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The Effect of Metoclopramide on the Absorption and Pharmacology of Chlorpromazine in the Rat

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Abstract—The mechanism of interaction between metoclopramide (MCP) and chlorpromazine (CPZ) has been examined in rats. MCP given intraperitoneally 30 min before orally administered CPZ significantly enhanced the cataleptic and hypothermic effects of CPZ, and also initially increased its plasma and brain concentrations. However, MCP had no effect on the plasma and brain concentrations of CPZ given as an intravenous bolus, indicating that MCP interacts with CPZ during its intestinal absorption. Furthermore, co-administration of MCP (i.p.) with CPZ (p.o.) markedly accelerated gastric emptying compared with CPZ alone, and MCP (i.v.) did not alter the uptake of CPZ by the intestinal membrane. Therefore, it is concluded that MCP causes an increase in the rate of CPZ absorption, by accelerating the gastric emptying.

Metoclopramide (MCP) is widely used in the prevention of nausea and vomiting induced by disease, radiation, anaesthesia and drugs. When given to man in combination with phenothiazines such as chlorpromazine (CPZ) and prochloperazine, undesirable extrapyramidal symptoms are often produced (Bochner et al 1983). The mechanism of the interaction between MCP and phenothiazines has not yet been fully examined. Since MCP is known to accelerate gastric emptying (Jacoby & Brodie 1967; Connell & George 1969), it may potentiate the extrapyramidal effects of phenothiazines by increasing the rate of intestinal absorption. The present study was designed to elucidate the mechanism of interaction between MCP and CPZ in rats.

Materials and Methods

Drugs and animals

Metoclopramide dihydrochloride hydrate and chlorpromazine hydrochloride were kindly supplied by Fujisawa Pharmaceutical Industry Co. (Osaka, Japan) and Yoshitomi Pharmaceutical Co. (Tokyo, Japan), respectively. All other reagents were commercial products and of analytical grade.

Male Wistar rats, 200–250 g, were fasted for about 24 h before the experiments, but had free access to water.

Drug administration

CPZ (10 mg kg^{-1}) was dissolved in 1 mL of distilled water for oral administration or 0·3 mL of isotonic saline for intravenous bolus administration. MCP (2 mg kg^{-1}), dissolved in 0·3 mL of saline and adjusted to pH 2 with 1 M HCl, was administered intraperitoneally 30 min before administration of CPZ, or intravenously as a bolus 45 min after the beginning of the in-situ absorption experiment. Control rats received an equivalent volume of saline adjusted to pH 2 in the place of MCP injection.

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Evaluation of catalepsy

Catalepsy was evaluated by placing one forepaw of the rat on a 9 cm high cork stopper according to Wirth et al (1958). The cataleptic effect of CPZ was expressed as the duration of complete immobility.

Evaluation of hypothermia

The hypothermic effect of CPZ was expressed as the percentage fall in rectal temperature (Smolen et al 1976) in rats kept at constant room temperature (20 °C).

Measurement of plasma CPZ concentration

Blood samples were collected by cardiac puncture at appropriate times after oral or intravenous bolus administration of CPZ, and centrifuged to obtain the plasma for analysis. The procedure for extraction of CPZ in the plasma followed the modified method of McKay et al (1982). The assay of CPZ was by a gas chromatograph-mass spectrometer-computer system. Separations were made on a 100 × 3 mm (i.d.) glass column packed with 1·5% OV-17 on 80–100 mesh Chromosorb Q. The chromatographic conditions were: column temperature 260 °C; injection port temperature 280 °C; helium flow-rate 30 mL min^{-1}. Selected ion monitoring was performed under the following conditions: ion source and separator temperature 250 °C; ionizing voltage 75 eV; trap current 300 μA. The instrument was used in the selected ion monitoring mode. The fragment ions used for the quantification were m/z 318·8 for CPZ and m/z 324·9 for CPZ-d_6 as internal standard.

Measurement of brain CPZ concentration

Animals were decapitated at different times following oral administration of CPZ and the whole brain immediately removed and homogenized in 10 mL of 0·1 M HCl. The homogenate was centrifuged for 30 min at 13 000*g* to obtain the supernatant fraction for analysis. The extraction of CPZ and its estimation were as described above.

In-situ absorption experiments

The in-situ absorption experiments were according to the method of Koizumi et al (1964). Animals were anaesthetized with urethane (1·5 g kg^{-1}), and the small intestine exposed by a midline abdominal incision. A glass cannula was inserted into a small slit at the upper end of the jejunum and another cannula into a slit 40 cm lower. The cannulae were connected with polyethylene tubing to a flask containing 50 mL of drug solution prepared by dissolving CPZ, 20 μg mL^{-1}, and phenol red, 5 μg mL^{-1}, in pH 6·8 isotonic phosphate buffer, and recirculated at 5 mL min^{-1} by a perfusion pump. The flask was kept in a water-bath at 37 °C. The concentration of CPZ in the perfusate was measured by HPLC (Bernard et al 1978).

Gastric emptying experiments

The effect of drugs on gastric emptying was determined according to Jacoby & Brodie (1967). Small glass pellets (about 1·0 mm in diameter, 40 pellets per rat) were introduced into the stomach. The animals were killed 3 h after administration of the pellets and the number of pellets remaining in the stomach counted. Gastric emptying was expressed as the percentage of pellets introduced that passed from the stomach into the small intestine.

Statistical analysis

The results were analysed statistically with the Student's *t*-test or Cochran-Cox test. A P value of 0·05 or less was considered to be significant.

Results and Discussion

MCP given intraperitoneally 30 min before orally administered CPZ significantly enhanced the cataleptic (Fig. 1) and hypothermic (Fig. 2) effects of CPZ. These pharmacological effects were not observed when MCP (2 mg kg^{-1} i.p.) was given alone (data not shown). As shown in Fig. 3, MCP (i.p.) increased the plasma concentration of CPZ (p.o.) 0·5 and 1 h, but had little effect 2–6 h after CPZ administration. Furthermore, MCP (i.p.) caused a significant increase in the brain concentration of orally administered CPZ during the early stages (0·25, 0·5, 1 and 2 h) after administration (Fig. 4). However, MCP (i.p.) did not alter the plasma and brain concentrations of CPZ given as an intravenous bolus (Figs 5, 6), indicating that the interaction may occur during intestinal absorption.

Although MCP (i.p.) increased the plasma and brain concentrations of CPZ (p.o.) for only 1 and 2 h, respectively (Figs 3, 4), it potentiated CPZ-induced catalepsy for at least 4 h (Fig. 1). Since catalepsy is thought to be due to blockade of dopamine receptors, the potentiation by MCP (i.p.) of CPZ (p.o.)-induced catalepsy may be the result of an increase in CPZ concentration at dopamine receptors rather than that in the plasma and brain. Better insight into the mechanism of the potentiation of the catalepsy might be gained by measuring the CPZ concentration at dopamine receptors.

Gastric emptying is an important factor determining the rate of drug absorption (Prescott 1974). For example, CPZ

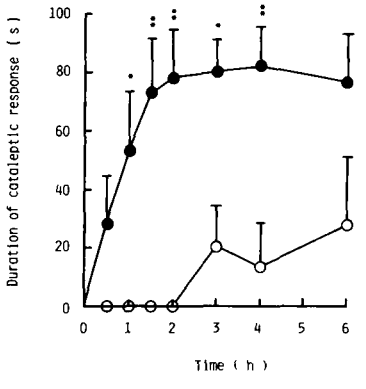

FIG. 1. Effect of MCP on CPZ-induced catalepsy. MCP (2 mg kg^{-1}) was administered i.p. 30 min before the oral administration of CPZ (10 mg kg^{-1}). (○) CPZ alone, (●) CPZ + MCP. Each point represents the mean ± s.e. (n = 6). $^{*}P < 0·05$, $^{**}P < 0·01$, significantly different from CPZ alone.

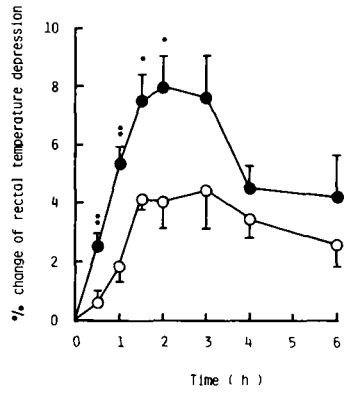

FIG. 2. Effect of MCP on CPZ-induced hypothermia. The hypothermic effect is expressed as the percentage change of rectal temperature depression, $(T_0 - T_t)/T_0 \times 100$, where T_0 and T_t are the temperature at 0 and time t, respectively. The mean rectal temperature of the rats under control conditions was 35·9 ± 0·1 °C. Drug administration and symbols as in Fig. 1. Each point represents the mean ± s.e. (n = 6). $^{*}P < 0·05$, $^{**}P < 0·01$, significantly different from CPZ alone.

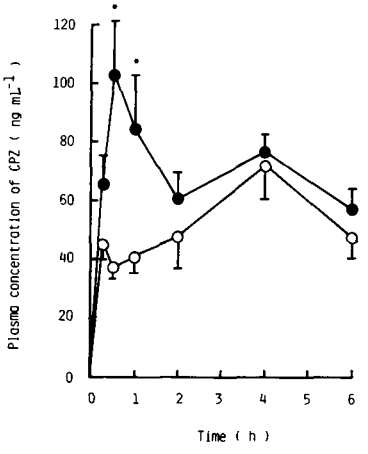

FIG. 3. Effect of MCP on plasma concentration of CPZ after oral administration. Drug administration and symbols as in Fig. 1. Each point represents the mean ± s.e. (n = 4–10). $^{*}P < 0·05$, significantly different from CPZ alone.

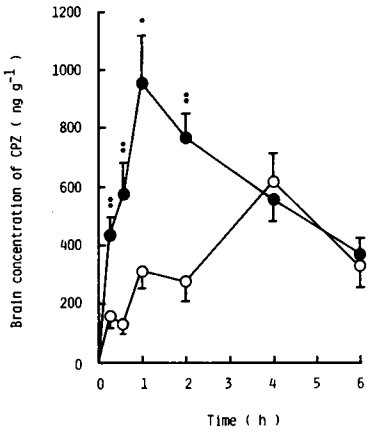

FIG. 4. Effect of MCP on brain concentration of CPZ after oral administration. Drug administration and symbols as in Fig. 1. Each point represents the mean ± s.e. (n = 5–9). *$P < 0.05$, **$P < 0.01$, significantly different from CPZ alone.

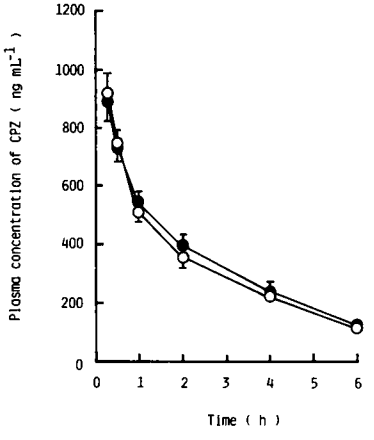

FIG. 5. Effect of MCP on plasma concentration of CPZ after intravenous bolus administration. MCP (2 mg kg^{-1}) was administered i.p. 30 min before the intravenous bolus administration of CPZ (10 mg kg^{-1}). Symbols as above. Each point represents the mean ± s.e. (n = 3–5).

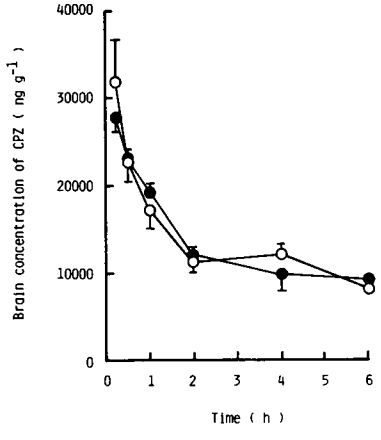

FIG. 6. Effect of MCP on brain concentration of CPZ after intravenous bolus administration. Drug administration and symbols as in Fig. 5. Each point represents the mean ± s.e (n = 3).

delays gastric emptying and markedly decreases the rate of paracetamol absorption (Imamura et al 1980), while MCP markedly increases the rate of paracetamol absorption by accelerating gastric emptying (Nimmo et al 1971). As shown in Fig. 7, co-administration of MCP (i.p.) antagonized the delaying effect of CPZ (p.o.) on gastric emptying, resulting in markedly accelerated gastric emptying compared with CPZ given alone. Therefore, it is concluded that MCP causes an increase in the rate of CPZ absorption by accelerating gastric emptying.

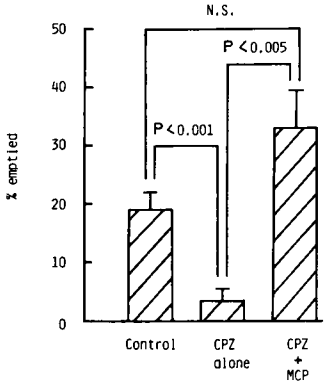

FIG. 7. Delaying effect of CPZ on gastric emptying and antagonism of this effect by MCP. Drug administration as in Fig. 1. Results are expressed as the mean ± s.e. (n = 6–7).

Fig. 8 shows the effect of MCP (i.v.) on the in-situ intestinal absorption of CPZ. The MCP did not alter the percentage of CPZ remaining in the perfusate compared with the control. Therefore, MCP appears to have no effect on the uptake of CPZ by the intestinal membrane, supporting the hypothesis that MCP-CPZ interaction during intestinal absorption results from modification of gastric emptying as described above. In addition, our preliminary studies have shown that MCP does not influence the serum protein binding and metabolism of CPZ (unpublished).

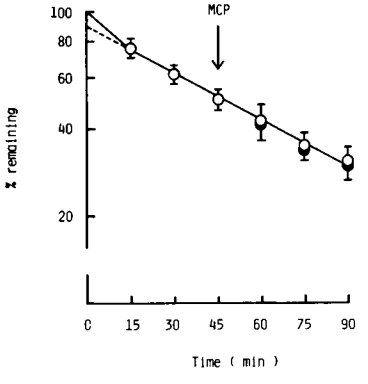

FIG. 8. Effect of MCP on the in-situ intestinal absorption of CPZ. MCP (2 mg kg^{-1}) was administered intravenously as a bolus immediately after sampling the perfusate at 45 min. (○) Control, (●) MCP treatment. Each point represents the mean ± s.e. (n = 3).

When MCP is given in combination with phenothiazines in man, extrapyramidal symptoms such as akathisia and acute dystonia are often produced (Bochner et al 1983). We have obtained evidence that in rats MCP enhances the cataleptic and hypothermic effects of CPZ, and increases the rate of CPZ absorption by accelerating gastric emptying.

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