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Effect of Methamphetamine and Dopamine Receptor Antagonists on Cholecystokininlike Immunoreactivity in the Rat Medial Prefrontal Cortex

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KAWAI, N., Y. TAKAMATSU, H. YAMAMOTO, E. HASEGAWA, A. BABA, T. SUZUKI, T. MOROJI, AND O. O. OGUNREMI. *Effect of methamphetamine and dopamine receptor antagonists on cholecystokininlike immunoreactivity in the rat medial prefrontal cortex.* PHARMACOL BIOCHEM BEHAV **58**(2) 517–523, 1997.—A single intraperitoneal administration of methamphetamine (MAP) reduces cholecystokininlike immunoreactivity (CCK-LI) in medial prefrontal cortex (mPFC) of the rat brain. This report examines the effects of various dopamine (DA) receptor antagonists [haloperidol (HAL), sulpiride (SUL), YM09151-2 (YM), and SCH23390 (SCH)] on MAP-induced abnormal behaviors and the changes of CCK-LI in the rat mPFC. A single subcutaneous administration of HAL (0.25 mg/kg), YM (0.1 mg/kg), or SUL (250 mg/kg) significantly reduced the basal CCK-LI in mPFC by 20–40%; a selective D_1 antagonist, SCH (up to 1.0 mg/kg), had no effect on basal CCK-LI. However, the reduction of CCK-LI induced by MAP (20–40%) was abolished by the pretreatment with HAL (0.025 and 0.25 mg/kg), YM (0.01 and 0.1 mg/kg), or SCH (1.0 mg/kg), without being affected by SUL (up to 250 mg/kg). This effect of DA antagonists on MAP-induced change in CCK-LI was associated with an inhibition of MAP-induced stereotyped behaviors. These data suggest that the CCK-containing neurons in rat mPFC are functionally related to the mesocortical DA system and may participate in a development of abnormal behaviors induced by MAP. © 1997 Elsevier Science Inc.

Cholecystokinin Methamphetamine Haloperidol YM09151-2 Sulpiride SCH23390 Medial prefrontal cortex Rat

SINCE cholecystokinin (CCK) was found colocalized with dopamine (DA) in certain dopaminergic neurons in the mesolimbic system (15), attention has been focused on its modulatory interactions with DA systems in connection with the DA-related neuropsychiatric diseases such as schizophrenia and drug addictions with cocaine and amphetamine (10). Numbers of biochemical and physiological studies have revealed a close relationship between CCK neurons and DA systems in the central nervous system (CNS). For example, CCK release in the rat striatum and/or the nucleus accumbens (NAc) is modulated by a depletion or a stimulation of DA systems (7,9,13,14,23,37). Conversely, the administration of CCK affects the DA release in the striatum or the NAc (2,3,17,18).

However, studies concerning the distribution of CCK throughout the rat brain have revealed the highest concentration to be present in the cerebral cortex. Immunohistochemical studies have shown that the majority of these cortical CCK

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derives from intrinsic CCK-containing neurons (27,35). Although physiological roles of these CCK neurons are unknown, numbers of studies have reported the modulation of CCK metabolism and/or CCK-receptor expression in the medial prefrontal cortex (mPFC) by amphetaminelike substances (5,11, 26,30,39,40,42). Considering that the amphetaminelike substances affect the DA metabolism in the mPFC (25,26,32) and that the amphetamine-induced abnormal behaviors are affected by the lesions in mPFC (4,45), the CCK-containing neurons in the mPFC may have some interactions with mesocortical DA system and participate in the abnormal behaviors induced by amphetaminelike substances.

Previously, we reported that an acute single administration of methamphetamine (MAP) induced increased DA metabolism and a reduction of the CCK-like immunoreactivity (CCK-LI) in the rat mPFC (26). In the present study, the possible interaction of the DA system and the CCK-containing neurons in the mPFC were investigated further by examining the effects of a series of DA receptor antagonists [*i.e.*, potent D_2-like receptor antagonists, haloperidol (HAL), YM09151-2 (YM) and sulpiride (SUL), and a selective D_1-like receptor antagonist, SCH23390 (SCH)], on the MAP-induced behavioral changes and the CCK-LI in the rat mPFC.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 250–300 g were used. Animals were housed in groups of two rats per cage under controlled temperature (22 ± 2°C), humidity (45%) and a standard 12/12-h light/dark cycle. Unrestricted access to the food and tap water was provided.

Chemicals

MAP was purchased from Dainippon Pharmaceutical Co. Ltd. (Osaka, Japan). HAL and SUL were purchased from Sigma Chemical Co. (St. Louis, MO, USA). SCH was purchased from Research Biochemicals, Inc. (Wayland, MA, USA). YM was generously provided by Yamanouchi Pharmaceutical Co. Ltd. (Tokyo, Japan). Synthetic sulfated CCK-8 and nonsulfated CCK-8 were purchased from the Peptide Research Foundation (Mino, Japan). Rabbit antiserum against nonsulfated CCK-8 (first antibody) was kindly supplied by Dr. T. Higuchi (Saitama Medical College, Saitama, Japan).

Behavioral Measurements

Before starting experiments, animals were adapted to the individual experimental cages for 1 h. A series of DA antagonists [HAL (0.025 and 0.25 mg/kg), YM (0.01 and 0.1 mg/kg), SUL (10 and 250 mg/kg), SCH (0.1 and 1.0 mg/kg)] or appropriate vehicles were subcutaneously (SC) injected prior to the intraperitoneal (IP) administration of MAP or saline. Two doses of MAP were used in this study: a relatively high dose (8 mg/kg) and a low dose (4 mg/kg) were chosen to obtain maximal effects on stereotyped behaviors and locomotor activities, respectively, by a single injection. The time lags between the pretreatment with DA antagonists and the MAP administration (15 min for HAL, 30 min for YM and 60 min for SUL and SCH) were determined in the preliminary studies so that the peak effect of each DA antagonist on MAP-elicited behavioral changes was obtained.

The assessment of behavioral changes was started immediately after the MAP injection and continued for 60 min. The locomotor activity was assessed by measuring a moving distance with a behavioral tracing analyzer (Model BTA-1: Muromachi Kikai CO, Tokyo, Japan), as previously described (21). The locomotor activity was expressed as total moving distances during the initial (0–20 min), middle (20–40 min), or final (40–60 min) observation period. The intensity of stereotyped behavior elicited by MAP was assessed every 5 min according to the following scoring system slightly modified from the original description by Akiyama et al. (1).

0. Asleep or standing still.
1. Locomotion as a normal exploration with a normal pattern of sniffing.
2. Hyperlocomotion with increased rate of sniffing.
3. Discontinuous compulsive sniffing with periodic locomotion.
4. Almost continuous compulsive sniffing with brief locomotion.
5. Continuous compulsive sniffing, licking and biting without locomotion.

Statistical analysis for the locomotor activity was performed with Cochran's *t*-test. Stereotyped behavior scoring data were analyzed by the Kruskal–Wallis analysis of variance, followed by the Williams–Wilcoxon multiple comparison test.

Enzyme Immunoassay (EIA) Procedure for CCK-LI

Immediately after the behavioral assessment, rats were killed by microwave irradiation. The brain was quickly removed and dissected into four discrete regions [i.e., medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), nucleus accumbens (NAc), and caudate-putamen (C-P)] according to the method of Marley et al. (21). The dissected tissues were homogenized in 2 ml of 0.1 N acetic acid, boiled for 10 min, and centrifuged (25,000*g*) and 20 min at 4°C. The su-

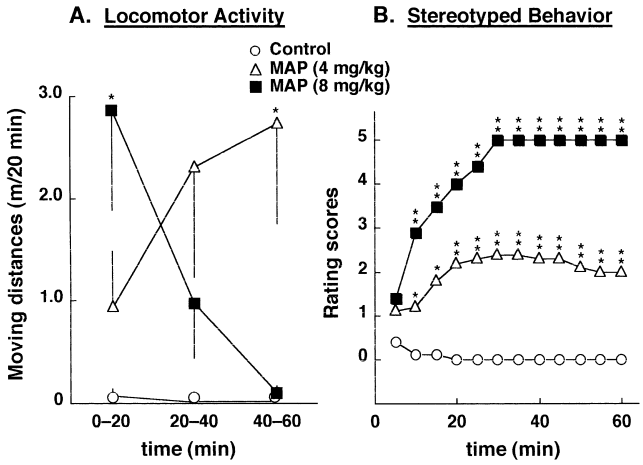

FIG. 1. Behavioral changes induced by a single administration of MAP. Rats were treated (IP) with MAP (4 or 8 mg/kg) or physiological saline (control) and behavioral changes were assessed for 60 min as described in Materials and Methods. A: The moving distances measured for 20-min intervals. Data represent means ± SEM values for 9–11 individual experiments. Values differ significantly from control group at $*p < 0.05$ and $**p < 0.01$ by Cochran's *t*-test. B: The rating scores for stereotyped behaviors. Data represent means for 9–11 individual experiments. SEM values were always less than 10% of the mean values and omitted from the figure for the clarity. Values differ significantly from control group at $p < 0.05$ and $p < 0.01$ by a Kruskal–Wallis analysis of variance followed by a Williams–Wilcoxon multiple comparison test.

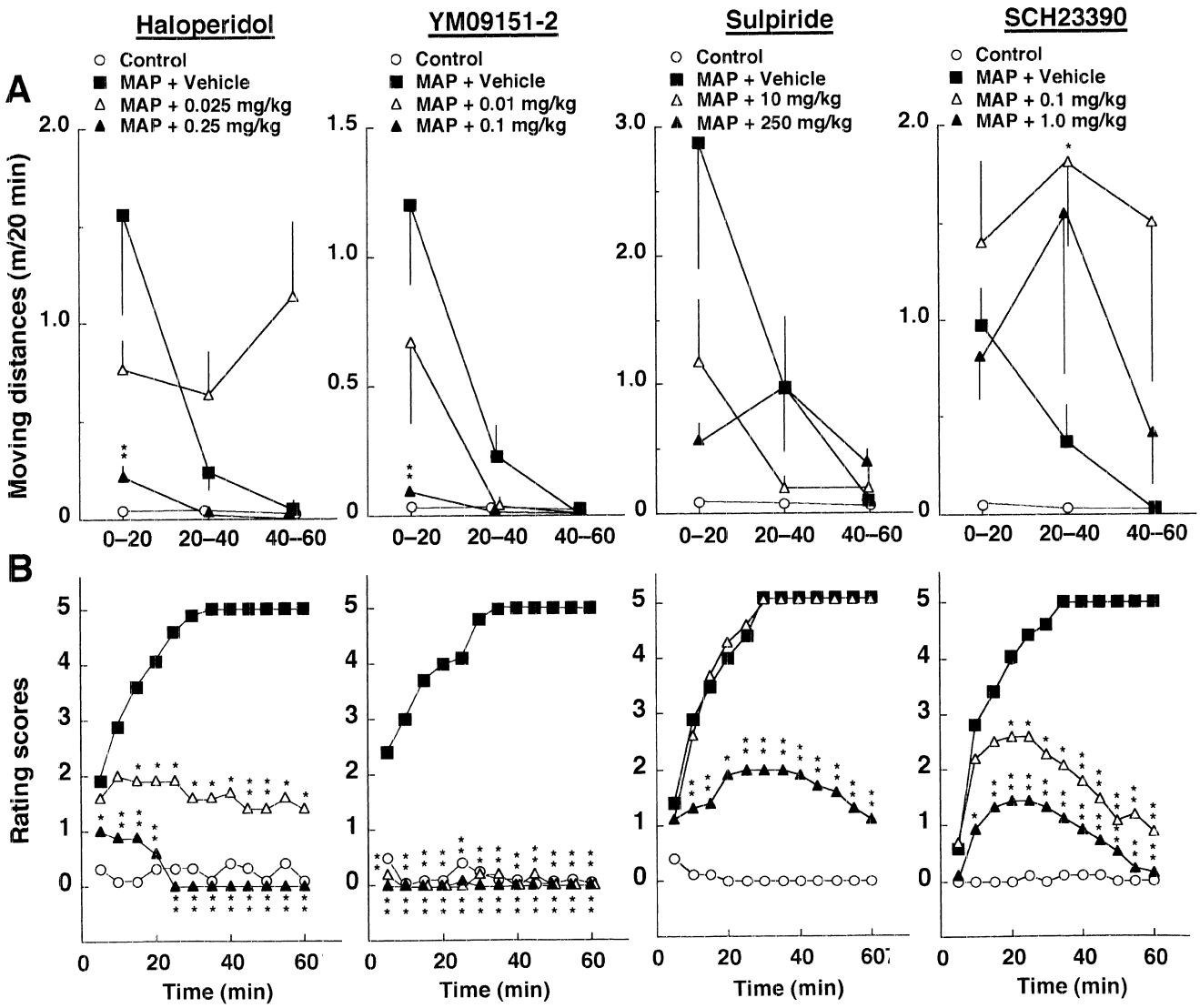

FIG. 2. The effects of DA antagonists on the MAP-induced behavioral changes. The animals were pretreated (SC) with HAL (0.025 and 0.25 mg/kg), YM (0.01 and 0.1 mg/kg), SUL (10 and 250 mg/kg), SCH (0.1 and 1.0 mg/kg) or appropriate vehicles prior to the IP injection of methamphetamine (MAP, 8 mg/kg) or physiological saline, and the behavioral changes were assessed as described in Materials and Methods. A: The moving distances measured for 20-min intervals. Data represent means ± SEM values for 7–11 individual experiments. Values differ significantly from control group at $*p < 0.05$ and $**p < 0.01$ by Cochran's *t*-test. B: The rating scores for stereotyped behaviors. Data represent means for 9–11 individual experiments. SEM values were always less than 10% of the mean values and omitted from the figures for the purpose of clarity. Values differ significantly from control group at $*p < 0.05$ and $**p < 0.01$ by the Kruskal–Wallis analysis of variance, followed by a Williams–Wilcoxon multiple comparison test.

pernatants were lyophilized and used for EIA; the amount of protein in the pellets was determined by the method of Lowry et al. (20).

The EIA for CCK-LI was performed as previously described (41). In brief, 96-well flat-bottomed polystylene microplates (Dynatech, Germany) were incubated with 250 μl of carbonate-bicarbonate buffer containing 5 μg/ml of goat anti-rabbit IgG antiserum pH 9.6) overnight at 4°C. After washing (5 times) with 0.02 M phosphate buffered saline containing 0.5% Tween 20 (pH 7.4), anti-CCK antibody (1:2500 dilution) and the samples or CCK standards were added to the wells and incubated overnight at 4°C in 200 μl of assay buffer (0.14 M phosphate buffer containing 25 mM EDTA, 0.5% bovine serum albumin, and 0.02% Tween 20, pH 7.4). Subsequently, horseradish peroxidase/CCK-8 conjugate (50 μl) was added and allowed to bind to the antibody for 4 h at 4°C. Each well was washed 5 times and incubated with 250 μl of peroxidase substrate (*O*-phenylenediamine and H_2O_2 in 0.2 M phosphate-citrate buffer pH 5.2) at room temperature for 40 min. The reaction was stopped by the addition of 50 μl of 5 N H_2SO_4, and the absorbance of the resultant chromogen was measured at 492 nm by a microplate photometer (MPT-22, Corona Electrics Co., Ibaraki, Japan).

Statistical analysis was performed with one-way analysis of variance (ANOVA), followed by Duncan's multiple comparison test.

TABLE 1
EFFECT OF A SINGLE IP INJECTION OF METHAMPHETAMINE ON CCK-LI IN THE RAT BRAIN

Treatment	*n*	CCK-LI (ng/mg protein) mPFC	ACC	NAc	C-P
Saline (control)	9	9.45 ± 0.84	6.83 ± 0.88	5.58 ± 0.63	1.96 ± 0.35
MAP (4 mg/kg)	10	6.66 ± 1.22	5.64 ± 0.61	3.81 ± 0.33	1.51 ± 0.24
MAP (8 mg/kg)	9	5.78 ± 0.63*	7.36 ± 1.17	3.50 ± 0.30	1.92 ± 0.32

Male Wistar rats were treated (IP) with indicated doses of methamphetamine (MAP) or saline (control) and killed immediately after the 60-min behavioral assessment. The CCK-LI in medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), nucleus accumbens (NAc), and caudate-putamen (C-P) was determined as described in Materials and Methods. Data are means ± SEM values from the indicated numbers (*n*) of independent experiments.

*Values differ significantly from control by ANOVA + Duncan's multiple comparison test at $p < 0.01$.

RESULTS

Behavioral Experiments

Behavioral changes elicited by a single injection of MAP. After a single IP injection of relatively low dose (4 mg/kg) of MAP, animals gradually developed increased locomotor activity, which became significant at 40–60 min (Fig. 1A). A development of moderate degree (rating score = 2–3) of stereotyped behavior was also observed (Fig. 1B). With a higher dose (8 mg/kg) of MAP, increased locomoter activity became significant immediately after the injection (initial hyperlocomotion; Fig. 1A). Subsequently, the locomotor activity decreased and was replaced by a forced stereotyped behavior such as continuous sniffing, gnawing and licking, which reached the highest intensity (rating score = 5) within 30–40 min and lasted until the end of the observation periods (Fig. 1A,B).

Effects of DA receptor antagonists on MAP-induced (8 mg/kg) abnormal behaviors. Pretreatment with HAL (0.25 mg/kg) and YM (0.1 mg/kg) significantly reduced the initial hyperlocomotion induced by MAP (Fig. 2A). Although SUL (250 mg/kg) showed a tendency to attenuate initial hyperlocomotion, the effect was not significant ($p > 0.05$; Fig. 2A). SCH showed no inhibitory effect on MAP-induced initial hyperlocomotion. The animals treated with SCH (0.1 mg/kg) + MAP showed significantly higher locomotor activity than the MAP-alone-treated animals during the 20–40 min period (Fig. 2A).

Pretreatment with HAL, YM or SCH significantly attenuated MAP-induced stereotyped behavior (Fig. 2B). By the end of the observation period, MAP-induced stereotyped behavior was completely suppressed (rating score = 0–1) by these substances at the dose of 0.25 mg/kg (HAL), 0.01 and 0.1 mg/kg (YM), and 1.0 mg/kg (SCH), respectively (Fig. 2B). Conversely, a low dose of SUL (10 mg/kg) had no effect at all on MAP-induced stereotyped behavior (Fig. 2B) (8,22,29, 31,46). Although significant attenuations of stereotyped behavior was observed with SUL at the higher dose (250 mg/kg), the mean rating score remained above 1 throughout the observation period (Fig. 2B).

None of the tested DA antagonists significantly affected the locomotor activity or elicited abnormal behavior in the control (saline-treated) animals (data not shown).

EIA for CCK

Effects of a single administration of MAP on CCK-LI in rat brain. A single IP administration of MAP at the dose of 8 mg/kg caused a significant reduction of CCK-LI in the mPFC; the effect was not significant at the lower dose (4 mg/kg; Table 1). No significant change in CCK-LI was observed in the other three brain regions (Table 1).

Effects of DA receptor antagonists on basal and MAP-induced reductions of CCK-LI in mPFC. A single SC administration of HAL (0.25 mg/kg), YM (0.1 mg/kg) and SUL (250 mg/kg) significantly decreased CCK-LI in the mPFC (Fig. 3A–C). SCH had no effect on CCK-LI at the doses tested. None of the DA antagonists had a significant effect on CCK-LI in ACC, NAc or C-P (data not shown). Pretreatment of the rats with HAL (0.025 and 0.25 mg/kg), YM (0.01 and 0.1 mg/kg) or SCH (1.0 mg/kg) significantly reversed the MAP-induced reduction of CCK-LI in mPFC (Fig. 3A,B,D). Conversely, pretreatment with SUL had no significant effect on MAP-induced reduction of CCK-LI at any dose tested.

DISCUSSION

Marked reduction of CCK-LI in the mPFC induced by acute MAP treatment suggest the functional interaction between CCK and DA systems in this area. Because the majority of CCK-LI in the rat cerebral cortex belongs to local circuit neurons (27,35), these data may indicate that the MAP treatment stimulates CCK release from intrinsic CCK neurons in the mPFC through enhanced mesocortical DA transmission. This possibility is consistent with the previous finding that the activation of DA receptors by apomorphine increases the CCK release in the rat mPFC slices (5). The observed reduction of CCK-LI by D_2-like receptor antagonists (but not by a selective D_1-like receptor antagonist) does not contradict this notion. The D_2-like receptor antagonists probably enhance mesocortical DA system (33,36,47) by blocking the release-modulating autoreceptors on the DA terminals (6,24) and, subsequently, stimulating intrinsic CCK-containing neurons in the mPFC. The increased CCK release induced by SUL was also reported in the rat mPFC by a brain microdialysis method (42). Because D_2 antagonists block both pre- and postsynaptic D_2-like receptors, the observed changes of CCK neuronal activity may be mediated by D_1-like receptors. In this regard, Brog and Beinfeld (5) reported the D_1-mediated CCK release in the rat cortex.

Several *in vivo* and *in vitro* studies have reported the altered CCK release in the NAc and/or the C-P in response to the stimulation of DA system (5,13,14,23). However, no significant changes of CCK-LI in these areas were detected in the present study. This discrepancy may be due to the differences in assay protocols used, especially the case in NAc, where the pattern of CCK/DA interactions may differ be-

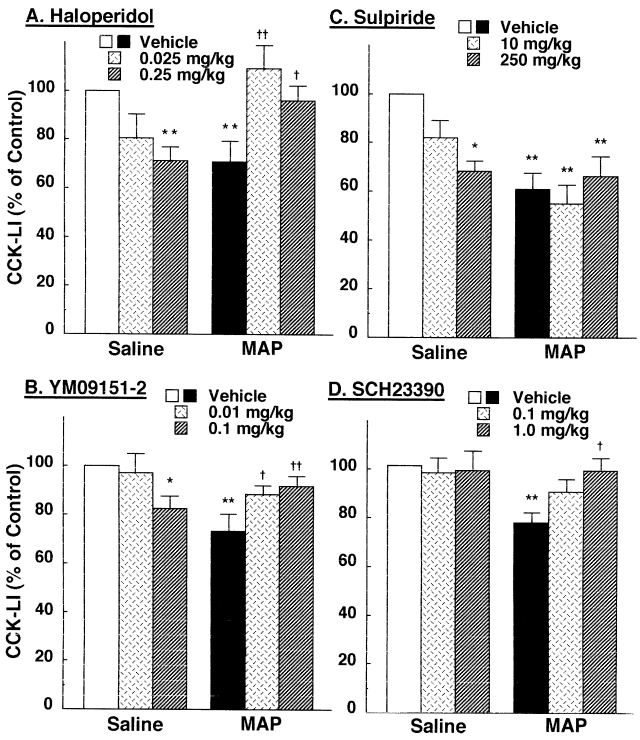

FIG. 3. The effects of DA antagonists on CCK-LI in mPFC of the control and MAP-treated animals. Animals were pretreated (SC) with (A) HAL (0.025 and 0.25 mg/kg), (B) YM (0.01 and 0.1 mg/kg), (C) SUL (10 and 250 mg/kg), (D) SCH (0.1 and 1.0 mg/kg) or appropriate vehicles prior to the IP injection of methamphetamine (MAP, 8 mg/kg) or physiological saline, and CCK-LI in medial frontal cortex was determined after the 60-min behavioral assessment as described in Materials and Methods section. Data (expressed as percentage of control) are means ± SEM values obtained from 7–11 independent animals, and each assay was performed in duplicate. Control values (vehicle + saline group) are similar to those presented in Table 1. Values differ significantly from control group at $*p < 0.05$ and $**p < 0.01$. Values differ significantly differ significantly from vehicle + MAP-treated group at $*p < 0.05$ and $**p < 0.01$ by ANOVA + Duncan's multiple comparison test.

tween rostral and caudel part (17,45). Thus, the changes in CCK neuronal activities may not be detected by measuring the CCK-LI in the whole tissue.

The behavioral changes induced by a single administration of MAP in the present study are consistent with a previous report (16,27). An increased locomotor activity is elicited by a relatively low dose of MAP. With a higher dose, hyperlocomotion is initially observed for a short period and soon replaced by intense and continuous sniffing, gnawing and licking. It has been generally accepted that the mesolimbic DA system is essential for the increased locomotor activity, whereas nigrostriatal DA system plays a predominant role in forced stereotyped behaviors, which mask the expression of hyperlocomotive activity under the use of high dose of MAP (16).

The data demonstrated that HAL and YM significantly attenuated both the initial hyperlocomotion and the stereotyped behavior induced by 8 mg/kg of MAP. In contrast, SCH blocked the stereotyped behavior without significantly affecting the initial hyperlocomotion. The animals treated with a low dose (0.1 mg/kg) of SCH + MAP showed significantly higher locomotor activity than the animals treated with MAP alone during the 20–40-min intervals. A similar effect of SCH on high dose amphetamine induced locomotor activity has been reported (28). Unlike the other DA antagonists, SUL at the lower dose (10 mg/kg) had no effect on MAP-elicited behavioral changes. At a considerably high dose (250 mg/kg), SUL showed significant, but still incomplete (mean rating score > 1) inhibition of stereotyped behavior; the initial hyperlocomotion was not significantly attenuated. Such atypical pharmacological features of SUL against the abnormal behaviors induced by the amphetaminelike substances have been described (30,48).

In the present study, the effects of these DA receptor antagonists on the MAP-induced changes of CCK-LI and the abnormal behaviors were compared. Pretreatment with HAL (0.025 and 0.25 mg/kg), YM (0.01 and 0.1 mg/kg) or SCH (1.0 mg/kg) significantly reversed the MAP-induced reduction of CCK-LI in the mPFC. The mechanisms by which HAL or YM (which reduce the CCK-LI in mPFC) can reverse the MAP-induced CCK-LI reduction is unknown. Moreover, the fact that either the D_1- or D_2-like receptor specific antagonist (SCH and YM, respectively) can prevent the MAP-induced CCK-LI reduction underscores the complexity of the CCK/DA interactions in this area.

As previously reported, CCK in the cerebral cortex derives predominantly from the intrinsic local circuit neurons, which is likely to be responsible for the observed changes of CCK contents in the mPFC. However a small number of the cerebrocortical CCK neurons have long projections to subcortical areas including striatum; mPFC also receive ascending CCK neuronal innervation from substantia nigra ventral tegmental area (35). In this regard, the MAP-induced reduction of CCK-LI was significant enough at the dose which induces stereotyped behavior and was not significant enough at the dose which induces maximal locomotive response. Furthermore, our data showed that the reversing effect of DA antagonists on the MAP-induced CCK-LI reduction coincided with the attenuation or complete blockade of the MAP-induced stereotyped behaviors. At present, however, we cannot determine the exact neuronal networks responsible for the observed response of CCK-LI because all the drugs used in this study were given systematically. Nevertheless, these results might indicate a close relationship between mPFC and a negrostriatal system in terms of a DA and CCK neuronal interaction. Further studies should be done to clarify this notion.

Interestingly, pretreatment with SUL did not affect the MAP-induced reduction of CCK-LI in mPFC, although it significantly attenuated MAP-induced stereotyped behaviors. The incomplete inhibition of the MAP-induced behavioral change or a lack of affinity to D_1-like receptors by SUL does not explain this discrepancy because low doses of HAL (which did not completely block the MAP-induced stereotyped behaviors) or YM (the other highly selective D_2-like receptor antagonist) efficiently reversed the MAP-induced CCK-reduction. One possible explanation may be provided by recent studies showing the interaction between 5-hydroxytryptamine$_2$ (5-HT$_2$) receptors and the DA systems. For example, decreased firing rate of rat A10 neurons induced by amphetamine was completely blocked by selective 5-HT$_2$ receptor antagonists (MDL 28, 133A, or ritanserin) or by the pretreatment with a tryptophan hydroxylase inhibitor (para-chlorophenyl-alanine) (38), indicating the regulation of the midbrain DA system via 5-HT$_2$ receptors (44). It has been reported that HAL, YM, and SCH have appreciable affinities for 5-HT$_2$ receptors, whereas SUL does not (12,43). Thus, the observed inhibitory effect of HAL, YM and SCH on the

MAP-induced reduction of CCK-LI in mPFC and/or the behavioral changes may be due in part to their 5-HT_2 antagonistic properties. In addition, recent advances in molecular biology have revealed the presence of at least five distinct DA receptors [*i.e.*, two D_1-like receptors (D_1 and D_5) and three D_2-like receptors (D_2, D_3, and D_4)], which has provided clues for a better understanding of the actions of antipsychotic drugs (34). Considerable differences of the relative binding affinities to the $D_2/D_3/D_4$ receptors previously reported between SUL and HAL (19,34) may also be responsible for the atypical pharmacological characteristics of SUL observed in this and other reports.

In conclusion, present findings provide evidence for a functional relationship between the mesocortical DA system and the CCK-containing neurons in the mPFC. Furthermore, the data have demonstrated that the alterations in CCK-LI in mPFC coincides with the development and the inhibition (by DA antagonists) of the MAP-induced abnormal behaviors. These results indicate the need for further studies to elucidate the roles of CCK neuronal systems in the mPFC in connection with the MAP-induced behavioral changes.

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