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Selective effects of low doses of apomorphine on spatiotemporal contrast sensitivity in healthy volunteers: a double-blind placebo-controlled study

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1 Apomorphine (1 and 5 $\mu g\ kg^{-1}$) and placebo were given to nine normal volunteers, using a Latin-square design and double-blind procedures. The visual perception of static and moving patterns (static and motion contrast sensitivity) was evaluated before and 15 min after the dose administration.

2 Apomorphine (1 and 5 $\mu g\ kg^{-1}$), as compared with placebo, led to a significant overall reduction of the visual perception of movement. This effect was dose-related, and apomorphine (5 $\mu g\ kg^{-1}$) induced a more pronounced decrease in the visual perception of movement than apomorphine (1 $\mu g\ kg^{-1}$). With apomorphine (5 $\mu g\ kg^{-1}$), the reduction was more pronounced for low spatial frequencies, and was linearly inversely correlated to the spatial frequency for a temporal frequency of 3 Hz. Finally, no significant effect of apomorphine was observed for sensitivity to static patterns.

3 Several non exclusive hypotheses may be suggested:

The effects of apomorphine may result from stimulation of retinal D_1- and/or D_2-dopaminergic receptors.

Apomorphine may increase the surround inhibition of ganglion cells' receptive-fields. This modification of the centre-surround balance may explain the decrease in contrast sensitivity for low spatial frequencies.

The specific effects of apomorphine on the visual perception of movement support the hypothesis that apomorphine preferentially affects the magnocellular pathway which mediates sensitivity to moving patterns.

Keywords apomorphine dopamine spatio-temporal contrast sensitivity receptive fields magnocellular pathway

Introduction

Since Malmfors (1963) observation that reserpinized rats have increased sensitivity to light, and following the identification of dopaminergic neurons in the retina of animals (Häggendal & Malmfors, 1965) and humans (Frederick *et al.*, 1982), there is increasing morphological, electrophysiological and pharmacological evidence that dopamine plays a major role in visual perception.

Administration of 1-methyl-4-phenyl-1,2,5,6, tetrahydropyridine (MPTP) induces parkinsonian signs in primates, accompanied by alterations in visual evoked potentials (VEP) and electroretinogram (ERG). These alterations are reduced by levodopa administration (Ghilardi *et al.*, 1988a). Moreover, in primates, the intraocular administration of 6-OH-dopamine, a neurotoxin of dopaminergic cells, induces alterations of VEP and ERG similar to those induced by systemically administered MPTP (Ghilardi *et al.*, 1989). In the retinas of the MPTP treated primates, dopamine concentrations are lower than in normals (Ghilardi *et al.*, 1988b). Tyrosine hydroxylase immunoreactivity (N'Guyen Legros, 1988) and dopamine concentrations (Harmois, 1990) are also lower in retina of parkinsonians as compared with control subjects. Abnormalities of pattern-VEP and ERG have also been demonstrated in parkinsonians (Bodis-Wollner *et al.*, 1987; Ellis *et al.*, 1987; Nightingale *et al.*, 1986; Stanzione *et al.*, 1989). The

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VEP abnormalities depend on the spatial and temporal frequencies of the visual stimulus (Bodis-Wollner *et al.*, 1986) and are reversed by levodopa treatment (Bodis-Wollner, 1990; Bodis-Wollner *et al.*, 1986). Moreover, thioridazine, a neuroleptic, alters ERG in normal subjects (Filip & Balik, 1978), and chlorpromazine, another dopaminergic blocker, induces alterations of VEP and ERG which are dependent on the spatial frequency of stimulation (Bartel *et al.*, 1990).

Thus, there is converging evidence that dopamine plays an essential role in visual function in man and may have differential effects depending upon spatial and temporal aspects of the visual stimulation. In this context, spatio-temporal contrast sensitivity quantifies the visual perception of patterns of various widths (i.e. spatial frequency), which can be either static or moving at various speeds (i.e. temporal frequency). Spatio-temporal contrast sensitivity is in this sense a better predictor of the human visual system's performance than the evaluation of visual acuity (the perception of fine static details). The normal human contrast sensitivity function is an inverted U-shaped curve. The reduction of sensitivity for high spatial frequencies can be due to optical factors, but low frequency attenuation is attributed to neural mechanisms (Robson, 1966).

Previous studies have shown that static contrast sensitivity is modified in patients with Parkinson's disease (Bodis-Wollner *et al.*, 1987; Bulens *et al.*, 1986; Mestre *et al.*, 1990a; Regan & Maxner, 1987). Moreover recent reports suggest a specific deficit in sensitivity to moving patterns in Parkinson's disease: Bodis-Wollner *et al.* (1987) showed a reduction of peak sensitivity but no apparent attenuation of low spatial frequency in the spatio-temporal contrast sensitivity function. We also demonstrated specific impairment of motion sensitivity in parkinsonians as compared with elderly controls (Mestre *et al.*, 1990a).

Such alterations in contrast sensitivity in parkinsonians may be reduced following administration of levodopa (Bulens *et al.*, 1987). Other studies show that patients treated with neuroleptics demonstrate pattern of contrast sensitivity similar to that found in idiopathic Parkinson patients (Bulens *et al.*, 1989). In healthy volunteers, administration of levodopa or nomifensine, a dopamine reuptake inhibitor changes the shape of the static contrast sensitivity function with respect to spatial frequency (Domenici *et al.*, 1985). In a preliminary open study in normal volunteers, we found that spatio-temporal contrast sensitivity was enhanced by high doses of apomorphine, a reference dopaminergic agonist (Mestre *et al.*, 1990b).

Apomorphine is a useful pharmacoclinical tool in humans. It increases spontaneous blink rate and induces yawning in healthy volunteers (Blin *et al.*, 1990a). Thus, it may serve for studying central dopaminergic mechanisms in man.

Here we sought generalized *vs* differential effects of low doses of apomorphine on spatio-temporal contrast sensitivity, using various temporal and spatial frequencies. Dose-ranging effects of apomorphine on visual perception were also investigated. A double-blind placebo controlled procedure was employed. We used low doses of apomorphine since such doses neither lead to sedation as assessed on visual analogue scales (Blin *et al.*, 1990b), nor significantly impair reaction time (Blin, 1987). Dopaminergic agonists do not modify pupil diameter (Al-Sereiti *et al.*, 1989).

Methods

Healthy volunteers

Nine healthy volunteers with normal vision were selected for the study. Only male subjects were included since physiological data indicate that sex may modulate apomorphine-induced effects (Lal *et al.*, 1987). Their ages ranged from 22 to 24 years (mean 22.6), their weight from 65 to 82 kg (mean 71.2) and their height from 175 to 192 cm (mean 180). All were physically healthy according to general, neurologic and ophthalmologic examinations. Subjects were asked not to drink alcohol for 24 h prior to each treatment and up to the end of each session, and to abstain from all central nervous system (CNS) drugs. Subjects were advised not to drive on treatment days. Approval was obtained from the Ethics Committee of the Timone Hospital and each subject gave written informed consent before the study.

Drug supply

Apomorphine chlorhydrate and placebo were prepared extemporaneously by a physician who was not part of the study.

Treatments were administered subcutaneously with the same volume (0.1 ml) and consisted of: (1) Apomorphine (1 or 5 $\mu g\ kg^{-1}$) (2) A placebo: saline.

Experimental design

Each subject was given each of the three treatments, which were assigned to the nine subjects according to a balanced latin-square design under double-blind conditions. At least 48 h were allowed between the treatments to ensure wash-out of the study medication.

Assessment

During each experimental session, the contrast sensitivity to static and moving gratings (spatio-temporal contrast sensitivity -STCS-) was measured by the same experimenter before and 15 min after drug administration. Side effects were assessed throughout the session by the experimenter.

STCS was measured using a micro-computer (Hewlett Packard QS 20) with appropriate software. Static vertical sinusoidal gratings with adjustable contrast (Figure 1), with spatial frequencies of 0.25, 1 or 4 cycles/degree (cpd) were used to measure static contrast sensitivity. Motion sensitivity was tested using the same gratings drifting laterally with temporal frequencies of 1, 3 or 9 Hz. The subjects were instructed to look at a display subtending a visual angle of 10 × 7 degrees at a viewing distance of 1.7 meters. Testing was binocular. Mean luminance of the display was held constant at 1 cd/m^2.

In the static condition, the subjects had to identify the vertical gratings. In the moving condition, they had to

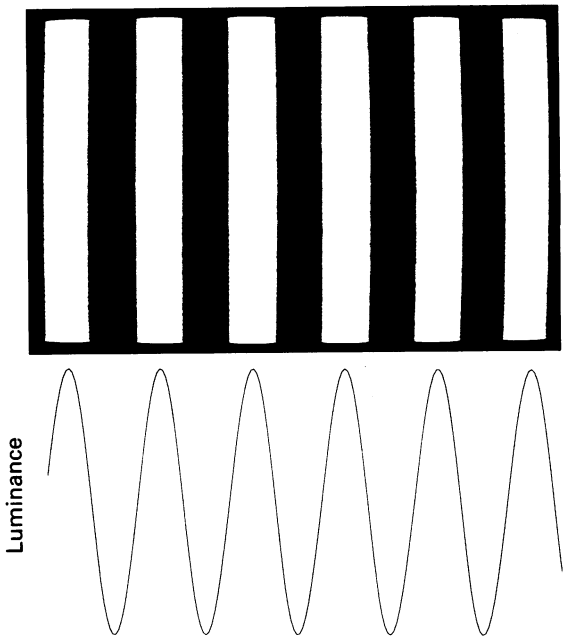

Figure 1 Screen copy of static vertical sinusoidal gratings generated on a microcomputer. The schema under the screen copy shows the sinusoidally modulated luminance. Contrast is defined as: (L max − L min)/(L max + L min) L max: Luminance maximum; L min: Luminance minimum.

detect the direction of motion of the gratings. Contrast threshold measurement was based on a modified version of the Von Bekesy's tracking procedure. At the beginning of the test, the grating's contrast was increased from 0 (uniform field). The subject depressed a button whenever the pattern or direction of movement became visible on the screen, signaling the computer to decrease contrast. The subject then depressed the button when the pattern or movement became invisible, signaling the computer to increase contrast and then depressed the button when the pattern or movement became visible again. Three successive contrast-reversal values were averaged, and this value was taken as the subject's threshold for each experimental trial. Randomization of trial presentation and response recording were performed by the computer. Subjects were extensively trained (four sessions) with this method during the week preceding the study and 15 min of adaptation to the ambiant illumination level was allowed before testing. All tests were performed at the same time of the day since circardian variations of contrast sensitivity have been reported at least in Parkinson patients (Struck *et al.*, 1990).

Calculations and statistical analysis

Contrast sensitivity was defined as the reciprocal of the contrast threshold. The effects of apomorphine administration were evaluated by comparing, for each subject at each combination of spatial and temporal frequency, the contrast sensitivity after treatment (SA) to that before treatment (SB). More specifically, we defined 'sensitivity gain' as 10*log (SA/SB). It will thus be positive (negative) if the sensitivity after treatment is superior (inferior) to that before treatment.

The effects of the studied drugs on sensitivity gain were evaluated using an analysis of variance computing Snedecor F-values (Lellouch & Lazar, 1974). We used linear regression methods to test the relationship between spatial frequencies and sensitivity gain.

Results

All the subjects reported a subjective improvement in visual sensitivity. Three subjects felt apathetic and one of them experienced nausea. Repeated yawns were observed in five subjects during apomorphine treatment (5 μg kg^{-1}).

Before treatment, STCS remained stable across the three sessions for all subjects. No significant variation in contrast sensitivity was observed between sessions ($F[1,16] = 0.79$; $P > 0.10$).

Following treatment, contrast sensitivity was modified, and differentially so by the three treatments (placebo, apomorphine 1 μg kg^{-1}, apomorphine 5 μg kg^{-1}) ($F[2,16] = 9.34$, $P < 0.005$) (Figure 2). *Post-hoc* analysis

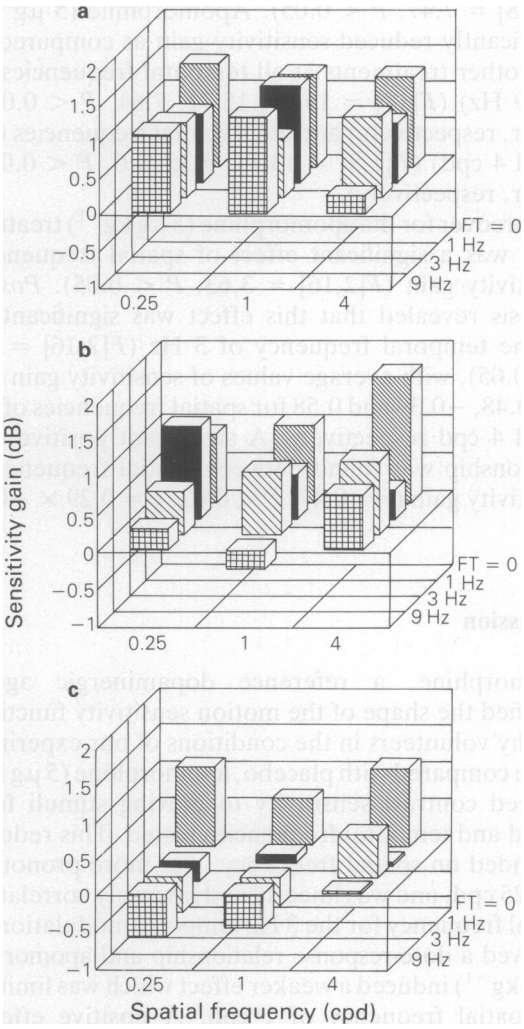

Figure 2 Sensitivity gain for placebo (Figure 2a), apomorphine 1 μg kg^{-1} (Figure 2b), apomorphine 5 μg kg^{-1} (Figure 2c), as a function of spatial frequency (in cycles per degree) and temporal frequency (in hertz) in nine healthy volunteers.

Sensitivity gain is expressed as 10*log(SA/SB) where SA is Contrast sensitivity after treatment and SB is Contrast sensitivity before treatment.

Sensitivity gain is positive (negative) if the sensitivity after treatment is superior (inferior) to that or before treatment.

revealed no differential effect of the treatments on sensitivity gain (the ratio between contrast sensitivity after and before treatment) for static contrast sensitivity (F [2,16] = 0.41, $P > 0.20$). However, with drifting gratings, the sensitivity gain was different for the three treatments (F [2,16] = 17.32, $P < 0.001$)).

Partial comparisons revealed that sensitivity gain was significantly lower with apomorphine 1 μg kg^{-1} as compared with placebo (F [1,8] = 6.89, $P < 0.05$), and that apomorphine 5 μg kg^{-1}, led to significantly reduced sensitivity gain as compared with apomorphine 1 μg kg^{-1} (F [1,8] = 15.84, $P < 0.005$). The average values of sensitivity gain were equal to 0.89, 0.60 and −0.17 for placebo, apomorphine 1 μg kg^{-1} and apomorphine 5 μg kg^{-1}, respectively. Placebo induced an increase in contrast sensitivity. This effect was weaker with apomorphine 1 μg kg^{-1}. Apomorphine 5 μg kg^{-1} markedly reduced contrast sensitivity (Figure 2).

Post hoc analysis revealed that apomorphine (1 μg kg^{-1}) significantly reduced sensitivity gain as compared with placebo only for the spatial frequency of 1 cpd (F[1,8] = 7.47, $P < 0.05$). Apomorphine (5 μg kg^{-1}) significantly reduced sensitivity gain as compared with both other treatments at all temporal frequencies (1, 3 and 9 Hz) (F[18] = 15.09, 15.71, 7.64, $P < 0.025$ or better, respectively) and at all spatial frequencies (0.25, 1 and 4 cpd) (F[1,8] = 13.14, 9.36, 9.0, $P < 0.025$ or better, respectively).

Moreover for the apomorphine (5 μg kg^{-1}) treatment, there was a significant effect of spatial frequency on sensitivity gain (F[2,16] = 3.63, $P < 0.05$). *Post hoc* analysis revealed that this effect was significant only for the temporal frequency of 3 Hz (F[2,16] = 4.25, $P < 0.05$), with average values of sensitivity gain equal to −0.48, −0.39 and 0.58 for spatial frequencies of 0.25, 1 and 4 cpd respectively. A significant positive linear relationship was found between spatial frequency and sensitivity gain ($r = 0.47$, $P < 0.02$, $y = 0.29 \times -0.61$).

Discussion

Apomorphine, a reference dopaminergic agonist, modified the shape of the motion sensitivity function in healthy volunteers in the conditions of our experiment. When compared with placebo, apomorphine (5 μg kg^{-1}) reduced contrast sensitivity to moving stimuli for all spatial and temporal frequencies tested. This reduction depended on spatial frequency, was more pronounced on 0.25 cpd, and was linearly and inversely correlated to spatial frequency for the 3 Hz temporal modulation. We observed a dose-response relationship and apomorphine (1 μg kg^{-1}) induced a weaker effect which was limited to the spatial frequency of 1 cpd. A positive effect of placebo on contrast sensitivity was observed and might be related to test-retest condition although the subjects were well trained and STCS stability was observed before treatment.

The observed effects of apomorphine in our experiment conform to previous results concerning inferred dopamine effects on spatio-temporal contrast sensitivity. First, no significant effect of apomorphine was observed on static sensitivity, when compared with placebo. In fact, in Parkinson's disease, motion sensitivity is impaired (compared to elderly controls) whereas static sensitivity remains normal (Bodis-Wollner *et al.*, 1987; Mestre *et al.*, 1990a). Secondly, the observed effects depend on the spatial frequencies and are predominant for low spatial frequencies. In Parkinson patients with ON-OFF syndromes (the ON and OFF states represent 'high' *vs* 'low' dopaminergic activity in parkinsonians who are undergoing treatment (Marsden, 1980)), Bodis-Wollner (1987) noted that contrast sensitivity decreased preferentially at 0.25 cpd and 1 Hz in the ON (compared with OFF) state. On the contrary, for 4 cpd and 1 Hz, there was an increase in contrast sensitivity in the ON (compared with OFF) state. In the same manner, Domenici *et al.* (1985) noted that administration of nomifensine in healthy volunteers reduced contrast sensitivity from 0.66 to 2 cpd and enhanced contrast sensitivity in a limited range of spatial frequencies (from 4 to 18 cpd).

These effects may be understood as a rightward horizontal shift of the contrast sensitivity curve, inducing a decrease in spatio-temporal contrast sensitivity at lower spatial frequencies and an increase at higher spatial frequencies. In the same manner, a vertical shift may be suggested: downward during a severe dopaminergic deficiency as observed in Parkinson's disease (overall sensitivity is decreased) (Bodis-Wollner *et al.*, 1987) or under neuroleptics in some patients (Bulens *et al.*, 1989); upward during a high dopaminergic stimulation as realized by high doses of apomorphine (Mestre *et al.*, 1990b) or levodopa (Domenici *et al.*, 1985) in healthy volunteers.

In the mammalian retina including human retina (Stormann *et al.*, 1989), dopamine is known as a neurotransmitter/neuromodulator acting through presynaptic D_2 and/or post-synaptic D_1- and D_2-dopaminergic receptors (Brann & Young, 1986; Dubucovich & Weiner, 1985; Watling & Iversen, 1981) or via a local hormone-like mechanism (Piccolino & Demontis, 1988). Dopaminergic drugs have an overall modulatory action on the activity of ganglion cells. In the rabbit, D_1-receptor antagonists (SCH 23390) affect the centre-surround balance of ganglion cells. D_2-receptor agonists (LY 141865) generally have similar effects to those of D_1-receptor antagonists whereas D_2-receptor antagonists (sulpiride) to tend to have opposite effects (Jensen & Daw, 1986; Thier & Alder, 1984). A possible explanation of the observed effects in our study is that apomorphine increases the surround inhibition of the receptive-fields of the ganglion cells, in the same manner as dopamine (Daw *et al.*, 1989). This modification of the centre-surround balance may explain the decrease in contrast sensitivity for low spatial frequencies and its improvement for high spatial frequencies (Enroth-Cugell & Robson, 1966). Our results are compatible with a dopaminomimetic effect of apomorphine possibly mediated via D_1-receptors. However, we cannot exclude either the involvement of D_2-receptors located post-synaptically on photoreceptor cells (Brann & Young, 1986) whose stimulation results in photoreceptors movement and metabolism and whose stimulation may produce a variety of light adaptative retina responses (Dearry & Burnside, 1988), nor a cooperation between D_1- and D_2-receptors (Hadjiconstantinou, 1990). Clinical investigations using selective D_1- and D_2-receptor

agonists and antagonists may help understand the function of dopaminergic systems involved in human visual perception.

There is conflicting evidence for retinal (Bulens *et al.*, 1986) *vs* cortical (Regan & Maxner, 1987) dopaminergic system involvement in primates pattern vision. Nonetheless, activity of retinal dopaminergic neurons could also be modulated by extraretinal mechanisms (Stell, 1972). Thus, rather than a specific retinal or cortical involvement, an overall neurotransmitter/neuromodulatory effect of dopamine along visual pathways may be suggested. At least two parallel processing retinocortical pathways of visual information. exist: the so-called parvocellular and magnocellular pathways (for a review see Shapley, 1990). The specific effects of apomorphine on low spatial frequencies and motion sensitivity support the hypothesis that apomorphine preferentially affects the magnocellular pathway which mediates sensitivity to coarse low contrast temporally modulated patterns (Livingstone & Hubel, 1987) and is principally involved in the low luminance condition (Purpura *et al.*, 1988) and spatial frequency range used in our study. However, no direct evidence is available, (Regan, 1988).

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