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Effects of the 5-$HT_{2C/2B}$ receptor agonist 1-(3-chlorophenyl)piperazine on plasma glucose levels of rats

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Abstract

Acute administration of the 5-$HT_{2C/2B}$ receptor agonist 1-(3-chlorophenyl)piperazine (mCPP, 5–10 mg/kg i.p.) induced hyperglycemia in rats. These changes were diminished in a dose-dependent manner by the 5-HT_1/5-HT_2 receptor antagonist methysergide and the 5-$HT_{2A/2B/2C}$ receptor antagonist ritanserin. In addition, mCPP-induced hyperglycemia was dose dependently diminished by the ganglionic blocker hexamethonium and was prevented by prior adrenodemedullation. Neither the 5-HT_{2A} receptor antagonist ketanserin nor the 5-HT_3/5-HT_4 receptor antagonist (3-α-tropanyl)-1*H*-indole-3-carboxylic acid ester (ICS 205-930) proved effective against mCPP-induced hyperglycemia. Lastly, administration of the 5-$HT_{2A/2C}$ receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)2-aminopropane (DOI) increased plasma glucose levels through ketanserin- and ritanserin-sensitive processes. Our results suggest that hyperglycemia elicited by mCPP is mediated by 5-HT_{2C} and/or $_{2B}$ receptors, and in turn adrenomedullary catecholamine release, whereas that elicited by DOI involves 5-HT_{2A} receptors.

Keywords: mCPP (1-(3-chlorophenyl)piperazine); Hyperglycemia; 5-$HT_{2C/2B}$ receptor; DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane); 5-HT_{2A} receptor

1. Introduction

1-(3-Chlorophenyl)piperazine (mCPP) is a metabolite of the antidepressant trazodone and induces various pharmacological actions such as hypertension, hypolocomotion and decreased food intake in rats (Kennett and Curzon, 1988, 1991; Bagdy et al., 1989a; Murphy et al., 1991). mCPP also elicits anxiogenic-like effects in animals which are antagonized by chlordiazepoxide (Kennett et al., 1989). The action of mCPP may involve the 5-HT receptor, since in receptor binding studies mCPP shows an affinity for 5-HT receptor subtypes (Hoyer, 1988). In recent reviews, 5-HT_2 receptors are classified as 5-$HT_{2A,\ 2B,\ 2C}$ receptors. The 5-HT_{2F} receptor and 5-HT_{1C} receptor were renamed the 5-HT_{2B} and 5-HT_{2C} receptor, respectively (Humphrey et al., 1993; Hoyer et al., 1994). mCPP is recognized as a ligand of the 5-HT_{2C} receptor, and the pharmacological effects of mCPP are mainly considered to be produced by the activation of 5-HT_{2C} receptor sites in the brain, based on the results obtained with 5-HT receptor antagonists (Kennett and Curzon, 1991; Murphy et al., 1991). Furthermore, the possibility that the pharmacological effects of mCPP may be partly associated with the 5-HT_{2B} receptor has been raised because recent evidence suggests that mCPP is an agonist at 5-HT_{2B} receptor sites (Baxter et al., 1995; Kennett et al., 1994).

The participation of the central 5-HT receptor in glucose regulation has been investigated in recent years. The involvement of central 5-HT_{1A} receptors is well documented. It has been demonstrated that 5-HT_{1A} receptor agonists including 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) or buspirone induce hyperglycemia in rats (Chaouloff and Jeanrenaud, 1987; Chaouloff et al., 1990a; Sugimoto et al., 1992; Bouhelal and Mir, 1992). In addition, the central 5-HT_{2A} receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)2-aminopropane (DOI) also produces hyperglycemia in rats (Chaouloff et al., 1990b). These hyperglycemic effects are closely connected to

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adrenaline release from the adrenal gland (Baudrie and Chaouloff, 1992; Chaouloff et al., 1990a; Sugimoto et al., 1992). However, glycemic responses to the 5-$HT_{2C/2B}$ receptor agonist mCPP have not yet been clarified.

In this study, we examined the effects of mCPP on plasma glucose levels of rats. Furthermore, we investigated the glycemic responses to the 5-HT_{2A} receptor agonist DOI and compared the involvement of the 5-HT receptor subtypes in DOI- and mCPP-induced effects.

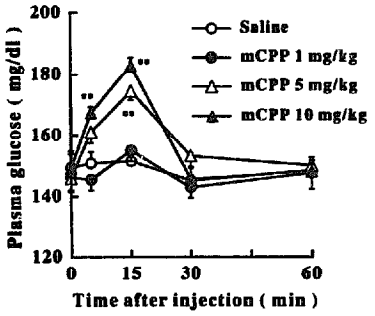

Fig. 1. Effects of mCPP on plasma glucose levels of rats. Results are shown as means ± S.E. ($n = 6$–9). mCPP was injected i.p. * $P < 0.05$, ** $P < 0.01$.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (180–230 g) were purchased from SLC Japan (Japan). They were maintained under a controlled 12 h/ 12 h light dark cycle (light from 7:00 a.m. to 7:00 p.m.), with room temperature at 24 ± 1°C and humidity at 55 ± 5%. Rats were given free access to food and water.

2.2. Drug treatment

1-(3-Chlorophenyl)piperazine (mCPP) and 1-(2,5-dimethoxy-4-iodophenyl)2-aminopropane (DOI) were purchased from Research Biochemicals (USA). mCPP and DOI were dissolved in saline and injected i.p. Methysergide hydrogen maleate, ketanserin tartrate, ritanserin and (3-α-tropanyl)-1*H*-indole-3-carboxylic acid ester (ICS 205-930) were purchased from Research Biochemicals (USA). Hexamethonium hydrobromide was obtained from Nakarai Tesq (Japan). Methysergide, ketanserin and hexamethonium were dissolved in saline. Ritanserin was suspended in 1% carboxymethylcellulose-Na. ICS 205-930 was dissolved with a few drops of 0.1 N HCl and diluted with saline. These drugs were injected i.p. 30 min before treatment with mCPP or DOI.

2.3. Determination of plasma glucose levels

Blood samples were taken from the caudal vena cava under light ether anesthesia. Only one sample was removed from each rat. Plasma glucose levels were measured by previously described methods (Sugimoto et al., 1992).

2.4. Operation of adrenodemedullation

Bilateral adrenodemedullation was performed under anesthesia with pentobarbital-Na at 50 mg/kg. Experiments were carried out 1 week after the operation.

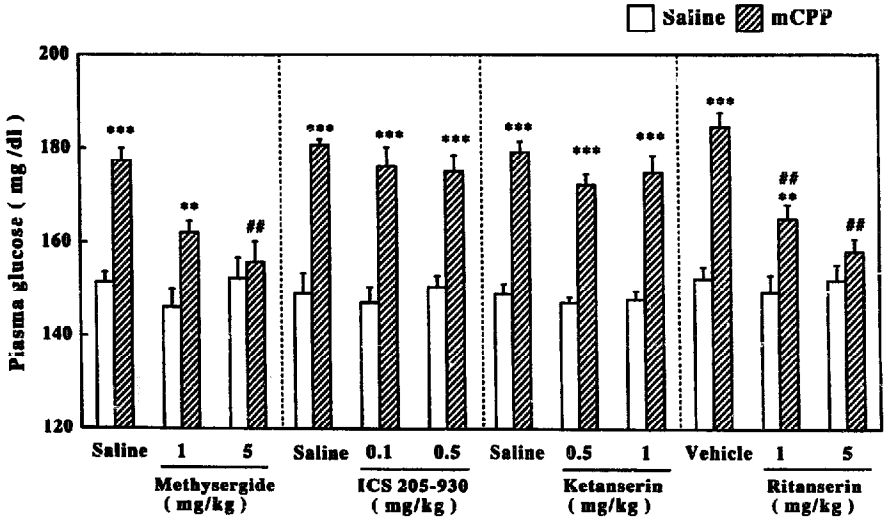

Fig. 2. Effects of 5-HT receptor antagonists on mCPP-induced hyperglycemia in rats. Results are shown as means ± S.E. ($n = 6$–10). mCPP at 10 mg/kg was injected i.p. Plasma glucose levels were determined 15 min after injection of mCPP. 5-HT receptor antagonists were injected i.p. 30 min before mCPP. ** $P < 0.01$, *** $P < 0.001$ vs. antagonist + saline of respective group. ## $P < 0.01$ vs. saline or vehicle + mCPP.

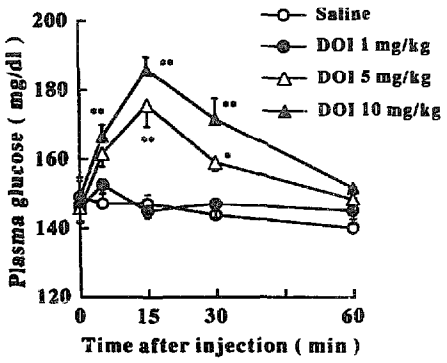

Fig. 3. Effects of DOI on the plasma glucose levels of rats. Results are shown as means ± S.E. ($n = 6$–9). DOI was injected i.p. $^{*}P < 0.05$. $^{**}P < 0.01$.

2.5. Statistics

Statistical significance was evaluated by Student's t-test between two groups. Dose-related effects of mCPP and DOI on plasma glucose levels were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test. Effects of 5-HT receptor antagonists on mCPP and DOI-induced effects were analyzed by two-way ANOVA followed by Tukey's test.

3. Results

3.1. Effects of mCPP on the plasma glucose and 5-HT receptor antagonists on mCPP-induced hyperglycemia

The effects of mCPP on plasma glucose levels are shown in Fig. 1. mCPP above the dosage of 5 mg/kg elicited significant hyperglycemia in rats. Fig. 2 shows the effects of 5-HT receptor antagonists on hyperglycemia 15 min after the treatment with mCPP 10 mg/kg. The 5-HT_1 and 5-HT_2 receptor antagonist methysergide strongly inhibited mCPP-induced hyperglycemia. However, the 5-HT_3 and 5-HT_4 receptor antagonist ICS 205-930 showed no effect. Although the 5-HT_{2A} receptor antagonist ketanserin did not affect mCPP-induced hyperglycemia, the 5-$HT_{2A/2B/2C}$ receptor antagonist ritanserin significantly reduced it. The antagonists used in this study did not affect basal glucose levels.

3.2. Effects of DOI on plasma glucose levels and 5-HT receptor antagonists on DOI-induced hyperglycemia

Fig. 3 shows the effects of DOI on plasma glucose levels. DOI administered i.p. induced significant hyperglycemia at doses above 5 mg/kg. The effects of 5-HT receptor antagonists on DOI-induced hyperglycemia are summarized in Fig. 4. Plasma glucose levels 15 min after the injection of DOI at 10 mg/kg were evaluated. As shown in Fig. 4, methysergide strongly inhibited DOI-induced hyperglycemia, whereas ICS 205-930 was without effect. Both ketanserin and ritanserin suppressed DOI-induced hyperglycemia in rats.

3.3. Effects of mCPP on plasma glucose levels in adrenodemedullated rats

As shown in Fig. 5, mCPP induced significant hyperglycemia in sham-operated rats as well as in normal rats.

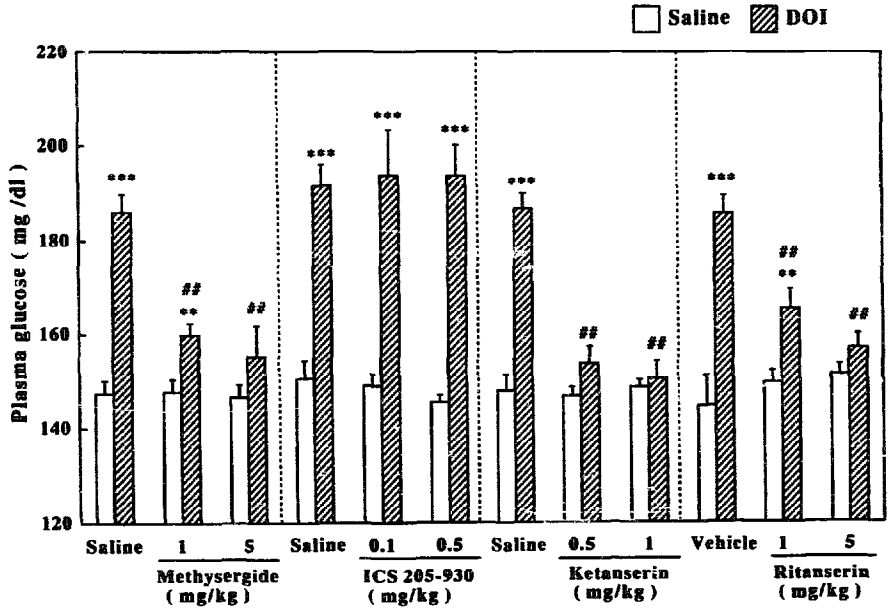

Fig. 4. Effects of 5-HT receptor antagonists on DOI-induced hyperglycemia in rats. Results are shown as means ± S.E. ($n = 6$–9). DOI at 10 mg/kg was injected i.p. Plasma glucose levels were determined 15 min after the injection of DOI. 5-HT receptor antagonists were injected i.p. 30 min before DOI. $^{**}P < 0.01$, $^{***}P < 0.001$ vs. antagonist + saline of respective group. $^{\#\#}P < 0.01$ vs. saline or vehicle + DOI.

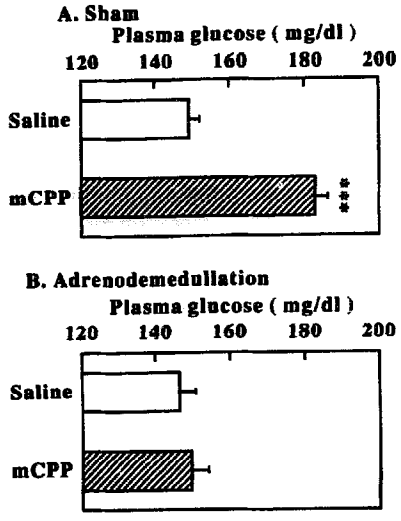

Fig. 5. Effects of mCPP on the plasma glucose levels of adrenodemedullated rats. Results are shown as means ± S.E. ($n = 6$–9). mCPP at 10 mg/kg was injected i.p. Plasma glucose levels were determined 15 min after the injection of mCPP. *** $P < 0.01$.

However, in adrenodemedullated rats, mCPP did not elicit hyperglycemia.

3.4. Effects of hexamethonium on mCPP-induced hyperglycemia

The effects of hexamethonium on hyperglycemia induced by mCPP are shown in Fig. 6. Hexamethonium significantly inhibited mCPP-induced hyperglycemia. Treatment with hexamethonium at 5 mg/kg induced a slight decrease in basal plasma glucose levels, which is consistent with previous data by Chaouloff et al. (1990a).

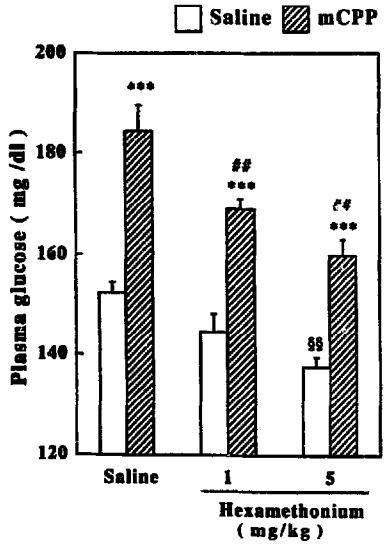

Fig. 6. Effects of hexamethonium on mCPP-induced hyperglycemia in rats. Results are shown as means ± S.E. ($n = 6$-10). mCPP at 10 mg/kg was injected i.p. Plasma glucose levels were determined 15 min after the injection of mCPP. Hexamethonium was injected i.p. 30 min before mCPP. §§ $P < 0.01$ vs. saline + saline. *** $P < 0.01$ vs. hexamethonium + saline of respective group. ## $P < 0.01$ vs. saline + mCPP.

4. Discussion

The effects of mCPP on circulating glucose levels have not been thoroughly analyzed before. Thus, it has been shown that a 1 mg/kg dose of mCPP i.v. elicits slight hyperglycemia in Sprague-Dawley rats (Chaouloff et al., 1992) whereas a 2 mg/kg dose of mCPP i.v. proved ineffective in Wistar rats (Chaouloff et al., 1990b). In confirmation of this, we were able to observe that i.p. administration of mCPP at 5 or 10 mg/kg elicited a short-lasting but significant increase in plasma glucose levels in Sprague-Dawley rats. The hyperglycemic effects of mCPP appeared at somewhat high doses than previously shown pharmacological effects of mCPP, such as hypolocomotion, anxiety or hypophagia, which appear at doses of 1–2 mg/kg (Kennett and Curzon, 1988, 1991).

To clarify the involvement of 5-HT receptor subtypes, the effects of several 5-HT receptor antagonists on mCPP-induced hyperglycemia were studied. The 5-HT_1 and 5-HT_2 receptor antagonist methysergide suppressed mCPP-induced hyperglycemia in a dose-dependent manner, although the 5-HT_3 and 5-HT_4 receptor antagonist ICS 205-930 was without effect. We further examined the effects of the 5-HT_{2A} receptor antagonist ketanserin and the 5-$HT_{2A/2B/2C}$ receptor antagonist ritanserin. Ketanserin at doses of 0.5 and 1 mg/kg did not affect mCPP-induced hyperglycemia. In contrast, ritanserin, which has affinity for 5-$HT_{2A/2B/2C}$ receptors, dose dependently inhibited the effects of mCPP.

It has been suggested that mCPP acts as a 5-HT_{2C} receptor agonist, but is a 5-HT_{2A} receptor antagonist (Conn and Sanders-Bush, 1987). Previous reports also indicate that mCPP can antagonize DOI-induced head shakes which are mediated by the 5-HT_{2A} receptor (Simansky and Schechter, 1987; Kennett and Curzon, 1991). However, reports that mCPP can induce low-intensity head twitches and hyperthermia in rodents may indicate that it has partial 5-HT_{2A} receptor agonist properties (Maj and Lewandowska, 1980; Klodzinska and Chojnacka-Wójcik, 1992). It has been reported that DOI has affinity for both 5-HT_{2A} and 5-HT_{2C} receptors, although it has higher affinity for 5-HT_{2A} receptors (Hoyer et al., 1994). It has been reported that DOI-induced hyperglycemia is related to the 5-HT_{2A} receptor (Chaouloff et al., 1990b; Baudrie and Chaouloff, 1992). Therefore, to investigate whether the 5-HT_{2A} receptor plays a role in mCPP-induced hyperglycemia, we compared the role of 5-HT receptor subtypes in mCPP-induced hyperglycemia with the role of the same receptor subtypes in DOI-elicited effects. As shown in results, DOI i.p. elicited significant hyperglycemia at doses above 5 mg/kg, which is consistent with previous findings (Chaouloff et al., 1990b; Baudrie and Chaouloff, 1992). DOI-induced hyperglycemia was inhibited by methysergide, ketanserin and ritanserin. However, ICS 205-930 did not affect DOI-induced hyperglycemia. Results showed the inhibitory effects of 5-HT receptor antagonists, which have an affinity

for 5-HT_{2A} receptors, and that DOI-induced hyperglycemia is elicited by the activation of 5-HT_{2A} receptors. There is a distinct difference between the blocking effects of the 5-HT_{2A} receptor antagonist ketanserin on the hyperglycemia induced by mCPP or by DOI. Doses of ketanserin that can block DOI-induced hyperglycemia did not affect mCPP-elicited hyperglycemia. From these results, it is indicated that the 5-HT_{2A} receptor is involved in DOI-induced hyperglycemia but not in mCPP-induced hyperglycemia. Chaouloff et al. (1992) reported that fenfluframine (a 5-HT releaser)-induced hyperglycemia was antagonized by the 5-HT_{2A} receptor antagonist ketanserin. Our results obtained with DOI further indicate that the 5-HT_{2A} receptor may have a role in glucose regulation.

Kennett and Curzon (1991) suggested that mCPP (5 mg/kg)-induced hypophagia is mediated by the 5-HT_{2C} receptor, based on the results of the blocking activity of 5-HT receptor antagonists. At present, mCPP-induced hypophagia may be also mediated by the 5-HT_{2B} receptor (Baxter et al., 1995; Kennett et al., 1994). The doses of ritanserin tested in this study are near those causing 50% inhibition of the hypophagia elicited by mCPP. As described above, mCPP-induced hyperglycemia was antagonized by ritanserin, which has affinity for the 5-HT_{2B} and $_{2C}$ receptors. This suggests that the 5-$HT_{2C/2B}$ receptor plays an important role in mCPP-induced hyperglycemia in rats, and that mCPP-induced hyperglycemia is induced by the activation of 5-$HT_{2C/2B}$ receptors. Our results indicate that the 5-$HT_{2C/2B}$ receptor, in addition to 5-HT_{1A} and 5-HT_{2A} receptors, is involved in glucose regulation in rats. However, since the 5-HT receptor antagonists used in our study did not affect basal plasma glucose levels, the physiological significance of these receptors remains unclear.

It has been suggested that mCPP acts as a partial agonist at 5-HT_{1A} receptors and as an antagonist at 5-HT_3 receptors. As shown in the results, the 5-HT_3 receptor antagonist ICS 205-930 was without effect on plasma glucose levels. This suggests that mCPP-induced hyperglycemia is not related to the 5-HT_3 receptor. Our results indicated that, on the basis of results of 5-HT receptor antagonists, hyperglycemia elicited by mCPP is predominantly mediated by the 5-$HT_{2C/2B}$ receptor, although the involvement of 5-HT_{1A} receptors cannot be completely excluded at present.

It has been suggested that mCPP elevates the levels of various neuroendocrine hormones in blood including those of prolactin and corticosterone (Murphy et al., 1991; Bagdy et al., 1989a,b). It has been reported that mCPP increases catecholamine levels and stimulates sympathetic activity in rats (Bagdy et al., 1989a,b). Previous reports suggest that mCPP increases first noradrenaline levels and then at higher doses adrenaline levels (Bagdy et al., 1989a,b; Chaouloff et al., 1992). The functional role of the 5-HT receptor in the release of adrenaline has been investigated and the activation of central 5-HT_{1A} receptors increases adrenaline release from the adrenal gland (Bagdy et al., 1989b; Chaouloff et al., 1990a). Furthermore, activation of central 5-HT_{2A} receptors has stimulatory effects on adrenaline release (Chaouloff et al., 1992). It is well known that an increase in adrenaline release results in hyperglycemia. Bagdy et al. (1989a) demonstrated that mCPP at doses of 2 and 10 mg/kg i.v. increased adrenaline levels, an effect that was suppressed by ritanserin, although ketanserin was ineffective. They therefore assumed that mCPP-induced increases in adrenaline levels were mediated by 5-HT_{2C} receptors (now may be also 5-HT_{2B} receptor) (Bagdy et al., 1989a). This is consistent with the antagonistic effects on mCPP-induced hyperglycemia in the present study. Since adrenaline triggers hyperglycemia, it is speculated that the hyperglycemic effects of mCPP are also caused by the facilitation of adrenaline release. Thus, we examined the effects of mCPP on plasma glucose levels in adrenodemedullated rats.

Adrenodemedullation abolished mCPP-induced hyperglycemia, although in sham-operated rats mCPP elicited hyperglycemia. This suggests that mCPP-induced hyperglycemic effects are the result of facilitation of adrenaline release from the adrenal medulla. Moreover, mCPP-induced hyperglycemia was blocked by treatment with a ganglionic blocker hexamethonium. These results suggest that stimulation of the 5-$HT_{2C/2B}$ receptor by mCPP activates the sympathoadrenomedullary system and results in facilitation of the release of adrenaline from the adrenal medulla and in hyperglycemia.

In conclusion, our results suggest that mCPP can induce hyperglycemia in rats and that this is mediated by the activation of 5-HT_{2C} and/ or $_{2B}$ receptors. The effects of mCPP are considered to be connected to the activation of the sympathoadrenomedullary system. These findings demonstrate that the 5-$HT_{2C/2B}$ receptor may participate in glucose regulation, through the facilitation of adrenaline release, in addition to 5-HT_{1A} and 5-HT_{2A} receptors.

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