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Glucocorticoids and 3,4-methylenedioxymethamphetamine (MDMA)-induced neurotoxicity

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The present study was carried out in order to explore the role of glucocorticoids in 3,4-methylenedioxymethamphetamine (MDMA)-induced neurotoxicity of the central serotonergic system. The activity of tryptophan hydroxylase (TPH) was used as an index of this drug-induced neuronal degeneration. One week after a single high dose of MDMA (20 mg/kg), a significant decrease in the enzyme activity was measured in both the frontal cortex and hippocampus. Adrenalectomy (ADX) attenuated or blocked this decrease in TPH activity in the hippocampus but not in the frontal cortex. This protective effect of ADX on hippocampal serotonergic neurons disappeared with concurrent administration of corticosterone (CORT) and MDMA administration. The long-term MDMA-induced decreases in hippocampal serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations were similarly affected by CORT replacement. However, ADX did not alter the short-term decline in hippocampal TPH activity and 5-HT concentrations measured 3 h after a single dose of MDMA (10 mg/kg s.c.). This study suggests that CORT play a role in the development of neurotoxicity induced by MDMA in the hippocampal serotonergic system, but may be less important in other brain structures.

Adrenalectomy; Corticosterone; 3,4-Methylenedioxymethamphetamine (MDMA); Serotonin (5-HT); Tryptophan hydroxylase; (Neurotoxicity)

1. Introduction

As with many other amphetamine analogues, high doses of 3,4-methylenedioxymethamphetamine (MDMA) can induce long-term depletion of serotonin (5-HT) and decrease the activity of its biosynthetic enzyme, tryptophan hydroxylase (TPH) (Schmidt, 1987; Stone et al., 1986; 1987). These long-lasting changes are associated with the destruction of serotonergic neurons as demonstrated by the decrease of 5-HT uptake sites (Commins et al., 1987b; Schmidt, 1987) and by immunocytochemistry (O'Hearn et al., 1988). Similar to p-chloroamphetamine, MDMA can produce this neuronal degeneration after a single administration (Sanders-Bush et al., 1975; Schmidt, 1987). The mechanism by which MDMA induces this effect remains elusive. It is interesting to note that direct injection of MDMA (Molliver et al., 1986) or methamphetamine (Matsuda, 1987) into brain tissue, or intraventricular administration of p-chloroamphetamine (Gál et al., 1975), does not induce the neurochemical changes or the neurotoxicity associated with systemic administration of these amphetamine analogs. This raises the possibility that amphetamine and its analogues induce the formation or release of some endogenous substance(s) in the periphery rendering the neuron vulnerable to the drug insult.

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Glucocorticoid hormones, which are secreted by adrenal glands, could be such released compounds, since it is well established that amphetamine analogues such as MDMA increase the blood concentration of these hormones (Nash et al., 1988). Interestingly, glucocorticoids have been implicated in the loss of hippocampal neurons observed during aging (Meaney et al., 1988), or produced by hypoxia-ischemia following vascular occlusion (Sapolsky and Pulsinelli, 1985), or following the microinfusion of neurotoxins such as kainic acid and 3-acetylpyridine (Sapolsky, 1985a,b; 1986). The depletion of glucocorticoids resulting from adrenalectomy (ADX) attenuates or prevents the neuronal loss induced by these treatments (Landfield et al., 1981; Sapolsky and Pulsinelli, 1985; Sapolsky, 1986). It is suggested that glucocorticoids make hippocampal neurons vulnerable to certain insults by interfering with the cellular generation of energy (Sapolsky, 1986). Thus, although dopamine (DA), 6-hydroxydopamine and 5,6-dihydroxytryptamine have been described as mediators of the amphetamine-induced neurotoxicity (Commins and Seiden, 1986; Commins et al., 1987a; Schmidt et al., 1985), the possible detrimental action of glucocorticoids on central brain neurons may be a significant factor contributing to the MDMA-induced neurodegenerative process.

This study also examines the role of glucocorticoids on the immediate action of MDMA on the central serotonergic system. 5-HT concentrations and TPH activity are significantly reduced within 1 h following the administration of MDMA (Stone et al., 1986; 1987). Contrary to the decrease measured 1 week after the drug administration, the immediate decline is not associated with neuronal degeneration. The biphasic action of MDMA is best illustrated by the changes in 5-HT concentrations which are depleted maximally by 3 h following a single dose of MDMA and are completely restored to normal by 24 h; a subsequent decrease occurs within the next week resulting from neuronal degeneration (Schmidt, 1987; Stone et al., 1987). It is not yet clear if the immediate effect of MDMA is a prerequisite for the ultimate drug-induced degeneration of the serotonergic system; thus, the study of the immediate effects of MDMA should help to understand the mechanism leading to both phases of the response to MDMA.

2. Materials and methods

Male Sprague-Dawley rats weighing 180-260 g were housed in groups (3-4 per cage) in a temperature-controlled room (24°C) having a 12-h light/dark period. Bilateral ADX was performed under ketamine anaesthesia (175 mg/kg i.p.) through a midline dorsal incision. Sham-operation was carried out according to a similar procedure but without removal of the glands. Adrenalectomized rats had access to food and 0.9% saline ad libitum whereas sham-operated rats were given water instead of saline. Five days later, rats were administered a single s.c. injection of 0.9% NaCl or MDMA (10 or 20 mg/kg, expressed as free base) and killed either 3 h or 1 week later. In the corticosterone (CORT)-treated group, adrenalectomized rats were injected s.c. with 10 mg of CORT (Sigma) in 1 ml of sesame oil at 24 h and 15 min before the MDMA administration as well as 24 h after the administration, while the control group received only vehicle. After decapitation, blood from the trunk was collected in heparinized tubes while the brain was quickly removed from the skull and placed on a cold plate. Frontal cortex and hippocampus were removed, frozen on dry ice, and stored at −80°C until assayed. The success of the ADX was assessed by measuring the plasma CORT concentrations, the major adrenal hormone in the rat (Bush, 1953), according to the micromethod described by Glick et al. (1964).

Frontal cortex and hippocampus were homogenized in 80 and 200 μl, respectively, of 5 mM dithiothreitol, 50 mM N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid (HEPES) buffer (pH 7.4) containing 0.2% (v/v) Triton X-100, and centrifuged for 15 min at 40000 × *g* (4°C). Duplicate 7.5 μl aliquots of the supernatant were used to measure TPH activity by a modified $^{14}CO_2$-trapping procedure using (±)-6-methyl-5,6,7,8-tetrahydrobiopterin as cofactor. Further details of the method are described by Hotchkiss et al. (1979).

The concentrations of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) were measured by high-performance liquid chromatography (HPLC) using electrochemical detection (model LC-4B, Bioanalytical Systems Inc, West Lafayette, IN). Details of the assay have been previously reported (Johnson et al., 1987).

A one-way ANOVA analysis with a Student-Newman-Keuls multiple comparisons test was used to analyze the statistical significance of the results presented in this study.

3. Results

One week after a single administration of MDMA (20 mg/kg), cortical and hippocampal TPH activity in sham-operated rats were reduced to 51 and 49% of control, respectively (fig. 1). ADX significantly attenuated the MDMA-induced decrease measured in the hippocampus

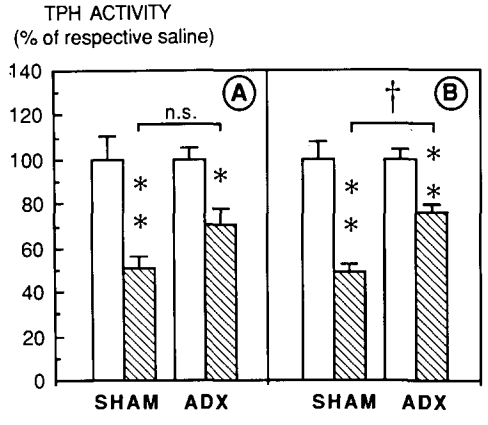

Fig. 1. TPH activity was measured in the frontal cortex (A) and in the hippocampus (B) of sham-operated or adrenalectomized rats 1 week after administration of a single dose of 0.9% NaCl □ or MDMA (20 mg/kg s.c.) ▨. ADX was performed 5 days before drug treatment. Means ± S.E. of the enzymatic activity are expressed as percent of respective saline-treated rats. The TPH activity of the sham-saline control expressed in nmol of hydroxylated tryptophan/h per g tissue were 112.4 ± 11.9 (n = 6) and 84.8 ± 6.4 (n = 6) for panels (A) and (B), respectively. ADX-saline values were 92.5 ± 5.0 (n = 6) and 76.0 ± 3.6 (n = 6) for panels (A) and (B), respectively. * $P < 0.05$; ** $P < 0.01$ versus corresponding saline-treated control. † $P < 0.05$ versus sham-MDMA group (n = 8-9 for MDMA-treated rats).

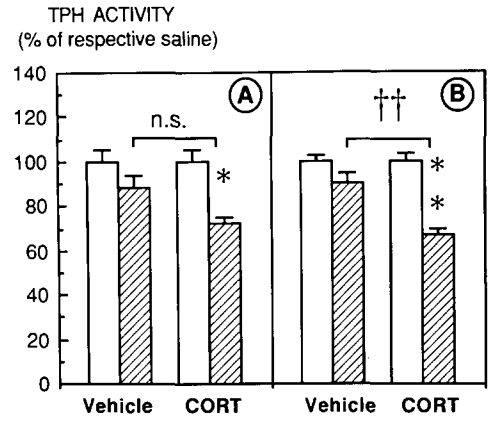

Fig. 2. Effects of CORT treatment on frontal cortex (A) and hippocampal (B) TPH activity measured in adrenalectomized rats 1 week after administration of a single dose of 0.9% NaCl □ of MDMA (20 mg/kg s.c.) ▨. All rats were adrenalectomized 5 days prior to administration of MDMA or saline. Means ± S.E. of TPH activity are expressed as percent of control. The frontal cortex TPH activity of the vehicle-saline and CORT-saline controls were (expressed in nmol of hydroxylated tryptophan/h per g of tissue) 103.7 ± 4.9 (n = 6) and 117.4 ± 6.5 (n = 6), respectively. The hippocampal TPH activity of the vehicle-saline and CORT-saline controls were 78.4 ± 2.2 (n = 6) and 84.1 ± 3.1 (n = 6), respectively. * $P < 0.05$; ** $P < 0.01$ versus corresponding saline-treated control. †† $P < 0.01$ versus vehicle-MDMA-treated group (n = 8-9 for MDMA-treated groups).

while failing to alter significantly the decline measured in the frontal cortex. ADX resulted in a total blockade of the MDMA-induced decrease in hippocampal TPH activity induced by a 10 mg/kg dose (results not shown). ADX alone did not affect significantly the TPH activity measured in saline-treated rats (results presented in fig. 1 legend).

In order to determine if CORT is the adrenal hormone contributing to the MDMA-induced changes in the hippocampal serotonergic system, adrenalectomized rats were subjected to a single dose of MDMA (20 mg/kg), with or without CORT treatment (for description of CORT treatment, see Materials and methods section), and killed 1 week later. The CORT administration alone did not alter TPH activity measured in either brain area (fig. 2 legend). In contrast to the previous experiment (fig. 1), MDMA treatment alone failed to decrease significantly the TPH

activity measured in adrenalectomized rats (fig. 2). This could be explained either from the variation in the degree of neuronal degeneration induced by a single dose of MDMA, or from better protection induced by ADX against the drug effect. When MDMA was administered to CORT-treated adrenalectomized rats, a significant depletion of TPH activity was measured in both the frontal cortex and hippocampus. The level of hippocampal TPH activity measured in CORT-treated rats was significantly lower than in the vehicle-MDMA-treated rats; there was no statistically significant difference between the MDMA-treated groups in the frontal cortex.

Figure 3 shows that CORT replacement in adrenalectomized rats potentiated the MDMA-induced decline in hippocampal 5-HT and 5-HIAA concentrations in a similar manner as described in fig. 2 for TPH activity. The administration of MDMA (20 mg/kg) to adrenalectomized rats significantly reduced the cortical and hippocampal 5-HT measured 1 week after drug administration while 5-HIAA concentrations remained unaffected by the treatment. The CORT replacement treatment did significantly potentiate the MDMA-induced decline in hippocampal 5-HT and 5-HIAA concentrations (fig. 3B and D) but did not modify the effects of MDMA on the cortical 5-HT and 5-HIAA concentrations (fig. 3A and C). The CORT replacement treatment alone failed to affect cortical and hippocampal 5-HT concentrations as well as cortical 5-HIAA concentrations; in contrast, the replacement treatment significantly increased the hippocampal 5-HIAA concentration by 19% suggesting a possible increase in 5-HT turnover (fig. 3D, means expressed as $\mu g/g$ tissue $\pm$ S.E.: 0.21 ± 0.009 ($n = 6$) in vehicle-saline-treated rats versus 0.25 ± 0.01 ($n = 6$) in CORT-saline-treated rats; $P < 0.05$).

While the results described above demonstrate that CORT affects the long-term MDMA-induced neurotoxicity in the hippocampus, the results presented in table 1 demonstrate that ADX fails to influence the reversible short-term decrease in TPH activity and 5-HT concentrations measured 3 h after administration of MDMA. A single dose of MDMA (10 mg/kg s.c.) decreased TPH activity to 37 and 48% of sham-saline control in the frontal cortex and hippocampus, respectively, whereas 5-HT concentrations were decreased to 20 and 27%, respectively. MDMA-induced decline in 5-HIAA concentrations reached 60 and 54% of

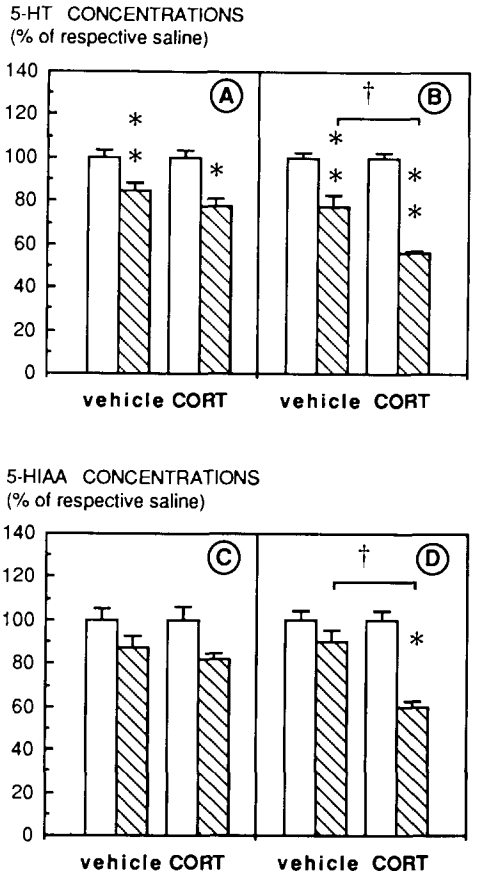

Fig. 3. Effects of CORT treatment on frontal cortex (A and C) and hippocampal (B and D) 5-HT and 5-HIAA concentrations measured in adrenalectomized rats 1 week after the administration of a single dose of 0.9% NaCl □ or MDMA (20 mg/kg s.c.) ▨. The rats were treated as in fig. 2. Means $\pm$ S.E. of transmitter concentrations are expressed as percent of respective saline-treated rats. The frontal cortex 5-HT concentration of the vehicle-saline and CORT-saline controls were (expressed in $\mu g/g$ of tissue) 0.58 ± 0.02 ($n = 5$) and 0.63 ± 0.02 ($n = 6$), respectively, while 5-HIAA concentrations were 0.16 ± 0.01 ($n = 5$) and 0.17 ± 0.01 ($n = 6$), respectively. The hippocampal 5-HT concentrations of the vehicle-saline and CORT-saline controls were 0.40 ± 0.01 ($n = 6$) and 0.43 ± 0.01 ($n = 6$), respectively, while 5-HIAA concentrations were 0.21 ± 0.009 ($n = 6$) and 0.25 ± 0.01 ($n = 6$), respectively. * $P < 0.05$; ** $P < 0.01$ versus corresponding saline-treated control. † $P < 0.05$ versus vehicle-MDMA-treated group ($n = 8$-9 for MDMA-treated groups).

TABLE 1

Effects of ADX on the MDMA-induced decrease in TPH activity and 5-HT, 5-HIAA concentrations measures 3 h after MDMA administration. ADX and sham operations were performed 5 days before the administration of MDMA (10 mg/kg s.c.), and the rats were killed 3 h after MDMA administration. Means ± S.E. of TPH activity are expressed as nmol of tryptophan hydroxylated/h per g tissue while means of 5-HT and 5-HIAA concentrations are expressed in μg/g tissue. The number of rats used in each group is indicated in parentheses. A one-way ANOVA analysis with a Student-Newman-Keuls multiple comparisons test was used to analyze the data.

	Sham-saline (n = 5)	ADX-saline (n = 5)	Sham-MDMA (n = 5)	ADX-MDMA (n = 6)
Frontal cortex				
TPH	88.5 ±11.7	71.4 ±2.4	32.7 ±5.4 [b,d]	32.9 ±6.7 [b,d]
5-HT	0.64± 0.04	0.52±0.01 [b]	0.13±0.02 [b,d]	0.14±0.01 [b,d]
5-HIAA	0.15± 0.02	0.13±0.01	0.09±0.01 [a]	0.09±0.01 [a]
Hippocampus				
TPH	66.8 ± 5.0	59.2 ±4.3	32.3 ±3.3 [b,d]	38.9 ±3.2 [b,d]
5-HT	0.37± 0.03	0.28±0.04 [b]	0.10±0.01 [b,d]	0.10±0.01 [b,d]
5-HIAA	0.24± 0.02	0.18±0.02 [a]	0.13±0.01 [b,c]	0.16±0.02 [a]

[a] $P < 0.05$ versus sham-saline; [b] $P < 0.01$ versus sham-saline; [c] $P < 0.05$ versus ADX-saline; [d] $P < 0.01$ versus ADX-saline.

sham-saline control in those respective brain structures. ADX did not affect the MDMA-induced changes. However, ADX alone reduced the concentration of 5-HT measured in the frontal cortex and hippocampus, as well as the hippocampal 5-HIAA concentration.

4. Discussion

This study suggests that CORT plays an important role in mediating the MDMA-induced neurotoxicity in the hippocampal serotonergic system. However, CORT involvement in this drug-induced neurotoxicity appears to be limited to this brain structure as ADX or CORT supplementation did not significantly alter the MDMA-induced deficits in the frontal cortex. This localized action of CORT may be explained by the high rate of accumulation and retention of glucocorticoids in the hippocampus (McEwen et al., 1986), which in turn could result in a greater influence on the hippocampal neurons. The CORT action is probably mediated through the Type I CORT receptor (CR) which is highly concentrated in the hippocampus (McEwen, 1987). While CORT treatment alone does not impair the serotonergic system, as demonstrated by the lack of changes in TPH activity in saline-treated animals (fig. 2), CORT appears to sensitize hippocampal serotonergic neurons to MDMA-induced neurotoxicity by a mechanism that remains unclear. A role for glucocorticoids has been established in the death of hippocampal neurons resulting from aging (Meaney et al., 1988), ischemia, or following infusion with kainic acid or 3-acetylpyridine (Sapolsky, 1985a,b; 1986). This study demonstrates for the first time that CORT also increases the vulnerability of hippocampal serotonergic neurons to the neurotoxic action of MDMA.

The administration of a single dose of MDMA produces neuronal degeneration of the central serotonergic system (Commins et al., 1987a; Schmidt, 1987) which results in the depleted TPH activity measured after 1 week (fig. 1). Shortly after the injection of MDMA, a rapid decrease in TPH activity, as well as in 5-HT and 5-HIAA concentrations, also occurs (Stone et al., 1986; 1987). These rapid changes are not associated with the development of neuronal degeneration because of their reversibility (Schmidt, 1987; Stone et al., 1987). This immediate and long-term effects of MDMA are similar to those of another amphetamine analogue, p-chloroamphetamine, which also elicits distinct immediate and long-term serotonergic effects (Fuller et al., 1975). The absence of impact of ADX on the acute MDMA-induced decrease in TPH activity (table 1) suggests

that adrenal hormones do not participate in this early drug effect. On the other hand, because ADX and CORT treatments affect the MDMA-induced changes in hippocampal TPH activity and 5-HT concentrations 1 week after the administration of MDMA, this study suggests that CORT could participate in the neurotoxic action of MDMA.

Because the mechanism by which MDMA induces neuronal degeneration is still unknown, a variety of causes can be suggested for the effect of CORT on the MDMA-induced hippocampal toxicity. Sapolsky (1986) suggested that CORT makes hippocampal neurons vulnerable to kainic acid or 3-acetylpyridine by reducing glucose uptake into the cells. It is possible that CORT sensitizes 5-HT neurons to MDMA in a similar fashion. Moreover, glucocorticoids increase DA turnover (McEwen et al., 1986) and thus could influence MDMA-induced toxicity as DA has been implicated as an essential etiological factor in the toxicity by amphetamine analogues (Commins and Seiden, 1986; Schmidt et al., 1985; Stone et al., in press). Other transmitter systems also are affected by ADX and could also be involved in the CORT response in the hippocampus (Gilad et al., 1987; McEwen et al., 1986). Another possible explanation for these findings is that the MDMA-induced toxicity is affected by the hormonal treatment as a result of a CORT-mediated change in the access or the diffusion of MDMA in the brain rather than a modification by CORT of a transmitter system. However, this is unlikely as previous studies with amphetamine or kainic acid showed that ADX or CORT treatment does not influence the central diffusion of these drugs (Bischoff et al., 1983; Sapolsky, 1985b).

Glucocorticoids could modify the MDMA-induced toxicity by affecting 5-HT synthesis and turnover. ADX decreases indices of 5-HT turnover in several brain structures (McEwen et al., 1986), while glucocorticoids and stress increase the activity of TPH (Gál et al., 1968; Azmitia and McEwen, 1974; McEwen et al., 1986). We, as others (Sze, 1976), failed to detect a significant decrease in TPH activity induced by ADX as previously reported (McEwen et al., 1986). However, the changes in 5-HT and 5-HIAA observed in fig. 3 and table 1 suggest that a change in 5-HT turnover may have taken place during the different hormonal manipulations. It remains to determine if an increase in 5-HT turnover can potentiate the MDMA-induced toxicity. It is currently believed that 5-HT itself does not participate in the amphetamine-induced toxicity as the depletion of this transmitter with p-chlorophenylalanine failed to protect the serotonergic system from the p-chloroamphetamine-induced toxicity (Fuller et al., 1975). This conclusion remains to be confirmed as this study was performed in the whole brain of the rat.

In contrast to systemic administration, direct local injection of MDMA (Molliver et al., 1986) into the brain, or intraventricular administration of p-chloroamphetamine (Gál et al., 1975) fails to produce serotonergic neurotoxicity. A first explanation for these observations could be that amphetamine analogues are metabolized into an active neurotoxic substance in the periphery before entering into the brain. However, this possibility appears unlikely since the inhibition of methamphetamine metabolism with iprindole (Peat et al., 1983) or of MDMA with SKF-525A (Yeh et al., 1986) failed to protect the central serotonergic system. In fact, the inhibition of methamphetamine metabolism appears to enhance the central effects of methamphetamine by increasing its availability to the brain (Peat et al., 1983). These observations led us to believe that the discrepancy between the neurochemical effects of central and systemic drug administration could be that systemic administration induces the release of a substance from the periphery making central neurons vulnerable to the action of the amphetamine analogues. The present data suggest that such a mechanism is involved in the destruction of hippocampal serotonergic neurons. However, because the ADX failed to protect every brain structure from MDMA-induced toxicity, factors other than the glucocorticoids may also be important in mediating neuronal damage induced by amphetamine analogues.

The results presented in this study are significant since they demonstrate that the hippocampal serotonergic system is more vulnerable to the MDMA action in the presence of CORT. Because

Ricaurte and collaborators (1987) have reported that monkeys are more sensitive than rats to MDMA toxicity, it is likely that MDMA-induced toxicity occurs in humans. Thus, it is important to determine if stressful conditions, which increase blood CORT concentrations (Azmitia and McEwen, 1974), make brain areas, such as the hippocampus, more vulnerable to the neurotoxic action of amphetamine and its analogues. Other conditions such as Cushing's disease, or the administration of a CORT analog, might also put individuals using MDMA at a greater risk of suffering brain damage.

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