The Effect of Apomorphine, MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine) and Placebo on Smooth Pursuit Gain and Corrective Saccades in Normal Subjects

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The effects of apomorphine (0.01 mg/kg SC) a direct-acting dopamine (DA) agonist, MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine) (20 mg PO), a direct-acting serotonin (5-HT) agonist, and placebo on smooth pursuit eye movements were evaluated in 10 to 12 normal volunteers. Smooth pursuit was tested just prior to administration of either apomorphine, MK-212, or placebo (on separate days), and then repeatedly tested at 30 min intervals for two hours after dose administration. The smooth pursuit targets were a series of predictable, constant velocity ramps with velocities of 5°/sec (slow target) and 20°/sec (fast target). Eye movements were recorded with infrared oculography, and the following six measures were obtained; steady-state gain (slow-target-gain; fast-target-gain), corrective catch-up saccade (CUS) rate (slow-target-CUS-rate; fast-target-CUS-rate), and CUS amplitude (slow-target-CUS-amplitude; fast-target-CUS-amplitude). The placebo test yielded a statistically significant monotonic decrease over time in slow-target-gain and corresponding increase in slow-target-CUS-rate, but no effects of placebo were noted for the fast target. Apomorphine injection produced a marked reduction in both slow-target-gain and fast-target-gain at 30 min, returning to baseline thereafter. Apomorphine injection also produced a statistically significant increase in slow-target-CUS-amplitude. Ingestion of MK-212 produced a statistically significant increase in slow-target-gain and fast-target-gain as well as a corresponding decrease in slow-target-CUS-rate and fast-target-CUS-rate at 90 min or 120 min. There was evidence that the decline in slow-target-gain after apomorphine was associated with side-effects such as sleepiness, but the decline in fast-target-gain was not related to side-effects. The improved smooth pursuit performance after MK-212 was not related to side-effects. The data suggest that serotoninergic stimulation can improve smooth pursuit performance, whereas dopaminergic stimulation worsens this performance. ***[Neuropsychopharmacology 11:49–62, 1994]***

KEY WORDS: *Smooth pursuit; Gain; Serotonin; Dopamine; Apomorphine; MK-212; Normal volunteers*

Although abnormal smooth pursuit eye-tracking is well documented in schizophrenia (Clementz and Sweeney 1990; Abel et al. 1992; Levy et al. 1993), there are few studies addressing the possible neurochemical underpinning of this deficit. Two neurotransmitters that have been implicated in the pathophysiology of schizophrenia are dopamine (DA) and serotonin (5-HT) (Meltzer and Stahl 1976; Meltzer 1989; Davis et al. 1991). Although some studies have attempted to relate eye movement dysfunction to neurochemical mechanisms of schizophrenia (see discussion), few studies have used direct-acting agonists, or addressed the role of 5-HT.

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Neuroleptic drugs share in common the ability to block D_2 DA receptors at clinically effective doses (Wiesel et al. 1990); thus, any effect produced by this chemically diverse class of drugs might indicate the existence of a tonic direct or indirect D_2 DA receptor-mediated influence on eye-tracking. The effect of chronic treatment with neuroleptic drugs on eye-tracking in patients with schizophrenia has been recently reviewed (Levy et al. 1983; Lipton et al. 1983; Abel and Hertle 1988; Spohn et al. 1988). No effect of typical neuroleptics has been documented. These results indicate that smooth pursuit eye-tracking in patients with schizophrenia is not sensitive to diminished D_2 receptor stimulation. This does not eliminate the possibility that smooth pursuit is modulated by dopaminergic stimulation in normal subjects, or that enhanced dopaminergic activity may affect smooth pursuit. To our knowledge there are no published studies of the acute effects of neuroleptics or dopamine agonists on specific quantitative smooth pursuit measures in healthy normal subjects, or schizophrenic patients.[1] Thus, firm documentation of the absence of an effect of D_2 DA receptor blockade, or stimulation on smooth pursuit performance is lacking.

Evaluation of the potential role of neurotransmitters in smooth pursuit by administering direct-acting agonists has considerable potential to clarify the regulation of this important function. Apomorphine is a mixed D_1 and D_2 direct-acting DA agonist (Schechter and Greer 1987) that can stimulate both DA autoreceptors and postsynaptic receptors (Cooper et al. 1991). Low doses are thought to preferentially stimulate autoreceptors (Meltzer 1981), because these receptors are more sensitive to agonists (Cooper et al. 1991). Autoreceptor stimulation leads to a decrease in DA neuronal firing, synthesis, and release (Meltzer 1982; Goldstein et al. 1990). At higher doses, postsynaptic responses should predominate (Cooper et al. 1991).

The role of 5-HT in smooth pursuit performance can also be addressed with a direct-acting agonist such as MK-212 (6-chloro-2[1-piperazinyl]-pyrazine). This compound is an arylpiperazine that has the behavioral and chemical effects of a direct-acting 5-HT agonist (Clineschmidt et al. 1977; Clineschmidt 1979). Most of the evidence suggests that MK-212 acts via the 5-HT_{2A} and 5-HT_{2C} receptors, but there is evidence linking MK-212 to 5-HT_{1A} and 5-HT_{2B} receptors. It has affinity for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} binding sites (Hoyer 1988; Roth et al. 1992); however, MK-212 has 25-fold greater affinity for the clonal 5-HT_{2C} than the 5-HT_{2A} receptor (Roth et al. 1992; Choudhary et al. 1993). Also, some endocrine effects of MK-212 in rodents have been suggested to be mediated by 5-HT_{2C} receptor stimulation (King et al. 1989). Furthermore, some effects of MK-212 (e.g., reinforcement of fixed interval responding, are blocked by ketanserin, a 5-$HT_{2A/2C}$ antagonist) (Mansbach and Barrett 1986). However, there is evidence that MK-212 may interact with the 5-HT_{1A} receptor. Thus, MK-212 markedly inhibits the firing of raphe neurons (Yarbrough et al. 1984), an effect it shares with 5-HT_{1A} agonists. The effects of MK-212 in man may be mediated by stimulation of 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C} receptors. Thus, the prolactin-stimulating effects of MK-212 in man are blocked by pindolol, a beta-adrenergic antagonist with selective 5-HT_{1A} antagonist activity (Meltzer et al., unpublished data) and are also blocked by clozapine, a 5-HT_{2A}/5-HT_{2C} antagonist (Roth et al. 1992). Finally, the 5-HT_{2B} receptor is implicated by a study demonstrating that MK-212 causes a dose-dependent contraction of rat fundus strips (Clineschmidt et al. 1985).

A proper evaluation of the neurotransmitter regulation of smooth pursuit also requires a sophisticated analysis of smooth pursuit performance. Because the function of the smooth pursuit system is to match eye-velocity to target-velocity, the ratio of eye-velocity to target-velocity, (i.e. gain), is the key smooth pursuit measure. Perfect performance yields a gain of 1.0, whereas subjects who track more slowly than the target have gains less than 1.0. Gain is inversely related to target velocity and generally increases with target predictability (Levin et al. 1988). When gain is less than 1.0, position error accumulates, because the eye falls behind the target. This position error is typically corrected with a small CUS in the direction of the target. The nonlinear relationship between gain, CUS amplitude, and CUS rate has been modeled by Friedman et al. (1991).[2]

The purpose of the present study was to test the effect of apomorphine and MK-212 on smooth pursuit gain, CUS rate, and CUS amplitude in normal volunteers.

[1] There are two published reports on the acute effects of neuroleptics on eye-tracking performance, but the eye movement analysis methods employed in these two studies were crude and difficult to relate to current findings. Holzman et al. (1975) reported on the qualitative effects ("normal" versus "deviant" tracking) and quantitative effects ("velocity arrests") of acute administration of chlorpromazine (0.67 or 1.33 mg/kg p.o.) on electro-oculogram (EOG) recordings of pendulum tracking, and noted no deviant recordings, and no increase in velocity arrests resulting from drug administration. Ando et al. (1986) reported that haloperidol, in a range of doses starting from 0.004–0.032 mg/kg (i.m.) produced ". . . disruptions in smooth pursuit (that) were characterized by eye fixation accompanied by some saccadic movements" (pp 697–698).

[2] The relationship is described by the equation $G = 1 - ((AR)/V_t)$, where G = gain, A = CUS amplitude, R = CUS rate and V_t = target velocity.

MATERIALS AND METHODS

Subjects

Twelve normal volunteers (10 male and two female) were recruited by advertisement. They underwent a physical and neurological examination, as well as a number of standard laboratory tests to screen for medical illness. Also, subjects with a past psychiatric history or a psychiatric history in first-degree relatives were excluded. The subjects were not taking any psychoactive medications at the time of the study, and had been free of all medication for at least one week before the study. The mean age was 27.5 years ± 5.9 years SD. All subjects provided informed consent.

Experimental Procedure

All subjects underwent all drug conditions (placebo, apomorphine, MK-212). Each drug was administered on a separate day, with a minimum of 48 hours between studies. For each test day, the subjects fasted from 12:00 A.M. and through the morning study. They reported to the eye-tracking laboratory at 9:00 A.M. The baseline eye-tracking recording was initiated after completion of visual acuity and ocular dominance tests, and a series of questions regarding the subject's ophthalmologic history. The subjects then received one of the following: (1) an injection of apomorphine (0.01 mg/kg SC) and a placebo tablet, (2) a placebo injection and a tablet of MK-212 (20 mg), or (3) a placebo injection and a placebo tablet. The drug to be given on a particular day was chosen randomly until each subject had been tested three times, once under each of the three drug conditions. Both the subject and the eye-tracking personnel were blind to the drug administered on a given day. The eye-tracking test was repeated every 30 min for 2 hrs.

Pharmacokinetics

The pharmacokinetics of apomorphine (bolus SC injection) in humans have been described by Gancher et al. (1989). According to them, apomorphine is rapidly absorbed following subcutaneous injection, with peak plasma concentrations occurring 3 min following administration. Apomorphine rapidly equilibrates between blood and brain due to its high lipid solubility. Concentrations are up to eight times higher in brain than plasma. Antiparkinsonian effects of apomorphine are observed within 7 min and last for up to 1 hr following injection (Gancher et al. 1989; Truelle et al. 1975).

Peak plasma levels were noted 2 hours after a single oral dose of MK-212 in man (Merck Sharpe and Dohme Pharmaceuticals Inc., personal communication). No pharmacokinetic studies or detailed metabolic studies of MK-212 in man have been published; however, the time course of central effects of MK-212 have been reported. The stimulating effects of MK-212 on serum cortisol and prolactin peaked between 90 min and 120 min (Lowy and Meltzer 1988). The temperature elevating effects of MK-212 peaked at 118 min (Lee et al. 1992).

Smooth Pursuit Stimulus

For ten of the twelve subjects, the tracking target was a red He/Ne laser reflected off a computer-controlled mirror galvanometer, and projected on a 5-ft radius arc located 5-ft from the eyelid of the subject's dominant eye. Subjects were seated and the head was held firmly in place in a headrest by chin and forehead straps. The galvanometer received its input from an amplifier-controller unit. The input to the galvanometer controller was an analog signal generated by a D/A converter in an IBM PC-type computer. The first target waveform was a set of 10 constant velocity (5°/sec) horizontal ramps (five ramps to the left and five to the right) with an excursion of ±15°. There was a 2.5 second pause between each ramp. The second waveform presented was identical to the first, except for velocity that was 20°/sec. For the first two subjects (subjects GU and MP), the target was a bright spot on a monitor, and only a 5°/sec velocity with ±10° excursion was presented, as described by Friedman et al. (1991). The monitor and laser stimuli were identical in all remaining respects.

As described previously, two subjects were not tested at the 20°/sec target speed. An additional subject failed to complete the 20°/sec recording session under the apomorphine condition. Thus $n = 12$ for all conditions at 5°/sec, $n = 10$ for placebo and MK-212 conditions at 20°/sec, and $n = 9$ for the apomorphine condition at 20°/sec.

Eye Movement Recording

The recording and analysis methods have been described in detail (Friedman et al. 1991; Friedman et al. 1992a; Friedman et al., 1992b). In brief, eye movements were recorded monocularly from the dominant eye with infrared oculography. The signal conditioning unit was operated in the filter-out position. The output was led to a 50-Hz notch filter and 5-pole Butterworth low pass filter at 125 Hz (3 dB). Target and eye position signals were digitally sampled at 400 samples per sec per channel (12 bit resolution) and stored on disk for offline analysis. Eye-velocity was obtained digitally, using the computational method of Usui and Amidror (1982) with parameters n = 1.5, L = 0.5 (bandwidth DC-52.5 Hz).

Eye Movement Analysis

All eye movement records were scored blind to drug condition.

To prevent the possible contamination of our pursuit measures by blinks, these events were marked interactively. Eye movement data from 150 msec before to 500 msec after each blink were omitted from the analysis. With infrared oculography, blinks appear as sharp, fast, bipolar waves or spikes.

Smooth pursuit recordings typically consist of straight-line segments interrupted by saccades. The start and end of these straight line smooth pursuit segments, between saccades, were marked interactively. To compute segment gain, a regression line (least squares) for the eye position data was computed, and the slope of this line was divided by the slope of the target position trace. The average gain was computed after removal of segments with pursuit gain with outlying or extreme gain values. Outliers were 1.5 times the interquartile range above the 75th percentile or below the 25th percentile (Norusis 1988). Gain averaged over time was calculated for each subject. For this, the sum of the product of gain and duration for each segment was divided by the summed durations of all segments (Friedman et al. 1991). The interrater reliability of this method of scoring gain, as assessed by the intraclass correlation coefficient, was 0.89 (Friedman et al. 1992b).

The detection and measurement of corrective catch-up saccade (CUS) was a multi-step process. Because by definition, saccades cannot occur during pursuit segments, the interval between consecutive segments was displayed, and the operator indicated if a CUS occurred. Because CUS compensate for the position error that accumulates during smooth pursuit, a CUS must have been preceded and followed by segments during which the subject was near the target, and the gain was clearly greater than 0. CUS must always be in the direction of target movement. After CUS detection, the beginning and ending points of a CUS were determined automatically according to the following algorithm: (1) scan the intersegment interval for the point of peak velocity; (2) find the starting point by moving backwards in time from the point of peak velocity to the first point at which the eye velocity was at or below the target velocity; and, (3) find the ending point by moving forward in time from the point of peak velocity to the first point at which the eye velocity was at or below target velocity. The difference between eye position at these two points was taken as a measure of saccade amplitude in degrees of visual angle. The number of CUS was divided by the tracking time to yield a measure of rate (CUS / sec).

Subjective Ratings of Side-Effects

Subjective ratings of side-effects were made after each eye movement measurement. The Stanford Sleepiness Scale (Hoddes et al. 1973) was used to assess sleepiness. It is a seven-point scale with descriptive anchors. Increasing scores are associated with increasing feelings of sleepiness. In addition, nausea, dizziness, restlessness, strangeness, and irritability were also rated with 11 point scales, with 0 indicating "not at all," and 10 indicating "very much."

Statistical Analysis

Nonparametric statistical tests were employed throughout, because much of the data was nonnormally distributed. Also, these tests are generally more conservative, and may be more appropriate with modest sample sizes. For each drug (placebo, apomorphine, MK-212), the drug effect was first tested with a Friedman Two-Way ANOVA by Ranks (Friedman test). This test can be thought of as a nonparametric repeated-measures ANOVA (Siegel and Castellan 1988). The test statistic is denoted F_r. Following a significant F_r, post-hoc comparisons between any postdrug time point (T30–T120) and the predrug baseline (T0) were performed using a procedure that controlled for such multiple, nonindependent comparisons (Siegel and Castellan 1988). In several cases, the time response appeared to be either a monotonic increase or decrease. In such cases, the monotonic trend was tested with the nonparametric Page Test for Ordered Alternatives ("Page Test") (Siegal and Castellan 1988). To assess the strength of association or effect size of a significant result, η^2 (eta-squared) was computed with parametric techniques (Tabachnick and Fidell 1989). This measure can be conceptualized as the proportion of the variance in a dependent variable that is accounted for by a particular effect. As a further check on the result, Wilcoxon Signed Rank Tests were computed comparing ondrug data to placebo data for each time point for each smooth pursuit measure.

The effect of the drugs or placebo on side-effects was tested with a Wilcoxon Signed Rank Test. Correlation analyses employed Spearman rank-order correlation coefficients (r_s). All p-values are two-tailed.

RESULTS

The Effects of Placebo on Smooth Pursuit Measures

The Friedman tests of the effect of placebo on the six smooth pursuit measures were all nonsignificant (Figures 1a, 1d, 2a, 2d, 3a, and 3d). However, there was a statistically significant monotonic decrease in slow-target-gain (Page test $p < .05$, Figure 1a, η^2 for the linear trend = 0.28) and a statistically significant monotonic increase in slow-target-CUS-rate (Page test $p < .05$, Figure 2a, η^2 for the linear trend = 0.23).

Individual slow-target-gain scores for each subject at baseline and at the time of peak effect of placebo (T120) are listed in Table 1. Two hours after placebo,

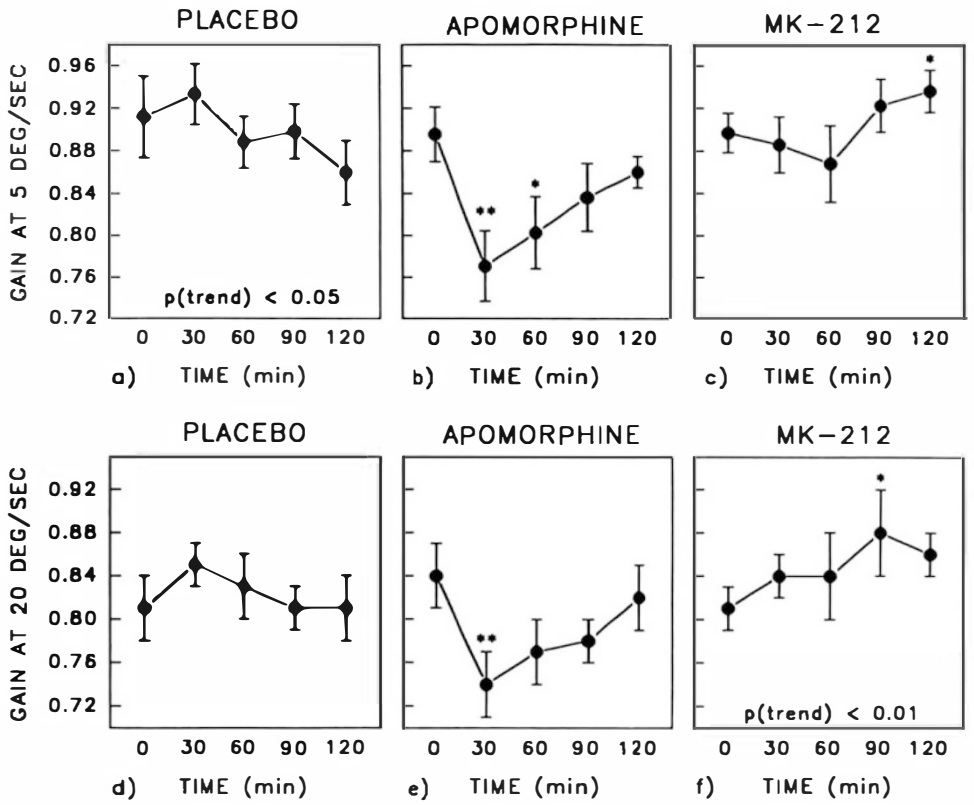

Figure 1. Effect of placebo, apomorphine or MK-212 on smooth pursuit gain. The data are plotted as mean ± standard error of the mean. Drugs or placebo were given after T0. (**a**) For placebo at 5°/sec, there was a statistically significant monotonic decrease in gain over time ($p < .05$), but there were no significant differences between any time points. (**b**) For apomorphine at 5°/sec, note the sharp decline in gain 30 min after injection. Gain was significantly reduced at T30 ($^{**}p < .01$) and T60 ($^{*}p < .05$) compared to baseline (T0). (**c**) After MK-212, gain was significantly elevated above baseline (T0) at T120 ($^{*}p < .05$). (**d**) For placebo at 20°/sec, there was a small initial rise in gain followed by an even more gradual decrease, but no significant differences between any time points was found. (**e**) For apomorphine at 20°/sec, note the same sharp decline in gain at 30 min post-injection. As with the slower target, gain was significantly reduced at T30 compared to baseline ($^{**}p < .01$). (**f**) For MK-212 at 20°/sec, there was a statistically significant monotonic increase in gain ($p < .01$). The peak gain at T90 was significantly higher ($^{*}p < .05$) than at baseline (T0).

slow-target-gain was reduced in eight of the twelve subjects.

The Effects of Apomorphine on Smooth Pursuit Measures

Apomorphine injection was followed by statistically significant decreases in both slow-target-gain (F_r = 14.68, p = .005, Figure 1b) and fast-target-gain (F_r = 17.60, p = .002, Figure 1e), as well as a statistically significant increase in slow-target-CUS-amplitude (F_r = 12.78, p = .01, Figure 3b). These effects of apomorphine were statistically significant at 30 min postinjection (all $p < .01$, η^2 for the decrease in slow-target-gain = 0.74, η^2 for the decrease in fast-target-gain = 0.64, η^2 for the increase in slow-target-CUS-amplitude = 0.47), and one effect (the decrease in slow-target-gain) was still significant at 60 min postinjection ($p < .05$). Thereafter, smooth pursuit performance gradually returned to baseline (predrug) levels. Although apomorphine appeared to cause a marked increase in slow-target-CUS-rate and fast-target-CUS-rate (Figures 2b and 2e), there changes were only trends (p = .08, 0.11, respectively).

Individual gain scores for each subject at baseline and at the time of peak effect for apomorphine (T30 for both speeds) are listed in Table 1. After apomorphine, slow-target-gain declined in all twelve subjects, and fast-target-gain declined in eight of nine subjects.

The Effects of MK-212 on Smooth Pursuit Measures

MK-212 ingestion was followed by statistically significant increases in both slow-target-gain (F_r = 11.07, p = .03, Figure 1c) and fast-target-gain (F_r = 9.84, p = .043, Figure 1f), as well as a statistically significant decrease in fast-target-CUS-rate (F_r = 14.00, p = .007, Figure 2f). The effect of MK-212 ingestion was delayed compared to apomorphine injection, occurring either at 90

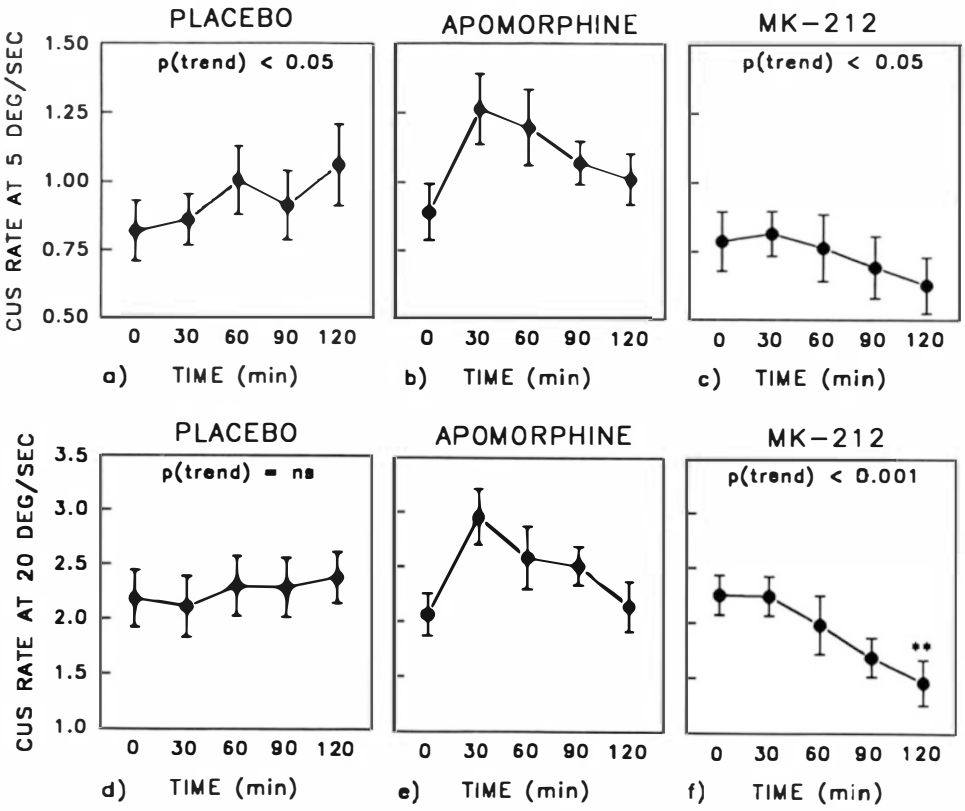

Figure 2. Effect of placebo, apomorphine, or MK-212 on CUS rate. The data are plotted as mean ± standard error of the mean. Drugs or placebo were given after T0. (**a**) For placebo at 5°/sec, there was a statistically significant monotonic increase in CUS rate over time ($p < .05$), but there were no significant differences between any time points. (**b**) For apomorphine at 5°/sec, there was an increase in mean CUS rate 30 min after injection, but it was not statistically significant. (**c**) After MK-212, there was a statistically significant monotonic decrease in CUS rate ($p < .05$). (**d**) For placebo at 20°/sec, there was a weak non significant trent toward increasing CUS rate, and no significant differences between any time points were found. (**e**) for apomorphine at 20°/sec, the mean increase in CUS rate 30 min post injection was not statistically significant. (**f**) For MK-212 at 20°/sec, there was a highly significant monotonic decrease in CUS rate ($p < .001$). The T120 time point was significantly lower than baseline ($p < .01$).

(Figure 1f) or 120 min (Figures 1c and 2f) postingestion. Page tests revealed a statistically significant monotonic increase in fast-target-gain ($p < .01$, $\eta^2 = 0.38$, Figure 1f) as well as statistically significant decreases in slow-target-CUS-rate ($p < .05$, η^2
target-CUS-rate ($p < .001$, $\eta^2 = 0.80$, Figure 2f). MK-212 did not significantly affect CUS amplitude (Figures 2b and 2e).

Individual gain scores for each subject at baseline and at the time of peak effect for MK-212 (T120 for the slow target, T90 for the fast target) are listed in Table 1. After MK-212, gain increased in ten of twelve subjects at 5°/sec, and in eight of ten subjects at 20°/sec.

Drug versus Placebo Comparisons

Table 2 lists the significance values for a series of Wilcoxon Signed Rank tests comparing apomorphine or MK-212 with placebo at each time point. These results essentially confirm the findings of the within-drug comparisons described above. Apomorphine was associated with an early, marked reduction in gain, and an increase in CUS rate, and amplitude at both target speeds. MK-212 was associated with an increase in slow-target-gain, and a decrease in slow-target-CUS-rate and fast-target-CUS-rate at T120.

Correlations between Drug-Induced Changes in Gain and Baseline Gain

The decline (T120–T0) in slow-target-gain after placebo at time of peak effect (T120) was correlated with the baseline slow-target-gain ($r_s = -0.66$, $p = .02$). The preapomorphine baseline gain was not correlated with the change in gain at T30 (the time of peak effect) after apomorphine at either target speed. Similarly, there was no correlation between pre-MK-212 baseline gain and the peak change in gain after MK-212 $(T120)^3$ at either target speed.

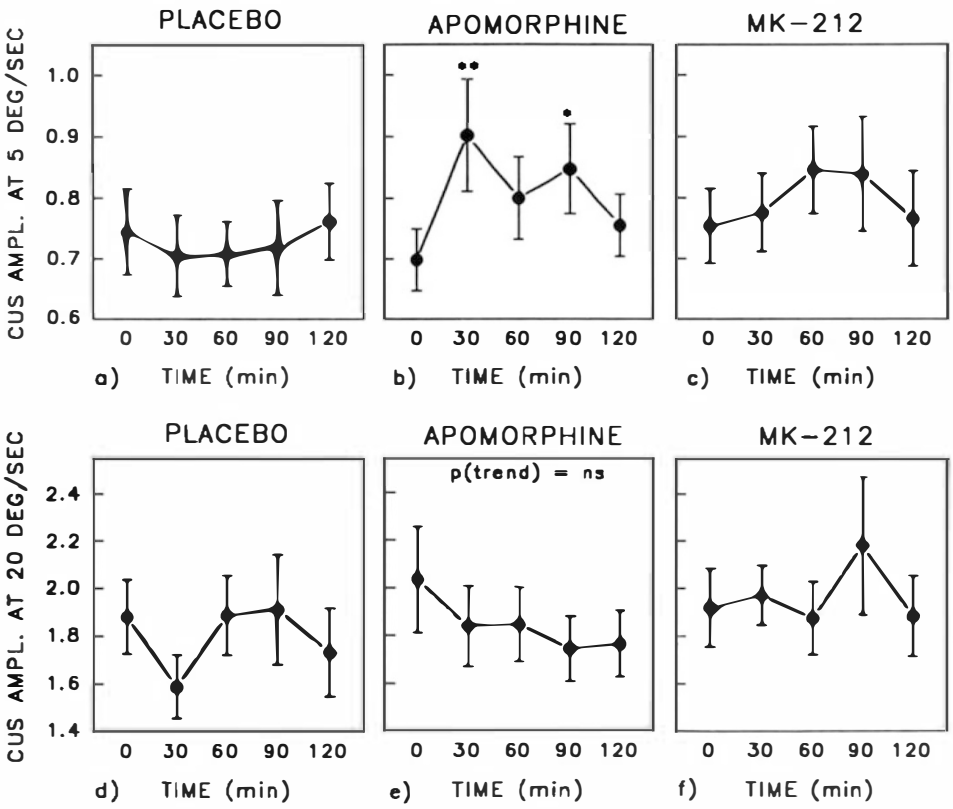

Figure 3. Effect of placebo, apomorphine, or MK-212 on CUS amplitude. The data are plotted as mean ± standard error of the mean. Drugs or placebo were given after T0. Significant effects occurred only for apomorphine at 5°/sec (b). In this case, CUS amplitude was significantly elevated at T30 ($p < .01$) and T90 ($p < .05$).

Correlations between Apomorphine-Induced Changes in Gain and MK-212-Induced Changes in Gain

The effect of apomorphine on slow-target-gain at T30 and the effect of MK-212 on slow-target-gain at T120 were correlated as follows: at the slower target speed, the larger the effect (T30–T0) of apomorphine for a particular subject, the smaller the effect (T120–T0) of MK-212 for the same subject ($r_s = 0.67$, $p = .017$). This relationship was not observed for fast-target-gain ($r_s = -0.28$, $p = .46$).

The effect size for apomorphine or MK-212 for subjects GU and MP were intermediate and completely consistent with the group effects (Table 1).

The Effects of Placebo, Apomorphine or MK-212 on Subjective Ratings of Side-Effects

The effects of placebo, apomorphine, or MK-212 on side-effects were tested at the time of peak effect for eye movement measures (T120[3] for placebo and MK-212, and T30 for apomorphine) (Table 3). The Stanford Sleepiness Scale score was the most sensitive of all subjective ratings to the effects of the drugs, or placebo. Thus, at the time of peak effect of placebo and apomorphine, subjects were significantly more sleepy (Table 3). Also, at the time of peak effect of MK-212 there was a trend toward increased sleepiness (Table 3). None of the other side-effect tests (nausea, dizziness, irritability, strangeness) were statistically significant (Table 3).

Correlations between Changes in Smooth Pursuit Gain and Changes in Subjective Ratings of Side-Effects

Correlations were computed relating changes in side-effect measures with change in gain at the time of peak effect (T120 for slow-target-gain after placebo, T30 for slow-target-gain and fast-target-gain after apomorphine, T120 for slow-target-gain, and T90 for fast-target-gain after MK-212) (Table 4). Side-effect data were analyzed only for subjects with complete side-effect data ($n = 9$). After placebo or MK-212, there were no significant correlations between change in smooth pursuit gain at either target speed and change in subjective ratings of any side-effect. After apomorphine, change in slow-target-gain was significantly inversely correlated with change in sleepiness, dizziness, and irritability at T30 (sleepiness: $r_s = -0.84$, $p = .005$; diz-

[3] The time of peak effect of MK-212 on slow-target-gain was T120 whereas the time of peak effect on fast-target-gain was T90. To minimize the number of tests performed, T120 was chosen to evaluate the effect of MK-212 on side-effects. This is supported also by the evidence of a monotonic increase in gain over the entire 120 min period.

Table 1. Effect of Placebo, Apomorphine, or MK-212 on Gain for Each Subject at Time of Maximum Effect, Sorted by Increasing Effect Size

Placebo
5°/sec

Subject	T0	T120	Change
FE	0.817	0.915	+0.098
MK	0.756	0.851	+0.095
WH	0.867	0.935	+0.068
GU	0.664	0.727	+0.063
DI	0.914	0.867	−0.047
AL	0.934	0.874	−0.060
BR	0.944	0.856	−0.088
CB	1.049	0.954	−0.095
JB	1.130	1.024	−0.106
DA	0.969	0.841	−0.128
PE	1.054	0.847	−0.207
YE	0.841	0.621	−0.220

Apomorphine

5°/sec				20°/sec			
Subject	T0	T30	Change	Subject	T0	T30	Change
DI	0.825	0.800	−0.025	CB	0.838	0.851	+0.013
PE	1.023	0.967	−0.056	DI	0.644	0.633	−0.011
YE	0.834	0.771	−0.063	BR	0.915	0.869	−0.046
CB	0.983	0.910	−0.073	FE	0.761	0.692	−0.069
JB	0.962	0.871	−0.091	JB	0.809	0.695	−0.114
MP	0.824	0.726	−0.098	YE	0.856	0.721	−0.135
WH	0.864	0.763	−0.101	PE	0.917	0.760	−0.157
FE	0.940	0.792	−0.148	WH	0.933	0.760	−0.173
GU	0.707	0.551	−0.156	AL	0.904	0.658	−0.246
BR	0.939	0.779	−0.160				
AL	0.956	0.714	−0.242				
DA	0.888	0.602	−0.286				

MK-212

5°/sec				20°/sec			
Subject	T0	T120	Change	Subject	T0	T90	Change
DA	0.933	0.876	−0.057	DA	0.850	0.694	−0.156
AL	0.921	0.891	−0.030	JB	0.826	0.728	−0.098
BR	1.004	1.013	+0.009	CB	0.905	0.939	−0.034
PE	0.956	0.966	+0.010	FE	0.796	0.847	+0.051
JB	0.834	0.848	+0.014	AL	0.725	0.786	+0.061
MP	0.847	0.873	+0.026	PE	0.891	0.959	+0.068
WH	0.895	0.952	+0.057	BR	0.870	0.950	+0.080
GU	0.766	0.839	+0.073	DI	0.720	0.857	+0.137
FE	0.896	0.978	+0.082	YE	0.699	0.884	+0.185
CB	0.934	1.029	+0.095	WH	0.855	1.161	+0.306
YE	0.851	0.946	+0.095				
DI	0.924	1.024	+0.100				

ziness: $r_s = -0.86$, $p = .003$; irritability: $r_s = -0.76$, $p = .018$), but no correlations were significant for fast-target-gain (p-values range from .226 to .743).

DISCUSSION

The major findings of the present study were: (a) that slow-target-gain gradually declined over a 2 hour period after placebo; (b) that slow-target-gain and fast-target-gain declined sharply 30 min after apomorphine injection; (c) that slow-target-gain at 90 min and fast-target-gain at 120 min were increased after MK-212; and (d) that the effects of apomorphine and MK-212 on slow-target-gain were inversely correlated. In general, these changes in gain were accompanied by compensating changes in corrective, CUS rate (placebo and MK-212),

Table 2. Significance (p) Values (Two-Tailed) for Wilcoxon Signed Rank Tests Comparing On-Drug with Placebo

Apomorphine			MK212		
Slow-Target-Gain			**Slow-Target-Gain**		
Time	**Direction of Drug Effect**	**p-Value**	**Time**	**Direction of Drug Effect**	**p-Value**
T0		0.433	T0		0.938
T30	↓	0.002*	T30		0.182
T60	↓	0.023*	T60		0.875
T90		0.060	T90		0.182
T120		0.906	T120	↑	0.028*
Slow-Target-CUS-Rate			**Slow-Target-CUS-Rate**		
T0		0.308	T09		0.480
T30	↑	0.012*	T30		0.347
T60		0.347	T60		0.158
T90		0.272	T90		0.182
T120		0.638	T120	↓	0.034*
Slow-Target-CUS-Amplitude			**Slow-Target-CUS-Amplitude**		
T0		0.286	T0		0.636
T30	↑	0.019*	T30		0.093
T60	↑	0.047*	T60	↑	0.018*
T90		0.066	T90		0.173
T120		0.944	T120		0.919
Fast-Target-Gain			**Fast-Target-Gain**		
T0		0.285	T0		0.879
T30	↓	0.012*	T30		0.314
T60		0.114	T60		0.879
T90		0.333	T90		0.139
T120		0.953	T120		0.169
Fast-Target-CUS-Rate			**Fast-Target-CUS-Rate**		
T0		0.575	T0		0.721
T30	↑	0.047*	T30		0.508
T60		0.241	T60		0.508
T90		0.333	T90		0.093
T120		0.678	T120	↑	0.013*
Fast-Target-CUS-Amplitude			**Fast-Target-CUS-Amplitude**		
T0		0.476	T0		0.767
T30	↑	0.013*	T30	↑	0.015*
T60		0.735	T60		0.919
T90		0.889	T90		0.333
T120		0.678	T120		0.386

* $p < .05$.

or CUS amplitude (apomorphine at 5°/sec). This is the first report of the effects of these agents on smooth pursuit gain and CUS.

The placebo effects were presumably caused by the passage of time and repeated testing, rather than any effect of placebo per se. The gradual decline in slow-target-gain and increase in slow-target-CUS-rate after placebo probably reflects the cumulative effects of fatigue. This is supported by the finding that subjects were significantly sleepier at T120 than at T0 after placebo. Although fatigue is frequently cited as a potential cause of low gain (Leigh and Zee 1991), we are not aware of any previous study that clearly documented this effect. The decline in slow-target-gain was mild in magnitude (from 0.912 to 0.859 over 120 min). It is noteworthy, furthermore, that no decline was observed

Table 3. Significance (p) Values for Tests of the Effects of Placebo, Apomorphine, or MK-212 on Subjective Ratings of Side-Effects: Wilcoxon Signed-ranks Test

Side-Effect	Placebo T120 p-Value	Apomorphine T30 p-Value	MK-212 T120 p-Value
Sleepiness	0.012	0.018	0.068
Nausea	1.0	0.128	0.109
Dizziness	1.0	0.106	0.361
Restlessness	0.178	0.201	0.138
Strange feeling	1.0	0.465	0.361
Irritability	1.0	0.715	0.423

for fast-target-gain. If one accepts the hypothesis that the decline in slow-target-gain is caused by fatigue, the absence of an effect for the fast target suggests that fatigue is less of a factor in tracking a substantially faster target. Other evidence, described below, is consistent with the hypothesis that performance when tracking a fast target is less susceptible to side-effects than when tracking a slow target. The susceptibility of slow-target performance to fatigue may simply reflect that this target is presented for a substantially longer period of time (82 sec) than the fast target (32.5 sec), because the same number of ramps are presented at both speeds. Perhaps the slow target would, therefore, demand greater sustained vigilance than the fast target.

Apomorphine led to a reduction in slow-target-gain and fast-target-gain 30 min postinjection. The reduction was marked and rapid (from .895 to 0.771 in 30 min for slow-target-gain and from 0.844 to 0.751 for fast-target-gain). As mentioned previously, the pharmacokinetic data, as well as studies of motor effects in Parkinson patients, indicate that apomorphine can act within 10 min (Gancher et al. 1989; Truelle et al. 1975). Further study is required to determine if the peak effect of apomorphine on gain occurs before 30 min. The decline in slow-target-gain was associated with a significant increase in corrective CUS amplitude, and there were trends toward increasing CUS rate at both target speeds.

Apomorphine also caused a statistically significant increase in sleepiness at T30, an effect that is well documented (Meltzer 1982). Furthermore, the effect of apomorphine on slow-target-gain was significantly correlated ($r_s = -.84$) with the effect on sleepiness. This pattern of results raises the possibility that the reduction in slow-target-gain after apomorphine was secondary to sedation. A number of compounds with sedating effects have been found to reduce smooth pursuit gain, including barbiturates (Padoan et al. 1992), benzodiazepines (Rothenberg and Selkoe 1981; Bittencourt et al. 1983; Padoan et al. 1992), alcohol (Baloh et al. 1979; Barnes et al. 1984; Tedeschi et al. 1984; Stapleton et al. 1986), nitrous oxide (Magnusson et al. 1989), and methadone (Rothenberg et al. 1980). However, in an acute study of the effects of chlorpromazine on eye movements, Holzman et al. (1975) found no effect on eye-tracking in the presence of a large soporific effect. In the present study, the effect of apomorphine on fast-target-gain was not related to increases in sleepiness ($r_s = -.26$), even though the two gain effects were comparable in magnitude. It is possible that the reduced correlation between increased sleepiness and decreased gain during the fast target resulted from less statistical power (two fewer subjects), or a restriction of the range of gain changes. However, the magnitude of the correlation was much less, suggesting that many more subjects (89 subjects, assuming power = 0.8 and 1-tailed alpha < 0.05) would be required to find a significant relationship (Cohen 1988). Also, the standard deviation of slow-target-gain change (0.078) was actually less than that of fast-target-gain change (0.083), indicating the absence of a "range restriction" limitation. Thus, the present evidence suggests that the effect of apomor-

Table 4. Relationship between Change in Gain and Change in Side-Effects at the Time of Peak Gain Effect

Maximum Change in	After		Spearman Correlation Coefficients					
			Sleepiness	Nausea	Dizziness	Restlessness	Strangeness	Irritability
Slow-target-gain	Placebo	r	0.04	NA	0.27	−0.08	NA	0.18
		p-Value	0.92	NA	0.48	0.84	NA	0.64
Slow-target-gain	Apomorphine	r	−0.84	−0.36	−0.86	−0.52	−0.37	−0.76
		p-Value	0.01	0.34	0.00	0.15	0.33	0.02
Fast-target-gain	Apomorphine	r	−0.26	−0.33	−0.13	0.32	−0.27	−0.45
		p-Value	0.50	0.38	0.74	0.40	0.48	0.23
Slow-target-gain	MK-212	r	−0.37	−0.05	−0.20	−0.44	−0.24	0.18
		p-Value	0.33	0.91	0.61	0.24	0.54	0.64
Fast-target-gain	MK-212	r	−0.09	−0.07	−0.46	−0.18	−0.63	−0.37
		p-Value	0.83	0.85	0.22	0.64	0.07	0.33

NA = A correlation coefficient could not be computed in the absence of variation.

phine on fast-target-gain was not strongly related to the sedative effects of apomorphine. One explanation for this pattern of results is that the effect of apomorphine on gain is not secondary to sedation at either target speed. In further support of this notion, MK-212 also tended to increase sleepiness ($p = .068$), but it was associated with an *increase* in gain. Nonetheless, the sedative effect of apomorphine may well have contributed to the decline in slow-target-gain, especially if performance when tracking the slow target is more susceptible to sedation, as suggested previously. Future studies employing levodopa for DA stimulation should help to clarify the role of sedation, because levodopa is associated with arousal (Bowen et al. 1975; Sassin 1975; Boivin and Montplasir 1991).

If the effect of apomorphine is due to DA stimulation at some point in the neural pathway controlling smooth pursuit, it would be of great interest to determine where this effect is mediated. The presence of several types of DA receptors, including autoreceptors and postsynaptic receptors, complicates the interpretation. In the present study, we employed a standard "subemetic," "nonsedating" dose of apomorphine (0.01 mg/kg, or approximately 0.75 mg/person). Although this dose is frequently referred to as an "autoreceptor dose," the evidence supporting this classification is scarce. Several dose–response studies in animals have documented biphasic effects of apomorphine, and thus provide dosages for presynaptic and postsynaptic effects (Ljungberg and Ungerstedt 1976; Protais et al. 1983; Stahle 1992). However, we are aware of only one dose response study in humans that addressed this issue: Lal et al. (1989) recently reported that doses from 0.0035 to 0.005 mg/kg antagonized yawning, whereas doses above 0.007 stimulated yawning. Lal et al. (1989) concluded that doses above 0.007 mg/kg stimulate postsynaptic receptors. This is consistent with the finding that doses at or above 0.01 mg/kg reduce motor symptoms in Parkinson's disease (Duby et al. 1972; Blin et al. 1990)—an effect that is presumably postsynaptic. On the other hand, evidence for a presynaptic effect was provided by Levy et al. (1984), who reported a decrease in CSF levels of the DA metabolite homovanillic acid (HVA) in patients with schizophrenia, after a 0.75 mg/person dose. Considering that only one study has documented a biphasic response in humans (Lal et al. 1989) and that reported results are not completely consistent, caution precludes a firm conclusion regarding autoreceptor versus postsynaptic receptor stimulation of the dose at this time.

Several studies have evaluated the role of catecholamines in smooth pursuit. Amphetamine increases synaptic DA and norepinephrine (NE) by promoting release and blocking reuptake (Cooper et al. 1991). Most studies have not found an effect of amphetamine on smooth pursuit in normal controls (Tedeschi et al. 1983) or psychiatric patients (Siever et al. 1987; Bylsma and Pivik 1989), although none of these studies measured gain or corrective saccades. Filip et al. (1978) noted an improvement in smooth pursuit after amphetamine in normal volunteers, although the data analysis was idiosyncratic. Ando et al. (1986) found that amphetamine disrupted eye-tracking in a dose-related manner in three monkeys; thus, no clear effect of amphetamine on eye-tracking has been established. Furthermore, Tychsen and Sitaram (1989) reported no effect on smooth pursuit gain in normal controls after alpha-methylparatyrosine, which blocks the synthesis of DA and NE. Also, Siever et al. (1986) found no correlation between CSF levels of the DA metabolites HVA or dihydroxyphenylacetic acid and smooth pursuit. As previously mentioned, chronic neuroleptic treatment does not appear to affect smooth pursuit. These results do not consistently implicate DA in smooth pursuit; however, these studies generally employed nonspecific smooth pursuit measures and indirect manipulations or measures of the DA system.

Several studies have reported low gain in Parkinson's disease (White et al. 1983; Gibson et al. 1987), which is associated with degeneration of the nigrostriatal DA system and marked DA depletion. In one report, clinical improvement with chronic treatment of dopaminergic drugs was associated with an increase in gain (Gibson et al. 1987), although Sharpe et al. (1987) did not find an increase in gain after levodopa treatment in Parkinson's disease patients. This clinical evidence suggests that low DA in the striatum is associated with low gain and is consistent with an apomorphine-induced stimulation of DA autoreceptors on the nigrostriatal DA neurons in the present study; however, neurophysiological experiments have not implicated the nigrostriatal DA system in smooth pursuit function (Sharpe et al. 1989).

Thus, the extant literature does not provide strong support for or against a direct role of the DA system in the control of smooth pursuit; however, the evidence for a role of DA from the present study is based upon the application of a direct-acting agent and state-of-the-art smooth pursuit assessment, accompanied by assessment of subjective side-effects. Clarification of the role of DA in smooth pursuit thus deserves further investigation. Studies in normal subjects using specific, direct-acting agents, and state-of-the-art assessments are likely to provide the most interpretable evidence.

In contrast to the reduction in gain after apomorphine, MK-212 was followed by an elevation of slow-target-gain and fast-target-gain. The effect was delayed compared to the apomorphine effect probably as a result of the difference in the route of administration (PO versus SC). There were also statistically significant monotonic decreases in CUS rate for both target speeds after MK-212. Indeed, the strongest effect of MK-212

on eye movements was the monotonic decrease in fast-target-CUS-rate ($p < .001$). The finding that MK-212 can improve smooth pursuit performance in normal subjects is surprising, especially because we are not aware of any other agent that has this effect. The increases in gain were not large (0.897 to 0.936 for slow-target-gain, and 0.814 to 0.88 for fast-target-gain); however, the statistical analysis employed was conservative, and accounted for multiple, non-independent posthoc comparisons.

The increase in gain after MK-212 was probably unrelated to side-effects. First, there is no obvious a priori connection between improved smooth pursuit performance and side-effects. Also, there was no significant effect of MK-212 on side-effects, although there was a trend toward increased sleepiness. Moreover, at the time of peak effect of MK-212 (T120), there were no statistically significant correlations between changes in side-effects and changes in gain. One correlation approached statistical significance, namely change in feelings of strangeness ($r_s = -0.63$, $p = .067$). It is unlikely that the effect of MK-212 on gain was mediated by feelings of strangeness, however. Perhaps those subjects who felt most strange after MK-212 were more sensitive to the central 5-HT stimulatory effect of this agent, and thus were more sensitive to effects on smooth pursuit gain.

To our knowledge, only one study has evaluated the effect of a 5-HT specific agent on smooth pursuit gain. Stott et al. (1989) studied the effect of ondansetron, a 5-HT_3 antagonist, on smooth pursuit in normal volunteers and found a small, but statistically significant reduction in gain; however, this effect of ondansetron may be related to effects on the DA system, because 5-HT_3 antagonists have been shown to be extremely potent in antagonizing the behavioral consequences of increased mesolimbic DA activity (Costall et al. 1990). This notion assumes that increased mesolimbic DA is associated with increased gain. This would only follow if the gain reduction after apomorphine was mediated by DA autoreceptors, that similarly decrease DA release. The gain-elevating effect of MK-212 may also be related to effects on 5-HT_3 receptors, because MK-212 also interacts with these receptors (Glennon et al. 1989); however, it is premature to speculate which type of 5-HT receptor is stimulated by MK-212. Specific antagonists of 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, or even 5-HT_3 receptors will be needed for clarification.

The effects of 5-HT on the optokinetic slow phase response (that is similar to smooth pursuit) have been studied elegantly in the crab, *Leptograpsus variegatus*, by Erber and Sandeman (1989). They found that systemic and ocular injections of 5-HT increased optokinetic slow phase amplitude—a finding that is analogous to an increase in smooth pursuit gain.

It is of particular interest that the effects of apomorphine and MK-212 on slow-target-gain were inversely correlated. It is well established that serotonin can exert an inhibitory effect on the dopaminergic system (Korsgaard et al. 1985; Nash and Meltzer 1991). As a specific relevant example, MK-212 has been shown to block apomorphine induced hypothermia (Menon and Vivonia 1981); thus, the ability of MK-212 to increase gain may be due to inhibition of a tonic inhibitory effect of DA neurons on gain. The fact that there was a significant correlation despite the obvious contributions of pharmacokinetic variability in absorption, metabolism, and receptor dynamics of these agents, suggests that dopaminergic and serotoninergic mechanisms regulating gain are interconnected, either directly, or via an intermediary.

If confirmed, the present results could lead to the development of a new method to study central serotoninergic and dopaminergic mechanisms in man. Smooth pursuit performance may provide a nonhypothalamically mediated, behaviorally-based measure for acute challenge studies. The effect of apomorphine and/or MK-212, as well as specific D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} agonists on smooth pursuit could provide important new clues regarding receptor sensitivity in clinical populations, and on the effect of psychotropic drug treatment.

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