Effect of Levodopa on Contrast Sensitivity and Scotomas in Human Amblyopia

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The neurotransmitter dopamine (DA) is involved in several visual functions. Visual deprivation decreases retinal DA concentration in chickens and monkeys. In animals with deprivation amblyopia, several studies suggest that neurotransmitters are involved in visual-cortical plasticity and can restore partial visual acuity in adult cats. We investigated in a cross-over, double-masked study the influence of levodopa on contrast sensitivity and binocular suppression in human adult strabismic and amblyopic patients. After one single administration of levodopa, a significant increase in contrast sensitivity and decrease of the size of the fixation point scotoma was found. No changes could be detected after placebo administration. Levodopa did not induce changes in contrast sensitivity in the dominant eyes of the patients or in normal subjects. In conclusion, we found a short-term effect of levodopa on contrast sensitivity and fixation point scotomas in amblyopic eyes of adult patients.


Dopamine (DA) fulfills all criteria of a classical neurotransmitter in the retina of several species. By an action on D1 or D2 receptors, DA influences receptive field properties of retinal neurons, gap junctions between horizontal cells, light adaptive movements between rods and cones and appears also to be involved in visual information processing to the brain.2,3

In humans, high DA contents have been detected in amacrine and interplexiform cells.4 A physiological visual function of DA in man is indicated by alterations of visual evoked potentials (VEPs),3 electroretinograms (ERGs)5 and contrast sensitivity3 in Parkinson’s disease, which is characterized by a general dopamine deficiency. Furthermore, levodopa administration increases the ERG b-wave, selectively changes the amplitude of oscillatory potentials (Gottlob et al, submitted) and reduces the implicit time of the pattern-VEP and pattern-ERG in normal subjects.6

An association between functional changes in the visual pathway (ie, amblyopia) and neurotransmitter activity is strongly suggested by the literature. Form deprivation of chickens7 and occlusion of newborn infant monkeys9 decreased retinal DA concentration. Other studies demonstrated that catecholamines and other neurotransmitters, such as GABA, acetylcholine and glutamate are involved in neuronal plasticity in deprivation amblyopia and can restore partial visual acuity in adult cats.9,10

The purpose of this study was to investigate the short-term effect of levodopa on contrast sensitivity and binocular suppression in human adult amblyopic patients.

Material and Methods. Nine adult patients with severe strabismic or anisometropic amblyopia but no additional ocular pathology (for clinical details see Table 1) were included in a cross-over, double-masked, placebo-controlled study after the nature and possible consequences of the study had been fully explained and informed consent was obtained. Refractive errors were determined by retinoscopy under cycloplegia and fully corrected. For each patient, visual acuity and contrast sensitivity of the amblyopic and the dominant eye, as well as the area of the fixation point scotoma of the amblyopic eye were measured before and after oral administration of either LDBA (200 mg levodopa with 50 mg benzerazide, a peripheral decarboxylase inhibitor) or placebo. Benzerazide, which does not cross the blood-brain barrier, minimizes plasma DA levels and, therefore, peripheral side effects. The placebo was made with the same capsules used for LDBA but they were filled with lactose instead of the active drug. Neither patients nor the examiner were aware of the difference. The LDBA or placebo treatment was given on two different days separated by an interval of at least 1 week. Patients numbers 3, 4, 5 and 8 received LDBA on the first examination day and subsequently placebo. Benzerazide, which does not cross the blood–brain barrier, minimizes plasma DA levels and, therefore, peripheral side effects. The placebo was made with the same capsules used for LDBA but they were filled with lactose instead of the active drug. Neither patients nor the examiner were aware of the difference. The LDBA or placebo treatment was given on two different days separated by an interval of at least 1 week. Patients numbers 3, 4, 5 and 8 received LDBA on the first examination day and subsequently placebo. The treatment order was reversed in the other patients. The effect of LDBA or placebo was examined 90 min after administration, when the maximal plasma level is reached for the LDBA. In addition, contrast sensitivity was tested in the right eyes of a
group of 15 healthy control subjects without ocular pathology (mean age 27.7 years, standard deviation 3.4 years) before and 90 min after LDBA administration.

Visual acuity was tested with the tumbling E, presenting only single letters.

For contrast sensitivity testing, stationary sinusoidal gratings of vertical orientation with a mean luminance of 100 cd/m² were displayed with a Nicolet CS 2000 contrast sensitivity testing system. The monitor subtended 4.5° to 5.5° arc at a viewing distance of 3 m. Patterns of six different spatial frequencies were used: 0.5, 1, 3, 6, 11.4 and 22.8 cycles per degree (c/d). The display unit was recalibrated for contrast and luminance before each test session. During the session, the subject put his or her head in a chin-forehead rest, and dominant and amblyopic eyes were tested sequentially. After two practical trials, four thresholds were obtained using an ascending method and four thresholds were obtained using a descending method at each of the six spatial frequencies. Mean contrast sensitivity was obtained by averaging the eight values.

Scotomas were determined by dynamic perimetry with the Aulhorn phase difference haploscope¹ at a distance of 1.25 m. An asterisk was presented monocularly to the normal eye as a fixation mark. A circular test mark of 14 min arc diameter with a contrast of 60% to the background was presented to the amblyopic eye, without correction of the strabismus angle. Image separation was obtained using four wheels rotating at 50 Hz. Each wheel had two open and two closed sectors. Two wheels rotated simultaneously in front of the normal eye and a projector presenting the asterisk. The other two wheels rotated synchronously in front of the amblyopic eye and a projector with the circular test mark. The wheels in front of the normal and amblyopic eye rotated so that only one eye was viewing the respective projected mark, while the other eye was occluded. Scotomas were plotted on a chart and the areas of the scotomas were measured in relative units (1 cm diameter = 44 for all measurements) using a graphic tablet on an Atari computer with a morphometric program.

**Results.** Visual acuity improved in the amblyopic eyes of patients 1 and 4 from 0.15 to 0.2 after LDBA administration. No changes were found in the other patients or after placebo administration.

Figure 1 shows the contrast sensitivity function before and after LDBA and placebo administration of the amblyopic eye of each patient. The effect of levodopa was variable from patient to patient. A gain of contrast sensitivity was observed in patient 1 at five spatial frequencies, in patient 9 at four spatial frequencies, in patients 5 and 7 at three spatial frequencies and in patients 2, 3 and 6 at two spatial frequencies. In patient number 4, an improvement could only be seen at 0.5 c/d while the other spatial frequencies showed a decrease in contrast sensitivity. Patient 8, with a visual acuity of 0.03, could not recognize any spatial frequency. After levodopa he could detect the gratings at 1 c/d. Interestingly, 7 days later, during the examination with placebo, he still recognized the low spatial frequency gratings. In patients 3, 4 and 5, who also received LDBA during the first examination, no clear changes in contrast sensitivity before drug or placebo administration could be observed between the first and second examination day. In all nine patients, placebo administration did not cause a uniform contrast sensitivity change. In the normal eyes of all patients, the contrast sensitivity was higher than in the amblyopic eyes and no effect of either LDBA or placebo administration was observed. In Figure 2A mean values and standard deviations of all dominant eyes of the patients before and after LDBA administration are represented. No LDBA-related difference in contrast sensitivity was evident at any of the spatial frequencies tested.

A three factorial variance analysis (ANOVA) for repeated measures was performed with the following
Fig. 1. Means and standard errors of the eight measurements of contrast sensitivities from patients 1 to 9 before (●) and after (♦) levodopa (L) or placebo (P) administration at six different spatial frequencies.

In the amblyopic eyes, a significant increase of the contrast sensitivity ($P = 0.0109$) was found after LDBA, while placebo administration showed no significant effect ($P = 0.6452$). The changes in contrast sensitivity after LDBA ($\Delta$LDBA) and after placebo ($\Delta$placebo) administration were calculated for each patient. $\Delta$LDBA and $\Delta$placebo were compared by ANOVA and were significantly different ($P = 0.0097$). For the dominant eyes, no significant differences were found before and after levodopa treatment ($P = 0.796$), before and after placebo administration ($P = 0.175$) or comparing $\Delta$LDBA and $\Delta$placebo ($P = 0.3392$) (see Fig. 2A).

In order to investigate a possible LDBA effect on contrast sensitivity in normal subjects, contrast thresholds were measured before and after LDBA administration in 15 control subjects. The mean and standard deviations of the contrast thresholds of the normal subjects are plotted in Figure 2B. An increase in contrast sensitivity could not be detected at any of the spatial frequencies. The ANOVA did not reveal significant changes between before and after LDBA administration.
A clear decrease in the size of the fixation point scotomas was observed in all nine patients after LDBA administration (Fig. 3). The mean area of the scotomas was in relative units 157.0 (standard error 41.3) before levodopa administration and 58.4 (standard error 21.4) after levodopa treatment. After placebo administration, the area of the fixation point scotoma increased in four patients and decreased in five patients. The mean area of the scotomas before placebo was 159.1 (standard error 51.4) and 141.4 (standard error 42.5) after placebo. Compared by paired t-tests, the differences before and after LDBA treatment were highly significant \( P = 0.0042 \), while no significant differences were found before and after placebo \( P = 0.5097 \). For each patient, the changes between the area of the scotomas after LDBA (\( \Delta \text{LDBA} \)) and after placebo (\( \Delta \text{placebo} \)) administration were calculated and found to be significantly different compared by paired t-tests \( P = 0.0022 \).

**Discussion.** Our results clearly demonstrated by a double-masked, placebo-controlled study protocol that in adult patients one single administration of LDBA influences two different visual functions of the amblyopic eyes: the contrast sensitivity, reflecting the spatial analysis of the visual system, and the fixation point scotoma, indicating the degree of binocular suppression. While the improvement of contrast sensitivity was variable for the different patients, the fixation point scotoma was reduced in all subjects.

The specificity of LDBA on amblyopia is supported by two findings. First, LDBA had no effect on the contrast sensitivity of the dominant eyes. Second, LDBA also had no effect on the contrast sensitivity in a group of 15 normal subjects.
These findings suggest an involvement of dopaminergic function in amblyopia. DA is the primary catecholamine in the retina and is involved in several physiological functions. Since DA is reduced in the retina of chickens and monkeys with deprivation amblyopia, changes in the dopaminergic system of our patients with strabismic or anisometropic amblyopia are conceivable. The association between amblyopia and neurotransmitters is also strongly supported by extensive literature showing an involvement of catecholamines, GABA, glutamate, acetylcholine, serotonin and c-AMP in visual cortical plasticity.

Interactions between dopamine and other neurotransmitters, such as GABA, acetylcholine, serotonin or glutamate, have been shown. Therefore, in our study an indirect effect of dopamine, acting via other neurotransmitters/neuromodulators, can not be excluded.

As DA has been found in human retinal amacrine and interplexiform cells and it is likely that other sites of the visual system such as the lateral geniculate nucleus or the cortex contain this neurotransmitter, the dopaminergic effect in our experiments can not be localized in a specific part of the visual pathway. However, a retinal involvement is supported by several facts. First, reduced DA concentration has been found in the retina of chickens and monkeys with deprivation amblyopia. Second, measurements of latencies of evoked potentials recorded from the cortex, the lateral geniculate nucleus and the optic tract from DA depleted rats, suggest that changes at the retinal level delay the timing of the responses. And third, in patients with changes of the dopaminergic system because of Parkinson’s disease, ERG changes indicate an impairment initially at the retinal level.

In conclusion, our results show that LDBA improves contrast sensitivity and reduces binocular suppression in the affected eyes of adult human anisometric and strabismic amblyopic patients. Our results should encourage clinical trials investigating the therapeutic potential of levodopa on amblyopia.

**Key words:** dopamine, levodopa, human amblyopia, contrast sensitivity, fixation point scotoma

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