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Effects of Metoclopramide Hydrochloride, a D_2-Selective Dopamine Receptor Antagonist, on the Fast Oscillation of the Electrooculogram

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Fast oscillation (FO) of an electrooculogram (EOG) was recorded in both eyes of 10 healthy volunteers before and after administration of metoclopramide hydrochloride (MTCL), a D_2-selective dopamine receptor antagonist, paying particular attention to sex concerning sensitivity to dopamine in young subjects. Healthy volunteers were divided into male and female groups; 5 males (10 eyes) aged 21 to 23 years (average, 21.8 years) and 5 females (10 eyes) aged 19 to 25 years (average, 21.8 years). As an FO parameter, the df_{FO} (the averaged difference in μV between maximum amplitude in the dark period and minimum amplitude in the light period during FO measurement) was evaluated. The mean level of df_{FO} significantly increased between phase A (the initial 10 min before intravenous injection of 10 mg of MTCL) and phase B (10 min after the injection) in the male and female groups ($P < 0.01$ and $P < 0.025$) and between phase A and phase C (the additional 10 min after the injection) in both groups ($P < 0.01$ and $P < 0.05$). The mean level of df_{FO} in the female group was significantly higher than that of the male group in phase B ($P < 0.05$). As a control, the experimental procedure was performed with physiological saline administration, and no changes were observed. The data suggest that there exists some difference between young males and females generation concerning sensitivity to dopamine and that young females may show a higher-than-male sensitivity to dopamine in the occurrence of FO potential.

Key words: D_2-selective dopamine receptor antagonist; dopamine; electrooculogram; fast oscillation; metoclopramide hydrochloride

Fast oscillation (FO) of the electrooculogram (EOG) is the rapid initial deflection of opposite polarities occurring at the initial stage of the light and dark periods in the EOG procedure (Kolder and Brecher, 1966; Kolder, 1974). That is, FO shows a peak in the dark adaptation (dark peak) and a trough in the light adaptation (light trough) in response to dark and light periods of approximately 1.1 min each. FO is distinct from ordinary slow oscillation (SO) of the EOG which shows a

Abbreviations: df_{FO}, averaged difference in μV between maximum amplitude in the dark period and minimum amplitude in the light period during FO measurement; EOG, electrooculogram; FO, fast oscillation; MTCL, metoclopramide hydrochloride; SO, slow oscillation

trough in the dark adaptation (dark trough) and a peak in the light adaptation (light peak) in response to dark and light periods of approximately 12.5 min each (Kolder and Brecher, 1966; Kolder, 1974; Welber, 1989).

Concerning the origin and occurrence of FO and SO, Steinberg and others (1983) reported the involvement of the retinal pigment epithelium, mainly its basal membrane in the FO potential, while Arden and others (1962) reported the involvement of the retinal pigment epithelium and photoreceptor complex in the SO potential.

Joseph and Miller (1991) suggested that the downward oscillation of FO might result from a delayed hyperpolarization associated with increased electric resistance of the basal membrane of the retinal pigment epithelium. The delayed hyperpolarization is thought to be caused by a decrease in intracellular chloride, which is linked to the light-induced drop in subretinal potassium concentration (Joseph and Miller, 1991). The upward oscillation of FO is thought to result from a depolarized change associated with decreased electric resistance of the basal membrane of the retinal pigment epithelium. This depolarized condition of the basal membrane may be caused by an increase in intracellular chloride of the retinal pigment epithelium, which is linked to the dark-induced recovery in subretinal potassium concentration (Nikara et al., 1974).

On the other hand, dopamine, a retinal neurotransmitter, has been known to be indispensable for the process of generation and delivery of electric excitement in the ordinary SO potential (Dawis and Niemyer, 1986; Jaffe et al., 1987; Gallemore et al., 1988; Maruiwa et al., 1992). According to the results of an experiment in a report by Maruiwa and others (1992), metoclopramide hydrochloride (MTCL), a D_2-selective dopamine receptor antagonist (Schulze-Delrieu, 1979), which was given intravenously in 5 healthy volunteers aged 23 to 33 years, increased the dark-adapted SO amplitudes transiently and suppressed the light-adapted SO amplitudes.

However, little has been known of the reaction and influence of dopamine on the FO potential. In this report, we have tested the effects of MTCL on FO in 10 healthy volunteers aged 19 to 25 years, paying particular attention to the existence of difference in sex concerning sensitivity to dopamine in young subjects, since Nakao and others (1994) postulated the possibility in their experiment, in which fluctuations in the FO potential obtained from female normal subjects averaging 22.7 years of age were relatively larger than those from normal male subjects averaging 24.3 years of age.

Subjects and Methods

Subjects

In this study, 10 healthy volunteers aged 19 to 25 years with normal, functional eyes (20 eyes), in whom error of refraction did not exceed ± 3 diopters, were tested at the Department of Ophthalmology, Tottori University Hospital. The healthy volunteers were divided into male and female groups; 5 males (10 eyes) aged 21 to 23 years (average, 21.8 years) and 5 females (10 eyes) aged 19 to 25 years (average, 21.8 years).

Before the trial, the purpose of the experiment and the tasks to be performed were fully explained to each volunteer, and written consent was obtained. All procedures conformed to the tenets of the Helsinki Declaration.

Apparatus and methods for FO recording

Using a newly devised automated electrooculograph, a Nidek EOG-2 (Nidek, Gamagori, Japan) (Nakao et al., 1994; Inoue et al., 2003; Tamai et al., 2004), FO was recorded in each subject. The EOG-2 consists of a dome, a personal computer, an index controller, an amplifier, a printer and an EOG pen recorder. Inside the dome is a hemispheric screen with a radius of 300 mm. Four tungsten lamps (115 V, 50 W each) produce a background luminance of 1,270 lux when measured at the location of the subject's eyes. In this study, the background light was periodically

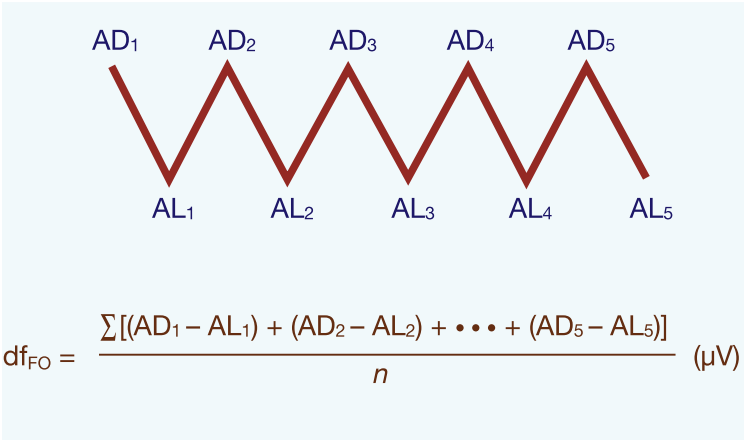

Fig. 1. Calculation method for df_{FO} as an FO parameter in this survey. AD, maximum amplitude in the dark period; AL, minimum amplitude in the light period during FO measurement. *n*, number of pairs (alternating dark-light period of 1 min each), 5 pairs in total. df_{FO} was calculated only if at least 3 successive pairs were observed ($5 \geq n \geq 3$).

turned on and off at intervals of 1 min with the aid of the computer.

For every subject, cup-shaped silver-silver chloride conductive electrodes, 8 mm in diameter, were placed beside both canthi of each eye on the orbital margin, and a grounding electrode with the same cup shape was placed on the left earlobe, as routinely used. Before setting these electrodes, the skin was cleaned with 90% alcohol, and then the electrodes were applied with a conductive paste. Electrode resistance was below 10 kΩ. Under these conditions, simultaneous recording of the FO potentials from each eye of every subject was possible.

Mydriasis can provide better control of retinal illumination. However, FO recording was performed without mydriasis, because mydriasis may increase discomfort in subjects. Before the FO recording, a 10-min pre-light adaptation period at a background luminance level of 1,270 lux was given. Then the subjects were introduced to fixate alternately on a pair of targets on the screen inside the dome. The two targets subtended 40˚ to the visual angle were presented alternately with a frequency of 0.5 Hz.

After this adaptation period, the dome was periodically illuminated for 1 min followed by 1 min of darkness for 30 min. The FO potentials showed peaks in darkness and troughs in light near the end of the dark and light periods respectively; that is, between 45 s and 55 s after the start of each period (De Rouck and Kayembe, 1981). Therefore, the FO measurements were performed at 40 to 60 s in each dark and light period; there were 10 measurements in each period. Six out of 10 EOG amplitudes were automatically averaged and recorded at the end of each period through the EOG artifact rejection system on the Nidek EOG-2 (Inoue et al., 2003; Tamai et al., 2004). In this study, the calibration sensitivity for the pen recorder was 200 μV/division on the printer. The time constant of the amplifier was set at 3 s, and a high frequency cutoff of –3 dB was set at 20 Hz.

Administered agent and control solution

After the initial 10 min of alternating dark and light periods (phase A), 10 mg of MTCL in 2 mL of Primperan injection (Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan) was given intravenously from the median cubital vein of each subject in less than 10 s. FO was further recorded for another 20 min (phases B and C, 10 min each, respectively). For the nonchemical control, each subject was asked to receive another set of examinations with an intravenous injection of 2 mL of physiological saline. The control examination was scheduled after an interval of at least 2 weeks.

FO parameter

As an FO parameter, df_{FO}, which is the averaged difference in μV between maximum amplitude in the dark period and minimum amplitude in the light period during FO measurement (De Rouck and Kayembe, 1981; Nakao et al., 2003; Tamai et al., 2004) (Fig. 1), was evaluated. In the present study, each phase showed 5 dark-rise and light-fall

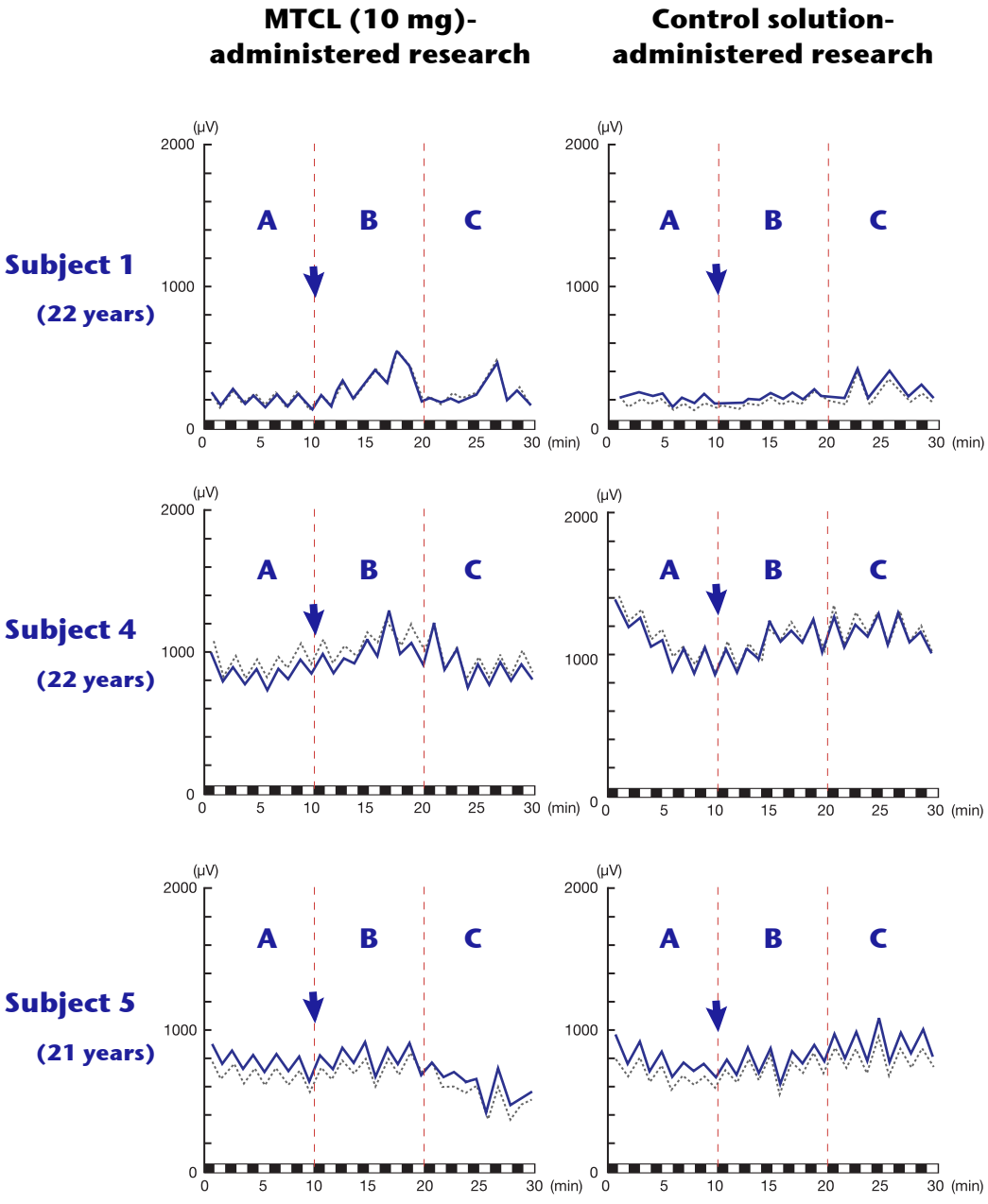

Fig. 2. Some samples of FO patterns of 5 male test subjects. The dotted line in each sample shows FO pattern in the right eye and the solid line shows that in the left eye. Control solution: physiological saline. A, phase A: initial 10 min before intravenous injection; B, phase B: following 10 min after the injection; C, phase C: additional 10 min after the injection. A dark arrow in each sample indicates the injection point. ■, dark period; □, light period (horizontal axis).

zigzag FO patterns (5 pairs of FO measurements), according to the alternating dark-light period of 1 min each. df_{FO} was calculated only if at least 3 successive pairs were observed (Fig. 1). Isolated and occasional FO patterns were not taken into account.

Statistical analysis

All values were expressed as mean ± SD. Statistical analysis was performed with Wilcoxon's rank sum test of correspondence or non-correspondence. Values of $P < 0.05$ were considered significant.