investigated with the electronic pupillometer, which can measure patency synchronously in both eyes.

Methods: The pupil sizes of 167 volunteers (291 eyes) with naked-eye vision above 1.0 and without ocular or autonomic nervous diseases were measured within 5 seconds with an electronic pupillometer FP-10000 (TMI Co. Ltd., Japan) while the subjects stared at an object over 5 m away or close by (30 cm) in a bright room (200-300 lux). The mean horizontal diameters measured within about 3 seconds, except during blinks, were analyzed. Statistical analysis was performed using Spearman's rank order correlation.

Results: Horizontal pupil diameter was negatively correlated with age during the staring at distant and nearby objects (horizontal diameters: y=-0.424x+5.241, r=-0.424, p<0.0001; and y=-0.0284x+4.811, r=-0.484, p<0.0001, respectively). The ages at which the pupil size remained above 3.5 mm were 70 years for distant objects and 46 for nearby objects.

Conclusion: Pupil size decreased with age. The results indicate that the maximum age at which satisfactory visual function could be obtained for nearby objects after refractive multifocal intraocular lens implantation was 50 years.

Measurement of ocular convergence, pupillary constriction and ocular torsion in near reflex

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Objective: It is known that ocular torsion is associated with convergence eye movements, however, the mechanism and biological meaning are not clear. In this study we measured ocular torsion simultaneously with ocular convergence, as well as pupillary constriction during vergence.

Methods: Ten healthy men with normal vision and stereopsis were subjects in this experiment. The visual target, a small light-emitting diode (LED) approached and recessed from the subject at the same speed. Each eye was photographed with an infra-red CCD camera and recorded on a digital tape. The pupillary area, the center of the pupil, and the pattern of the iris were detected using a computer-assisted procedure, from which horizontal and vertical eye movements, pupillary response, and ocular torsion was calculated. We tested six conditions: The visual target approached the central point between the eyes, with both eyes viewing (condition 1) or with the right eye viewing (2); the target approached the right eye with both eyes viewing (3) or with the right eye viewing (4); and the target approached the left eye with both eyes viewing (5) or with the right eye viewing (6).

Results: Three subjects showed obvious ocular torsion, which we thoroughly analyzed. In response to the approaching target, convergence eye movement started first, followed by pupillary response; ocular extorsion started slowly but even during the near fixation of the target, it continued gradually increasing to 2 - 5 deg extorsion. Even with one eye viewing, a similar amount of ocular torsion was observed in both eyes. This torsion was not artifact because such extorsion was not observed during horizontal conjunctive eye movement and during light reflex.

Conclusions: Without a binocular disparity cue, an accommodation cue could elicit ocular torsion. This ocular torsion occurred very slowly and even during near fixation indicating that it is not directly linked to the innervation to the medial rectus muscle or to the iris sphincter muscle.

Pupillary and vergence behaviors related to the cognition of motion induced by radial optic flow

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Objective: We investigated the relationship between pupillary response and vergence eye movement elicited by radial expanding-contracting optic flow stimuli. We focused on (1) vergence and pupillary responses to the switch of stimulus direction and the change in the flow velocities, and (2) sustained vergence and papillary responses to them.

Methods: There were 12 participants who were exposed to an expanding-contracting random dot radial optic flow pattern simulating oscillating translational motion in the anterior-posterior axis under four viewing conditions with fixation point at the focus of expansion; 1) contraction-stop pattern inducing backward and stop motion sensation; 2) contraction-expansion simulating backward and forward motion; 3) expansion-stop; and 4) expansion-contraction with three different frequencies of sinusoidal waves. Pupil size and vergence eye movement were measured with video-oculography.

Results: Pupil contraction was observed responding to the motion onset and to the switch of the stimulus direction while vergence eye movements showed convergence and divergence during forward and backward stimuli, respectively.

Discussion: The contraction of pupil may relate to cognition of object motion change and was supposed to be similar to the response elicited by translational coherent object motions [1] and this could not link to vergence eye movement. The vergence may be sustained component subsequent to the ultra-short latency vergence response [2].

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Surgical management of functional iris deficiencies with cataract

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Purpose: It is essential that the pupil size has relation to high order aberration. We experienced 4 cases for surgical management of functional iris deficiencies with cataract.

Methods: 4 case were as follows, Cataract surgery with intraocular lens and prostheric iris implantation was performed in 2 cases. Another 2 cases of the visual acuity and subjective degree of glare disability, postoperative anatomic results, and intraoperative and postoperative complications were evaluated.

Results: All eyes achived the desired anatomic result. Visual acuity was improved. Patiens were surveyed postoperatively to determine the change in glare disability.

Conclusions: In patients with iris deficiency, implantation of prostheric iris device, and intraocular lens implant following cataract surgery appears to be safe and effective in reducing glare disability and improving visual outcomes.

Possible mechanism of intraoperative floppy iris syndrome: A clinicopathological study

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Introduction: A recent report attributed "intraoperative floppy iris syndrome (IFIS)" occurring during cataract surgery to the α_1 -adrenoceptor antagonist tamsulosin¹. But, mechanism of IFIS is unknown. The present study examines three eyes of two patients with conditions similar to IFIS after administration of bunazosin (Detantol[®]; Santen). Histological examinations were also conducted.

Cases: Both patients, a 77-year-old woman and a 79-year-old man, had used bunazosin eye drops for three years, had unremarkable medical histories, with no trauma, had used only bunazosin orally or as eye drops. Slit-lamp biomicroscopy revealed no abnormalities other than glaucoma and cataract. Both patients underwent cataract surgery, during which IFIS was observed, but no other complications were seen in either. In each eye, we performed peripheral iridectomy and, after immediately fixing the extracted specimen in 2% glutaraldehyde, examined it in a transmission electron microscope. Two women underwent cataract surgery as controls during the same period.

Results: The histological examination of the irides of the patients revealed that the sizes of the pigment granules in the melanocyte cytoplasms were irregular. Some clump cells contained lipofuscin-like granules in addition to the pigment granules. The majority of the dilator muscle cells were markedly vacuolated, suggesting cellular degeneration. No nerve terminals innervating smooth muscle were observed in the present study.

Conclusion: In our detailed histological investigation of the results of bunazosin treatment, bunazosin was found to have an affinity with melanin that is important in the mechanism of IFIS. Also important is its effect on nerve terminals.

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