·研究报告·

猫视网膜神经节细胞显示对长时间光栅刺激的弱图形适应和明显的图形易化作用

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[摘要] 图形适应被认为仅存在于视觉皮质水平, 然而本实验室新近实验表明, 光栅图形适应也存在于正常猫和去视皮质猫的外膝体神经元。本研究目的在于澄清外膝体的图形适应是否来源于视网膜。研究了 79 个 X 和 Y 型猫视网膜神经节细胞对长时间的光栅刺激反应。结果显示: ①与外膝体中继细胞不同, 71% 的神经节细胞对长时间刺激反应不变, 只有 6% 的细胞显示光栅适应, 而有 23% 的细胞显示易化作用; ②上述对长时间的光栅刺激的效应与细胞类型(X 和 Y 型或 On-和 Off-中心型)无关; ③如同外膝体细胞, 视网膜神经节细胞的光栅易化作用在刺激后 30 s 内结束, 平均反应幅度上升 17%, 其时程符合指数函数, 平均时间常数为 17.7 s。本结果提示, 图形适应可能基本上起源于外膝体, 而图形易化则起源于视网膜, 因此外膝体内机制可能导致中继神经元的图形适应。

[关键词] 图形适应; 易化作用; 视网膜; 神经节细胞; 光栅; 猫

The cat's retinal ganglion cells show weak pattern adaptation but significant pattern facilitation to prolonged grating stimuli

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[**Abstract**] Pattern adaptation is believed to be a unique property of cortical cells. However, recent work in our laboratory has demonstrated grating adaptation of relay cells in the dorsal geniculate nucleus (dLGN) following prolonged exposure to a drifting grating in the normal and cortex-ablated cats[1]. The purpose of this study is to test if grating adaptation revealed in the dLGN originates from the retina. We studied the responses of 79 X- and Y-type ganglion cells in the cat retina to prolonged grating stimuli. In contrast to the dLGN relay cells, neither pattern adaptation nor facilitation was found in the majority of studied cells (71%) in the retina. Only 6% of the cells studied were adapted to the adapting grating, while 23% of the cells studied showed significant facilitation rather than adaptation. There was no significant dif-

[文章编号] 1008-0872(2000)04-0309-06 [中图分类号] R338.2 [文献标识码] A [收稿日期] 2000-03-21
[基金项目] 国家自然科学基金资助项目(39893340-3); 上海-联合利华研究和发展基金(9805)和中国科学院生物物理所视觉信息加工开放实验室项目 [通讯作者] 寿天德 [联系电话] 021-65642355
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ference either between X and Y cells or between On-center and Off-center cells in susceptibility to adapting grating stimuli. The facilitation observed in the retinal ganglion cells completed within 30 s with a mean response increase of 17%, whose time course was well fitted to an exponential function with a mean time constant of 17.7 s. The results suggest that the pattern adaptation may essentially originate from the dLGN, while pattern facilitation from the retina. Therefore, the intrageniculate mechanisms may cause the pattern adaptation in the dLGN.

[**Key words**] pattern adaptation; retinal ganglion cell; facilitation; grating; cat

Pattern adaptation is one of the most well-known properties in the visual systen[1~5]. It was believed that pattern adaptation occurs only in neurons of the visual cortex in mammals[2~14]. This phenomenon is specific to many visual parameters, such as contrast[4], spatial frequency[3,5], orientation[6], direction of mothion[7~9], velocity[10] and ocularity[11~14]. However, our recent study has shown that grating adaptation also exists in about half of X- and Y-type relay cells in the dLGN of the cat. The grating adaptation shown in these relay cells is of contrast gain control and orientation-selective. Furthermore, prolonged grating also reduces the responses of the dLGN cells after inactivation of cortical inputs to the dLGN (Shou, *et al*, 1996). Since relay cells in the dLGN receive visual inputs directly from the retina, it is natural to ask whether gating adaptation originates from the retinal ganglion cells.

In this study, we investigated the responses of the cat retinal ganglion cells following prolonged exposure to moving gratings of high contrast. The results surprisingly showed that little pattern adaptation was found in the retinal ganglion cells, compared with that in the dLGN, and about one fifth of retinal ganglion cells exhibited pattern facilitation. It is suggested that pattern adaptation may not originate from the retina, but initiate in the dLGN via intrageniculate mechanisms.

1 Materials and methods

1.1 Animal procedure and single unit recording

The detailed methods for recording single-unit activity of the retinal ganglion cells from the optic tract in anaesthetized and paralyzed cats are similar to those described previously[1,15]. Cats were initally anaesthetized with ketamine (20 mg/kg). During the rest of the experiment, light anesthesia was maintained with intravenous urethane given at an initial dose of 30 mg/kg followed by an infusion of 10 mg/kg per hour. Gallamine triethiodide (Flaxidil, Shanghai Dongfeng Chemicals Factory, China; 10 mg/kg per hour) was used for immobilization. An indication of the level of the anesthesia was gained from the heart rate and the blood pressure, which were continuously monitored. Pupils were maximally dilated with atropine sulfate (1%), and appropriate contact lenses were used to protect the cornea. Neosynephrine (5%) was administrated to retract the nictitating membranes. The animal's rectal temperature, heart rate, end-tidal CO_2 and blood pressure were routinely monitored and kept within normal limits.

The optic disks were projected onto a tangent screen positioned 114 cm from the eyes. The clarity of the eye optics was checked repeatedly during all experiments. Action potentials of the retinal ganglion cells were recorded extracellularly from the optic tract of the cat with a tungsten-in-glass microelectrode of 2~10 MΩ. Signals from the electrode were amplified, and fed to a window discriminator, whose output was stored in a computer and also fed to an audio-monitor. To ensure accurate isolation of a single unit, action potentials were displayed on an oscilloscope so that their shape and time course could be monitored.

1.2 Visual stimuli Visual stimuli were vertically oriented drifting sinusoidal gratings with a mean luminance of 3.5 cd/m^2. The contrast and temporal frequencies of stimuli were always kept at 80% and 3 Hz, respectively, except mentioned. The spatial frequency of gratings could be changed according

to the needs of the experiment. Details of the stimuli employed in the specific case are given in the resuts.

The stimuli were displayed on an Innisfree "Picasso" oscilloscope-based (Tektronix 608, USA) optical display with a screen of 12.5 × 10 square degrees, and controlled by the visual stimulation (CED, UK) software with a computer. The oscilloscope could be moved to any position of the animal's visual field, while maintaining a fixed distance of 57 cm from the animal's eyes. Thus, we were able to study cells with receptive fields throughout the visual field.

1.3 Experimental procedure Receptive fields of the isolated units were mapped on a tangent screen 114 cm from the cat's retina using a hand-held projector and categorized as On- and Off-center cells. The responses of signle cells to drifting and phase alternating gratings were then used to determine the cell's linearity and to detect frequency doubling in their responses. Spatial resolution, receptive field size, response to rapid motion, and sluggishness of response were also used to classify cells as X- and Y-types[16～19]. First, we measured spatial frequency tuning curves for each retinal ganglion cell. Then the time course of a cell's response to repeated stimuli of gratings was at its optimal spatial frequency in order to assess the changes in responsiveness during the period of stimulation.

1.4 Data analysis The post-stimulus time histograms (PSTH) of 10-ms bin width were accumulated and averaged for responses to six or more presentations of a test grating, which was temporally phase-locked with response data conection. The amplitude of fundamental Fourier components (FFT) of the PSTHs was taken as the cell's response amplitude in spike/s. To quantify and summarize the cell responses we computed a ratio between the response amplitude of the plateau following the prolonged grating stimulation and the response amplitude at the initial response (P/I, plateau/initial). The initial response was defined as the average response during the first two seconds of grating presentation, and the plateau following the prolonged grating stimulation was defined as the average response during last 50～60 s of the prolonged stimulation. The *t*-test was used to classify a cell's behavior in response as pattern adaptation, pattern facilitation and no change by comparison of the initial and the plateau.

2 Results

Seventy-nine retinal ganglion cells of 6 cats were analyzed quantitatively. Of these cells, 41 were classified as X cells and 38 as Y cells.

Fig 1 illustrates the time course of responses of three representative cells to constant drifting prolonged grating stimulation. In contrast to previous observation in the dLGN of the cat[1], the ganglion cell, responses to the repeated grating stimulation were rather stable with time for most cells studied, as the cell shown in Fig 1A. The variation of the cell's continuous responses was as low as 4%. Only 5 cells in the total samples exhibited significant grating adaptation as shown in Fig 1B. The cell's response declined after the onset of the stimulus, and then reached a relative stable plateau. The decrease in response for this cell was about 15% of the initial value. Some cells exhibited an increase in response with time, indicating a facilitation effect as shown in Fig 1C. Either the grating adaptation or facilitation observed in the majority of cells studied completed within 30 seconds after the onset of the stimulus.

To quantify and summarize the above phenomena we computed a ratio between the response amplitude of the plateau following the prolonged grating stimulation and the response amplitude at the initial response (P/I, plateau/initial). The histograms in Fig 2 (shaded columns) show distribution of plateau/initial ratios for all X- and Y-type retinal ganglion cells studied, respectively. For comparison, the distribution of plateau/initial ratios of the dLGN relay cells (data fitted from Shou, *et al*[1]) is also shown in Fig 2 (thick line columns). In contrast to the dLGN relay cells, 71% of X and Y retinal ganglion cells (56/79, including 30 X cells, 26 Y cells) studied showed no statistical-

ly significant change during responding to prolonged grating stimulation (t test, $P > 0.05$). However, 23% of the cells studied (18/79, 9 X cells, 9 Y cells) showed a clear facilitation effect similar to the relay cells in the dLGN (16%). The mean increase in response of cells facilitated was 17% (i e P/I ratio 1.17), which is similar to that of relay cells in the dLGN (22%). Only 5 cells (6%, 5/79, 3 X cells and 2 Y cells) exhibited significant grating adaptation with a mean decrease in response of 15% (i e mean P/I ratio 0.85), which is close to that of relay cells in the dLGN (19%, i e. mean P/I ratio 0.81). The lack of cells adapted to pattern stimuli (6%) for both X and Y cells was very significant in retinal ganglion cells, compared with the

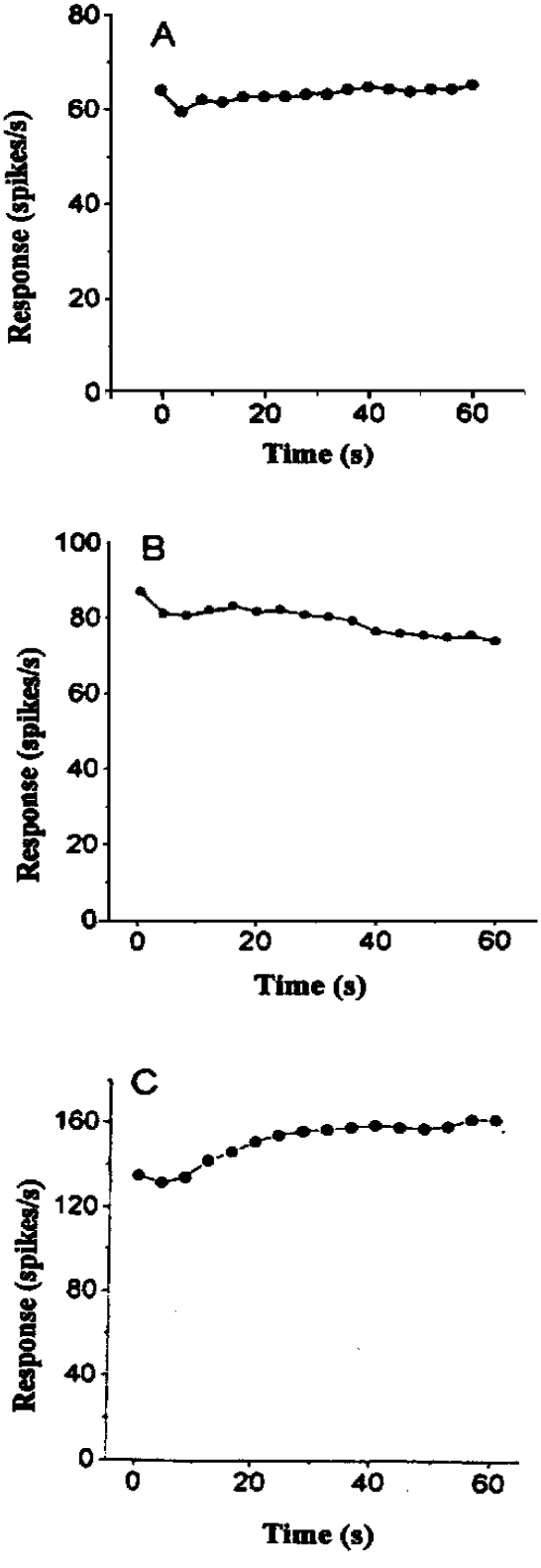

Fig 1 The time course of responses of four ganglion cells to prolonged high contrast (0.8) drifting grating in the cat. Each point represents the mean response fo six cycles of grating stimuli. The standard deviations of all cells' responses were less than 4 spikes/s. The time courses of the responses varied among the cells tested. Most cells studied exhibited stable responses to the repeatative stimuli with time, as shown in an On-center X cell (A). An Off-center X cell decreased its response to prolonged stimulation showing grating adaptation (B). An On-center X cell increased in response during prolonged stimulation (C). The temporal frequency employed was fixed at 3 Hz, and the spatial frequencies used were 0.3, 0.4 and 0.35 cycles/degree in A, B and C, respectively

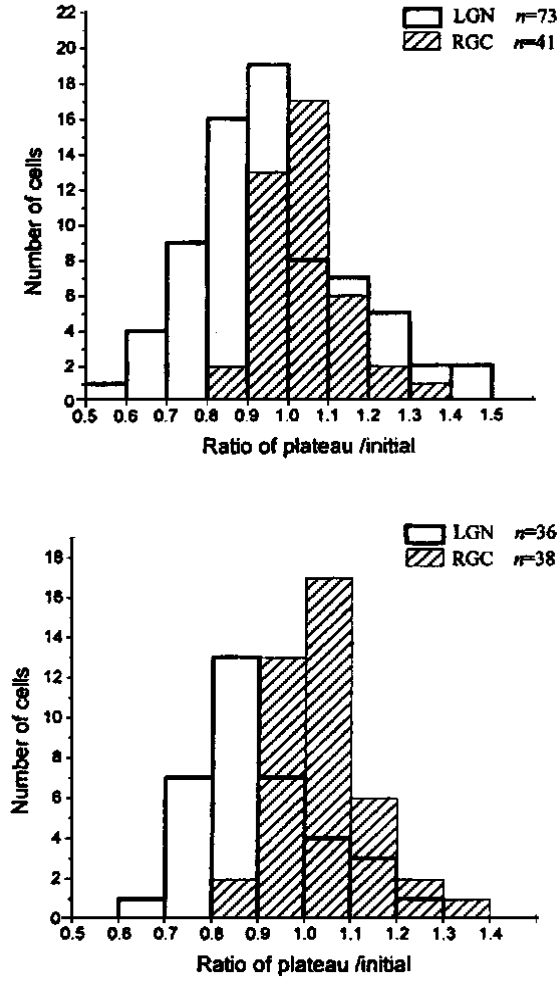

Fig 2 Histograms showing the ratio between the plateau following the grating stimulus and initial response amplitudes for X (A) and Y (B) retinal ganglion cells (RGC) of the cat. The

similar histograms for X(A) and Y(B) relay cells in the dLGN of the cat (data cited from Shou, *et al*, 1996[1]) were also shown for comparison. A cell with a ratio near 1 indicates neither pattern adaptation nor facilitation found during a prolonged grating stimulation. The lower than 1 the ratio, the greater the adaptation; and the higher than 1 the ratio, the greater the facilitation. Note that the histograms for retinal ganglion cells clearly shifts to the right of those for relay cells in the dLGN, indicating that litter grating adaptation and certain facilitation exist in the cat retina

large proportion of relay cells adapted in the dLGN (46%). Therefore, overall, the retinal ganglion cells, no matter what type of cells (X and Y; On- and Off-center), essentially show little grating adaptation, but certain facilitatory effect following prolonged exposure to drifting gratings.

The grating facilitation of each retinal ganglion cell was fitted by an exponential decay function, and its time constant was calculated. The mean time constant was 17.7 seconds indicating a relative slow course.

3 Discussion

In this study we demonstrated that the majority of X- and Y- type retinal ganglion cells in the cat respond constantly to prolonged drifting grating stimulation and the rest cells exhibit certain facilitatory effect, but little adaptation to the repeated grating stimulation. These properties may be physiologically useful for most retinal ganglion cells to send real information of visual pattern to the brain. Our previous study has demonstrated that about half of relay cells in the cat's dLGN exhibit grating adaptation either for X cells or for Y cells, which still appears after the cease of corticogeniculate inputs[1]. Therefore, it is logical to come to a conclusion that the grating adaptation of the dLGN cells we previously observed originates basically within the dLGN, rather than from the retina. Although the underlying intrageniculate mechanisms remain to be further studied, it is possible that the strong pattern adaptation seen in the cortical cells may depend partly on the intrageniculate processes.

Very recently, we found that the pattern adaptation of the dLGN relay cells also exists in the both monocular and binocular lid-sutured cats[20]. This finding suggests that the early visual experience does not affect the grating adaptation of the dLGN relay cells, but the genetic factores may play an important role in forming this pattern adaptation, indeed. Furthermore, the significant loss of Y relay cell caused by visual deprivation does not affect the pattern adaptation in the dLGN due to the cell type independence of grating adaptation[20]. This enhances the idea that the grating adaptation is a reserved, intrinsic property of the dLGN cells, and may contribute to the adaptation of the visual cortical cells.

The similarity in the cell proportion and response increase of the facilitated retinal ganglion cells and dLGN relay cells suggested that the pattern facilitation may originate from retina, and the pattern adaptation from the dLGN due to lack of it in the retina.

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消息简讯

第三届中国-诺华学术研讨会在沪召开

第三届中国-诺华小型学术研讨会于 11 月 22 日至 24 日在上海波特曼召开。本届研讨会的主题是“神经科学研究”。中国-诺华学术研讨会是为了加强新药研究领域的信息交流, 探讨这一领域的最新发展动态和趋势, 并寻找双方有兴趣共同合作的研究课题。国家科技部和诺华公司签订协议, 每年举办一次不同主题的小型研讨会, 参加人员为 10 名中方专家, 10 名诺华公司专家。1998 年和 1999 年, 双方已合作成功地举办了以“天然药物”和“人类基因研究”为主题的两届研讨会。

本届研讨会开幕式于 22 日在波特曼举行, 中国国家科技部和诺华公司官员、复旦大学神经生物研究所和中国科学院生理研究所杨雄里院士分别作了简短的发言。随后即进行为期二天的由上海第二军医大学免疫学研究所曹雪涛教授和诺华公司神经科学研究部主任 Bilbe 博士主持的学术报告。

以“神经科学研究”为主题的本届研讨会, 分“新基因发现以及新的治疗药物、手段的开发”、“发病机理及临床治疗”和“药理学”等三个分题, 共有 24 位中外专家作报告, 介绍了神经科学研究及其前景, 特别是神经科学应用研究和神经性疾病治疗的最新成果和进展。

诺华公司及其所属研究所介绍了其研究与开发情况, 包括诺华公司药学研究概况、神经系统研究概况与科学思路、Nurrl-帕金森病治疗的新方向、异聚 $GABA_B$ 受体-新复合物的产生、应用新的选择性配体鉴定一型代谢型谷氨酸受体的变构结合位点、外周及中枢大麻素样受体在慢性痛模型中的作用、早老性痴呆动物模型的建立、在 APP23 转基因小鼠上研究早老性痴呆的致病机理、表达人 α-synuclein 小鼠为人类神经退行性病变的研究提供了新的动物模型、TCH346 对神经退行性病变的治疗、NKP608——一种高选择性 NK1 受体拮抗剂及其抗焦虑和抗抑郁作用、感受伤害刺激的机理-行为和生理特点等内容。

我国专家介绍了人树突细胞免疫生物学的遗传学分析及树突细胞在神经免疫学中的作用、视网膜神经元 GABA 和甘氨酸受体的调节作用、人下丘脑-垂体-肾上腺轴基因表达谱和全长 cDNA 克隆、Netrin 家族一个新基因的初步研究、神经免疫性疾病-自身免疫机制和免疫治疗前景、帕金森病基因治疗的实验研究、重症肌无力的研究、多发性硬化的致病机理和治疗、自身免疫性脱髓鞘作用的免疫治疗、帕金森病动物模型基因治疗的实验研究、神经细胞糖皮质激素快速非基因组作用的细胞内多信号转导通路、细胞因子神经调节作用的结构基础等。

参加本届研讨会的有国家科技部和诺华制药公司领导, 诺华制药公司研究人员, 我国著名神经科学家陈宜张院士、杨雄里院士和杰出的青年免疫学家曹雪涛教授等。

(蒋春雷)