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In vivo modulation of rat hypothalamic histamine release by the histamine H_3 receptor ligands, immepip and clobenpropit. Effects of intrahypothalamic and peripheral application

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Abstract

We investigated the effect of the new potent and selective histamine H_3 receptor agonist, immepip, and the histamine H_3 receptor antagonist, clobenpropit, on in vivo neuronal histamine release from the anterior hypothalamic area of urethane-anesthetized rats, using microdialysis. Intrahypothalamic perfusion with immepip at concentrations of 1 and 10 nM reduced histamine release to 75% and 35% of its basal level, respectively. Peripheral injection of immepip (5 mg/kg) caused a sustained decrease in histamine release of 50%. Clobenpropit potently increased histamine release after intrahypothalamic perfusion. The maximal increase in histamine release was 2-fold, observed at a concentration of 10 nM clobenpropit. Peripheral injection of clobenpropit (5–15 mg/kg) increased histamine release to about 150% of the basal value. A more marked increase in histamine release was found after injection of the histamine H_3 receptor antagonist, thioperamide (5 mg/kg). In conclusion, intrahypothalamic perfusion of the histamine H_3 receptor agonist, immepip and the histamine H_3 receptor antagonist, clobenpropit, potently and oppositely modulated in vivo histamine release from the anterior hypothalamic area. The decreased histamine release after peripheral injection of immepip indicates that this novel agonist readily crosses the blood–brain barrier, making it a potential candidate for in vivo histamine H_3 receptor studies. The differential increase in histamine release after peripheral injection of clobenpropit and thioperamide is discussed.

Keywords: Histamine H_3 receptor; Histamine release; Microdialysis, in vivo; Hypothalamus; Immepip (VUF4708); Clobenpropit (VUF9153)

1. Introduction

Histamine is a well-established neurotransmitter in the invertebrate and vertebrate central nervous system, including that of mammals (Timmerman, 1990; Onodera et al., 1994; Schwartz et al., 1995). Histaminergic neurons originate from the posterior hypothalamus and project in a rather diffuse way to essentially all parts of the central nervous system (Schwartz et al., 1991; Wada et al., 1991). In vitro studies with brain slices and synaptosomes have demonstrated that neuronal histamine release is modulated by presynaptic histamine H_3 autoreceptors (Arrang et al., 1983; van der Werf et al., 1987) and by various heteroreceptors, i.e., α_2- adrenoceptors (Hill and Straw, 1988), muscarinic M_1 receptors (Gulat-Marnay et al., 1989), κ-opioid receptors (Gulat-Marnay et al., 1990), galanin receptors (Arrang et al., 1991), μ-opioid receptors (Itoh et al., 1988) and nicotine receptors (Ono et al., 1992). More recently, microdialysis methods were applied in order to study histamine release in vivo (Itoh et al., 1991; Mochizuki et al., 1991). It was shown that the histaminergic output from the rat hypothalamus displays a circadian rhythm (Mochizuki et al., 1992). Neuronal histamine release in vivo is reduced by peripheral injection of α-fluoromethylhistamine, an irreversible inhibitor of the histamine synthesizing enzyme histidine decarboxylase (Mochizuki et al., 1991). Microdialysis studies also demonstrated a role of histamine H_3 autoreceptors (Mochizuki et al., 1991; Itoh et

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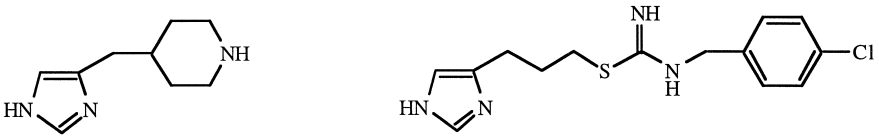

immepip
$pD_2 = 8.0^{1)}$

clobenpropit
$pA_2 = 9.9^{2)}$

Fig. 1. The chemical structures of the histamine H_3 receptor agonist, immepip, and the histamine H_3 receptor antagonist, clobenpropit. (1) Vollinga et al., 1994. (2) van der Goot et al., 1992. Activities were determined in an in vitro test system measuring histamine H_3 receptor-mediated relaxation of the electrically contracted guinea-pig jejunum.

al., 1992; Prast et al., 1994), α_2-adrenoceptors (Prast et al., 1991; Laitinen et al., 1995), NMDA receptors (Okakura et al., 1992), interleukin-1β (Niimi et al., 1994), μ-opioid receptors (Chikai et al., 1994; Chikai and Saeki, 1995) and GABA receptors (Okakura-Mochizuki et al., 1996) in the modulation of in vivo neuronal histamine release.

In vitro and in vivo release studies substantially contributed to current knowledge of histaminergic neuron (patho)physiology and of the possible ways to influence neuronal histamine-related effects, such as arousal, locomotor activity, learning and memory, appetite, autonomic regulation and pituitary hormone secretion (for review, see Schwartz et al., 1991; Onodera et al., 1994). To modify the activity of the histaminergic system, the development of brain-penetrating histamine H_3 receptor ligands is of major interest. The histamine H_3 agonist immepip (Vollinga et al., 1994) and the histamine H_3 receptor antagonist clobenpropit (van der Goot et al., 1992) have recently been described as novel potent and selective probes to study histamine H_3 receptors in vitro (Fig. 1). Both compounds belong to a chemical class different from the histamine H_3 receptor ligands which have predominantly been used for in vivo studies, i.e., the histamine H_3 receptor agonist (*R*)α-methylhistamine and the histamine H_3 receptor antagonist thioperamide (Arrang et al., 1987).

In the present study, we investigated the effect of intrahypothalamic and systemic administration of immepip and clobenpropit on in vivo neuronal histamine release from the anterior hypothalamus of the rat, using microdialysis, to get insight in the dynamics of hypothalamic histamine release and in the in vivo potential of the two histamine H_3 receptor ligands to modulate neuronal histamine release.

2. Materials and methods

2.1. Microdialysis method

The microdialysis procedure used was previously described by Mochizuki et al. (1991). In brief, male Wistar rats (200–250 g) were anesthetized with urethane (1.2 g/kg, i.p.) and placed in a stereotaxic frame. A hole was drilled into the skull and a microdialysis probe (CMA/12, Carnegie, Stockholm, Sweden) was inserted into the anterior hypothalamic area (coordinates: AP: 1.5, L: 0.5, V: 9.2 mm relative to the bregma and dural surface). The anterior hypothalamic area was continuously perfused with sterile artificial cerebrospinal fluid (2 mM sodium phosphate buffer, 140 mM NaCl, 3 mM KCl, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$ and 5 mM glucose, pH 7.4) at a constant flow of 1 μl min^{-1}. One hundred minutes after implantation of the microdialysis probe, samples were collected every 20 min. Administration of immepip and clobenpropit was started after collection of the third basal fraction. The histamine content of the samples was measured as previously described, using a high-performance liquid chromatography fluorometric method (Yamatodani et al., 1985). Briefly, 20 μl dialysate samples were mixed with 2 μl of 20% (v/v) perchloric acid and injected into a 4 × 50 mm column packed with a cation exchanger, TSK gel SP2SW (particle size 5 μm; Tosoh). Histamine was eluted with 0.25 M KH_2PO_4 (flow: 0.6 ml/min) and derivatized by the on-line automated Shore's *o*-phthalaldehyde method. The detection limit for histamine was 10 fmol/sample. Neither immepip nor clobenpropit interfered with the assay of histamine.

2.2. Drugs and chemicals

Immepip dihydrobromide (VUF4708); 4-(1*H*-imidazol-4-ylmethyl)piperidine dihydrobromide, thioperamide dimaleate and clobenpropit dihydrobromide (VUF9153) were from laboratory stock (Vrije Universiteit, Amsterdam, the Netherlands). All other chemicals used were of analytical grade.

2.3. Administration of drugs

For intrahypothalamic application, immepip and clobenpropit were dissolved in artificial cerebrospinal fluid and were infused through the microdialysis probe. When administered peripherally, drugs were dissolved in sterile

sodium chloride solution (0.9% w/v) and were injected subcutaneously (volume: 1 ml/kg body weight).

2.4. Statistical analysis

The histamine content of the samples collected after administration of the drugs was compared with the histamine content of the basal fraction preceding administration of the drugs. To determine the statistical significance of the drug effects, an unpaired two-tailed Student's *t*-test with a Bonferroni correction for multiple comparison was used. The histamine content of the samples was considered significantly different from that of the basal samples when *P*-values were smaller than 0.05.

3. Results

Under the experimental conditions used, a constant release of histamine from the anterior hypothalamic area was observed, and remained stable from collection of the first sample for at least 5 h (Mochizuki et al., 1991). The average histamine content in the dialysates was 58 ± 5 fmol/20 min (mean ± S.E.M.).

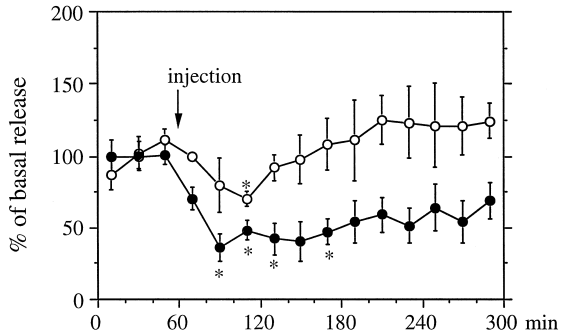

Fig. 3. The effect of s.c. injection of immepip on hypothalamic histamine release. Immepip was injected after collection of the third fraction as indicated by the arrow. Values are given as the means ± S.E.M. of four to five experiments (* $P < 0.05$ compared to the third basal fraction). Symbols used: (○) 1 mg/kg; (●) 5 mg/kg immepip. Injection of saline did not affect basal histamine levels (not shown).

3.1. Effect of local and peripheral application of immepip on hypothalamic histamine release

Histamine release from the anterior hypothalamic area was potently and concentration dependently inhibited by intrahypothalamic perfusion of the histamine H_3 receptor agonist immepip (Fig. 2). At a concentration of 1 nM immepip, histamine release decreased to 75% of the basal

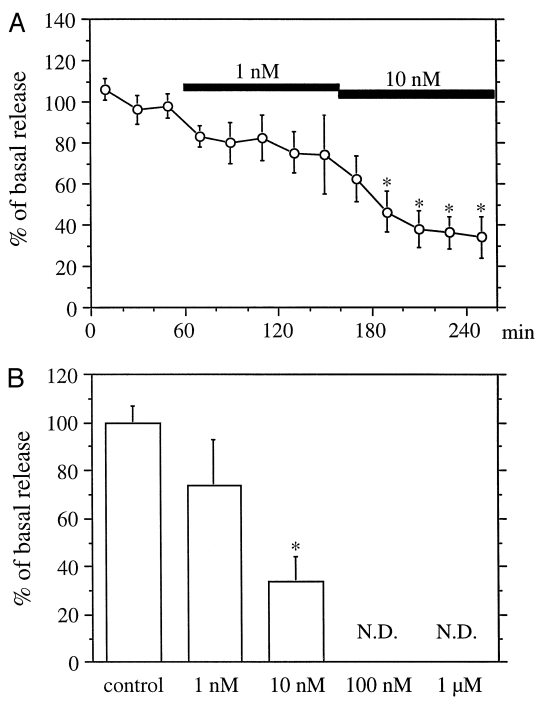

Fig. 2. The effect of intrahypothalamic perfusion of immepip on histamine release. Perfusion of immepip was started after collection of the third basal fraction, as indicated by the horizontal bars (A). The values in (B) correspond to the fourth fractions collected after perfusion of the corresponding concentrations of immepip. Values are given as the means ± S.E.M. of three to five experiments. * $P < 0.05$, compared to the third basal fraction; ND: not detected; histamine release below detection limit (10 fmol/sample).

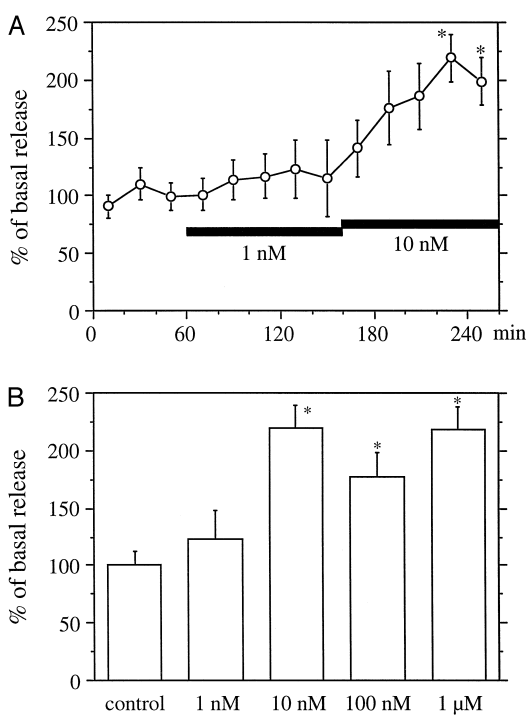

Fig. 4. The effect of intrahypothalamic perfusion of clobenpropit on histamine release. Perfusion with clobenpropit was started after collection of the third basal fraction, as indicated by the horizontal bars (A). The values in (B) are for the fourth fractions collected after perfusion with the corresponding concentrations of clobenpropit. Values are given as the means ± S.E.M. of five experiments (* $P < 0.05$, compared to the third basal fraction).

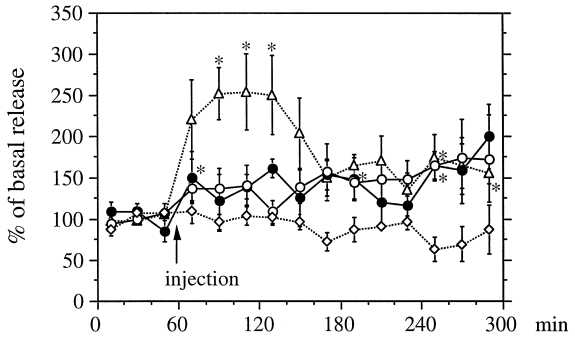

Fig. 5. The effect of s.c. injection of clobenpropit and thioperamide on hypothalamic histamine release. The drugs were injected after collection of the third fraction as indicated by the arrow. Values are given as the means ± S.E.M. of three to six experiments (* $P < 0.05$, compared to the third basal fraction). Symbols used: (◇) 2 mg/kg; (○) 5 mg/kg; (●) 15 mg/kg clobenpropit; (△) 5 mg/kg thioperamide. Injection of saline did not affect basal histamine levels (not shown).

value (Fig. 2A). Histamine release was significantly reduced to 35% of its basal value ($P < 0.05$) after perfusion of 10 nM immepip. At concentrations higher than 10 nM immepip, histamine release was below the detection limit (10 fmol/sample, Fig. 2B). Peripheral injection of immepip at a dose of 1 mg/kg (s.c.) induced a small and transient decrease in histamine release to 70% of the basal value 60 min after injection ($P < 0.05$). At a dose of 5 mg/kg, immepip caused a sustained decrease in histamine release to 50% of the basal value and this lasted for more than 3 h (Fig. 3).

3.2. Effect of local and peripheral application of clobenpropit on hypothalamic histamine release

Clobenpropit, administered through the dialysis probe, potently increased histamine release. At a clobenpropit concentration of 10 nM, histamine release was significantly increased by approximately 2-fold (Fig. 4A). Higher concentrations of clobenpropit caused no further increase in histamine release (Fig. 4B). Histamine release was moderately increased upon peripheral injection of clobenpropit (5–15 mg/kg, s.c.) to about 150% of its basal value (Fig. 5). In contrast, the histamine H_3 receptor antagonist, thioperamide (5 mg/kg), rapidly and markedly increased histamine release to about 250% of the basal value (Fig. 5).

4. Discussion

The histamine H_3 receptor agonist, immepip, and the histamine H_3 receptor antagonist, clobenpropit, were recently described as novel ligands exhibiting high affinity and selectivity for histamine H_3 receptors in the guinea-pig intestine (van der Goot et al., 1992; Vollinga et al., 1994) and rat brain (Jansen et al., 1994). Clobenpropit and immepip are among the most potent histamine H_3 receptor ligands in vitro. Yet, the in vivo potency of both compounds has been largely unexplored. In the present study, we demonstrated that intrahypothalamic perfusion with immepip and clobenpropit potently and oppositely modulated in vivo histamine release from the anterior hypothalamic area. These observations are in general agreement with in vitro studies describing the effects of histamine H_3 receptor agonists and histamine H_3 receptor antagonists on depolarization-induced histamine release from brain slices and synaptosomes (Arrang et al., 1983; van der Werf et al., 1987). Previous reports showed that histamine release from the anterior hypothalamic area is almost completely of neuronal origin, being sensitive to tetrodotoxin, Ca^{2+}-dependent and increased by electrical stimulation and infusion of potassium (Mochizuki et al., 1991; Itoh et al., 1992) In addition, the anterior hypothalamic area is almost devoid of mast cells (Olsson, 1968). As the anterior hypothalamic area is enriched with histaminergic nerve endings, the effect of intrahypothalamic perfusion of immepip and clobenpropit is likely to be caused by their action at histamine H_3 receptors located on these histaminergic nerve endings. The increase in histamine release produced by the histamine H_3 receptor antagonist clobenpropit may be explained by a tonic autoinhibition of histamine release from histaminergic neurons by endogenous histamine.

Intrahypothalamic perfusion with immepip induced a sustained decrease in neuronal histamine release. The effect of local perfusion with the histamine H_3 receptor agonist, (*R*)α-methylhistamine, on neuronal histamine release has been studied by using the push–pull technique (Prast et al., 1994). In that study, histamine release from the anterior hypothalamic area was transiently decreased after perfusion with (*R*)α-methylhistamine. The effective concentration of (*R*)α-methylhistamine (10 μmol/l) to decrease histamine release largely exceeded the concentration at which immepip inhibited histamine release in our study (10 nM). It may be noted however, that in the study of Prast et al., the concentration dependency of (*R*)α-methylhistamine was not studied, and drugs were examined over a shorter time-scale, using a different perfusion technique (i.e., push–pull cannula). Although we could not compare the effect of intrahypothalamic perfusion with (*R*)α-methylhistamine in our assay, because the compound interfered with the determination of histamine, immepip may be a more potent inhibitor of hypothalamic histamine release than (*R*)α-methylhistamine when administered directly into the tissue. Accordingly, in our laboratory, it was recently observed that immepip was about 20-fold more potent than (*R*)α-methylhistamine in inhibiting electrically stimulated [^{3}H]noradrenaline release from rat cerebral cortex slices in vitro (Alves-Rodrigues, unpublished observations). Moreover, in a recent in vivo microdialysis study, it was found that potassium-stimulated acetylcholine release from rat cerebral cortex was inhibited by local administration of histamine H_3 receptor agonists, with immepip

showing a 3-fold higher potency than (*R*)α-methylhistamine (Blandina et al., 1996).

Peripheral injection of immepip (5 mg/kg) induced a sustained decrease in histamine release of about 50% of its basal level. In line with this observation, peripheral injection of the same dose of (*R*)α-methylhistamine (5 mg/kg) has been previously shown to cause a sustained decrease in histamine release from the anterior hypothalamic area (Itoh et al., 1992). Thus, immepip has a comparable potency to (*R*)α-methylhistamine when the drugs are administered peripherally. The prolonged effect of immepip on hypothalamic histamine release indicates that immepip is potentially a new pharmacological tool to study histamine H_3 receptors in vivo, because it is able to cross the blood–brain barrier. The decreased histamine release observed after peripheral injection of immepip is in accordance with its effect after intrahypothalamic perfusion.

At present, (*R*)α-methylhistamine is the most commonly used histamine H_3 receptor agonist for in vivo histamine H_3 receptor studies. It is noteworthy though, that several studies reported non-histamine H_3 receptor-mediated effects of (*R*)α-methylhistamine in peripheral tissues. In vivo studies of the rat cardiovascular system and the guinea-pig respiratory system revealed a histamine H_1-receptor agonistic (Hey et al., 1992; Malinowska and Schlicker, 1993; Hegde et al., 1994) and an α_2 adrenoceptor agonistic (Malinowska and Schlicker, 1993) activity of (*R*)α-methylhistamine, at doses required to obtain histamine H_3 receptor-mediated effects in the central nervous system. Also for another brain-penetrating histamine H_3 receptor agonist, imetit, non-histamine H_3 receptor-mediated effects have been found in the rat cardiovascular system, probably resulting from the 5-HT_3 receptor agonistic activity of the compound (Coruzzi et al., 1995; Leurs et al., 1995). With respect to in vivo histamine H_3 receptor studies, immepip may therefore be a better tool, because it lacks the cardiovascular side effects observed with (*R*)α-methylhistamine and imetit (Coruzzi et al., 1995).

Histamine release was increased about 2-fold after intrahypothalamic perfusion of clobenpropit. This result is comparable to that obtained after local perfusion of thioperamide (Yamamoto, 1995, personal communication; Prast et al., 1994). Subcutaneous injection of clobenpropit increased histamine release to about 150% of the basal value. In contrast, a marked increase in histamine release to 250% of the basal value was observed after subcutaneous injection of thioperamide (5 mg/kg). The moderate effect of clobenpropit on histamine release probably does not result from a lack of brain penetration of the ligand, based on earlier reports. At a dose of 10 mg/kg (s.c.), clobenpropit completely abolished the increase in water consumption induced by (*R*)α-methylhistamine (Barnes et al., 1993). The ability of clobenpropit to penetrate the brain has also been shown in ex vivo receptor binding studies (Barnes et al., 1993; Mochizuki et al., 1996). It therefore seems reasonable to assume that the dose of clobenpropit used in the present microdialysis study was high enough to achieve a complete histamine H_3 receptor occupancy in the rat central nervous system.

It is not possible to give a straightforward explanation for the different effect of subcutaneous injection of clobenpropit and thioperamide on histamine release. We would however like to make the observation that the effect of peripheral injection of histamine H_3 receptor ligands on hypothalamic histamine release may not simply be explained by the binding of these compounds to hypothalamic histamine H_3 autoreceptors. It has been shown that histamine H_3 receptor ligands are able to modulate the release of other neurotransmitters such as noradrenaline (Schlicker et al., 1989), acetylcholine (Clapham and Kilpatrick, 1992; Mochizuki et al., 1994) and serotonin (Fink et al., 1990; Rodrigues et al., 1995), by activation of histamine H_3 heteroreceptors. Modulation of the release of neurotransmitters via histamine H_3 heteroreceptors may in return have an effect on histamine release if this release is influenced by neurotransmitters like noradrenaline (Hill and Straw, 1988) opioid peptides (Gulat-Marnay et al., 1990), acetylcholine (Gulat-Marnay et al., 1989), dopamine (Prast et al., 1993), glutamate (Okakura et al., 1992), GABA (Okakura-Mochizuki et al., 1996) and galanin (Arrang et al., 1991). Therefore, the effects on histamine release of histamine H_3 receptor ligands injected peripherally may reflect the overall effect of the binding of these drugs to both histamine H_3 autoreceptors and histamine H_3 heteroreceptors throughout the central nervous system. It was recently shown that the effect of peripheral injection of the selective α_2-adrenoceptor antagonist, atipamezole, on histamine release was different from both the effect of local perfusion of the compound on histamine release and the effect of the compound on in vitro histamine release from brain slices (Laitinen et al., 1995). For other α_2-adrenoceptor ligands, the effects on neurotransmitter release in vivo was in accordance with the effects on neurotransmitter release from brain slices in vitro. Hence, comparable differences in the pharmacokinetic profile of clobenpropit and thioperamide may explain the different effect of the two compounds on neuronal histamine release after peripheral application. In general, it may be argued that the observations of the present study and of Laitinen et al. cast some doubt on the usefulness of local intracerebral drug perfusion and of in vitro neurotransmitter release models to predict the effect of peripheral application of drugs on in vivo neurotransmitter release.

5. Conclusion

We demonstrated that intrahypothalamic perfusion of the new histamine H_3 receptor agonist, immepip, and the histamine H_3 receptor antagonist, clobenpropit, potently and oppositely modulated in vivo histamine release from the anterior hypothalamic area. These findings support

results from in vitro studies measuring histamine release from brain slices and synaptosomes. Histamine release was potently inhibited by subcutaneous injection of immepip. Hence, this histamine H_3 receptor agonist is potentially a new pharmacological tool to study histamine H_3 receptors in vivo, because it is able to cross the blood–brain barrier. The different increase in histamine release observed upon peripheral injection of clobenpropit compared to thioperamide may be related to the complex mechanism by which systemically administered drugs influence neurotransmitter release in a specific brain area.

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