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Curcumin May Exert Its Antipyresis Via Decreasing Glutamate, Hydroxyl Radicals and Prostaglandin E_2 Generation in the Hypothalamus and Circulating Tumor Necrosis Factor-α Production during Experimental Fever Model

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Abstract

Evidence has been acculated to suggest that systemic administration of staphylococcal enterotoxin A (SEA), in addition to elevating circulating levels of tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and interferon (IFN) as well as fever, induces overproduction of glutamate in the rabbit's hypothalamus. Current study was attempted to assess whether curcumin exerts its antipyresis by reducing circulating pro-inflammatory cytokines and hypothalamic glutamate, hydroxyl radicals and prostaglandin E_2 ($PGE_{2)}$ in rabbits. The microdialysis probes were stereotaxically and chronically implanted into the preoptic anterior hypothalamus of rabbit brain for determination of glutamate, hydroxyl radicals, and PGE_2 in situ. It was found that intravenous administration of SEA (30 ng/kg) induced increased levels of both core temperature and hypothalamic levels of both glutamate and hydroxyl radicals accompanied by increased plasma levels of TNF-α. Pretreatment with curcumin (5-40 mg/kg, i.p.) one hour before an i.v. dose of SEA significantly reduced the SEA-induced overproduction of circulating TNF-α and brain glutamate, PGE_2, and hydroxyl radicals. These results indicate that systemic injection of curcumin may exert its antipyresis by inhibiting the glutamate-hydroxyl radicals-PGE_2 pathways in the hypothalamus and circulating TNF-α accumulation during SEA-induced fever.

Keywords: Curcumin; Staphylococcal enterotoxin A; Tumor necrosis factor-α; Glutamate; Hydroxyl radical; Prostaglandin E_2

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Introduction

Staphylococcus aureus produces a family of enterotoxins that cause most common cases of acute food poisoning in humans and other primates (Marrack and Kappler, 1990). The staphylococcal enterotoxins(SE) are classified into several distinct

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immunological types designated SEA to SEE (Spero,et al., 1988). SEA stimulates the production of pyrogenic cytokines, including interferon (IFN), tumor necrosis factor (TNF), and interleukin-1(IL-1), IL-2, or IL-6 (Bjork, et al., 1992). In addition, intravenous(i.v.) injection of very small doses of SEA into rabbits induced fever (Huang, et al., 1997).

It has been documented that fever genesis begins with the production of pyrogenic cytokines by mononuclear cells, their release into the peripheral blood stream and transport to the hypothalamus, and their production of cyclooxygenase-2-dependent prostaglandin E_2 (PGE_2) (Blatteis et al., 2005). The increased production of PGE_2 in the hypothalamus following an i.v. dose of lipopolysaccharide (LPS) (Huang et al., 2006) can be significantly reduced by prior antagonism of antioxidants such as α-lipoic acid and N-acetyl-L-cysteine. In addition, the hypothalamic PGE_2 elevations caused by intravenous administration of LPS or central injection of glutamate are significantly reduced by N-methyl-D-aspartate (NMDA)-receptor antagonists (Kao et al., 2007). It is believed that the NMDA receptor-dependent hydroxyl radical-PGE_2 pathway in the hypothalamus is involved in the LPS-induced fever genesis (Huang et al., 2006; Kao et al., 2007). Curcumin, the major active component of turmeric, is extracted from the rhizome of *Curcuma long* (Nafisi et al., 2009). Curcumin has been demonstrated in modern medical practice as a anti-inflammatory, antioxidant, antitumorigenic and neuroprotective agent (Jiang et al., 2007; Leu and Maa 2002; Masheswari et al., 2006). Previous studies have shown that curcumin protected against LPS-induced endotoxaemia by blocking oxidative and cytokine production (Kaur et al., 2006)

Our previous study has demonstrated that the staphylococcal enterotoxin-A-induced fever can be reduced by pretreatment with curcumin. Both the fever and the increased levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in the supernalant fluids obtained from the staphylococcal enterotoxin A-stimulated peripheral blood mononuclear cells are decreased by incubating staphylococcal enterotoxin A-peripheral blood mononuclear cells with curcumin (Shao et al., 2004). However, it remains unclear whether curcumin can exert its antipyresis by inhibiting the glutamate-hydroxyl radicals-PGE_2 pathways in the hypothalamus as well as the circulating levels of TNF-α during SEA-induced inflammation in rabbits.

To deal with the question, the aim of the present study is attempted to determine the changes in core temperature (Tco), plasma levels of TNF-α and the hypothalamic concentrations of glutamate, hydroxyl radical and PGE_2 during SEA administration in rabbits with or without curcumin pretreatment.

Materials and Methods

Animals and pyrogen assay

Adult male New Zealand white rabbits, weighing between 2.2 and 3.2 kg at the start of the study, were used. The pyrogen assay was carried out with unanesthetized animals restrained in rabbit stocks. Between experiments the animals were housed individually at an ambient temperature of 22±1°C with a 12-h light-dark cycle, with the lights being switched on at 06:00 h. Animal chow and water were allowed *ad libitum*. Experiments were conducted between 09:00 and 19:00 h, with each animal being used at an interval of not less than 7 days. Throughout the experiment, Tco was measured every 5-min with a copper constantan thermocouple inserted into the rectum and connected to a thermometer (HR1300, Yokogawa, Tokyo, Japan). The Tco of each animal was allowed to stabilize for at least 120 min before any injections. Only animals whose Tco were stable and in the range of 38.5 to 39.6°C were used to determine the effect of drug application. All experimental animals were obtained from the animal center of Chi Mei Medical Center (Tainan, Taiwan, ROC). The animal protocol described here was approved by the Animal Care Committee of Chi Mei Medical Center.

Surgical techniques

An intracerebral or intra-cerebroventricular probe guide cannula was implanted into each animal under general anesthesia (sodium pentobarbital, 30 mg/kg, i.v.). Standard aseptic techniques were employed. The stereotaxic atlas and coordinates of Sawyer et al., (1954) were used. The cannula was located in the left preoptic anterior hypothalamus (A: 2.5 mm, L: 2 mm, and V: 15 mm) or lateral ventricle (P: 4 mm; R: 3 mm; V: 5 mm). The animal was placed in the stereotaxic apparatus, and the frontal and parietal bones were exposed by a midline incision into the scalp. After the appropriately located craniotomy has been trephined, two self-tapping screws were inserted into the parietal or frontal bones and the cannula was inserted to the depth through the craniotomy hole. The cannula was anchored with dental acrylic cement to the calvarium surface, which had been scraped clean of periosteum. The reflected muscles and skin were replaced around the acrylic mound containing the cannula and screws and were sutured with chromic gut (000). After surgery, the guide cannula was plugged with a stylet, and animals were returned to their cages for a minimal recovery period of 1 week.

Drug

All drug solutions were prepared in pyrogen-free glassware that was heated for 5 h at 180°C before use. All drug solutions were prepared in pyrogen-free sterile saline and passed through 0.22-μm Millipore bacterial filters. Sterile SEA (Sigma Chemical Co., St. Louis,Mo.) was made up in 0.9% saline

solution.Curcumin (Sigma-Aldrich, Chemical Co., St. Louis, MO, USA; 5-40 mg/kg in 1 ml of olive oil, i.p.) was dissolved in olive oil. Drugs used for determination of hydroxyl radical generation, including 2,3-dihydroxylbenzoic acid (DHBA), salicylic acid, monochloroacetic acid, disodium EDTA, and sodium octanesulfonate were purchased from Sigma-Aldrich.

Determination of TNF-α in rabbit serum

TNF activity in serum samples was measured by an in vitro cytotoxicity assay with TNF-sensitive L.P3 cells (a kind gift from H. Fujiwara, Biomedical Research Center, Osaka University Medical School, Osaka, Japan) as previously described with slight modifications. Briefly, 2.5 x 10^4 cells were plated in 96-well microplates (Nunc, Roskilde, Denmark) in RPMI 1640 (GIBCO BRL, Grand Island, N.Y.) containing 10% fetal bovine serum (FBS) (GIBCO BRL) and incubated in a humidified atmosphere of 5% CO2 at 37°C for 4 h. After incubation, samples (100 ml) in a series of dilutions, or recombinant human TNF-α (R&D, Minneapolis, Minn.) as an internal reference, were added to the well, followed by addition of 50 µl of actinomycin D (Sigma) at a final concentration of 1.6 mg/ml. After 24 h of incubation, the cells were washed with saline, stained with 0.05% crystal violet for 30 min, and then eluted with 50% ethanol in 0.1% acetic acid solution. The microplates were read at 590 nm on a Multiskan photometer (MR5000; Dynatech, McLean, Va.). The sensitivity of the TNF bioassay was 0.3 U/ml.

Microdialysis for detection of extracellular glutamate and hydroxyl radicals

For measurement of extracellular levels of glutamate in preoptic anterior hypothalamus of rabbit brain, the dialysates were collected every 20 min in a CMA 140 fraction collector. Aliquots of dialysates (2 µl) were injected onto a CMA 600 Microdialysis analyzer for measurement of glutamate. Glutamate is enzymatically oxidized by glutamate oxidase. The hydrogen peroxide formed reacts with N-ethyl-N-(2-hydroxy-3-sulfopropyl)-m-toluidine and 4-amino-antipyrine. This reaction is catalyzed by peroxidase and yields the red-violet colored quimonediimine. The rate of formation is measured photometrically at 546 nm and is proportional to the glutamate.

For measurement of extracellular levels of hydroxyl radicals in the preoptic anterior hypothalamus, a probe guide cannula was planted in the preoptic anterior hypothalamus. The morning before an experiment, after insertion of a microdialysis probe into the preoptic anterior hypothalamus, it was perfused with artificial cerebrospinal fluid (149 mM $NaCl_2$; 2.8 mM KCL, 1.3 mM $CaCl_2$, 1.2 mM Cl_2, 0.125 mM ascorbic acid, and 5.4 mM D-glucose, pH 7.2-7.4) containing 10 mM salicylic acid by a high pressure pump (CMA/Microdialysis; RosLagsvägen, Stockholm, Sweden) at a flow of 1.2 µl/min (Huang et al., 2006). The dialysis probe is a CMA12 microdialysis probe.

Measuring PGE_2 in the preoptic anterior hypothalamus

For measuring OVLT PGE_2, the dialysis system was connected to a microdialysis pump and perfused with artificial cerebrospinal fluid at a flow rate of 1.2 µl/min. The unanesthetized animals were restrained in rabbit stocks for at least 90 min for a stable dialysis level of PGE_2. Dialysis samples from the OVLT were collected into a microdialysis vial at 60-min intervals for 8 h, and they were stored at -80°C until analyzed within 7 days. Immunoreactive PGE_2 concentrations in dialysates were determined using commercially available enzyme immunoassay kits (Cayman Chemicals Co, Ann Arbor, MI, USA). Triplicate aliquots of 50 µl samples were added to each well of plate and each sample was assayed at a minimum of two dilutions. The quantitation limit for PGE_2 was 20 pg/ml.

Statistical analysis

Temperature response was assessed as changes from pre-injection values (Δ°C) or the fever index, the area under the curve produced in the 5 h period after the injection of SEA, in term of degrees centigrade per 5 h were calculated (Huang et al., 2006). The glutamate and hydroxyl radicals levels of samples were expressed as a percentages of three consecutive mean baseline. Results were expressed as mean ± standard errors of the mean (S.E.M) for n experiments. Two way analysis of variance (ANOVA) for repeated measurements (in the same animals) was used for the factorial experiment, whereas Dunnet's test was used for post hoc multiple comparisons among means. A *P* value less than 0.05 was considered to indicate a statistically significant difference.

Results and Discussion

Curcumin reduced the increased levels of both Tco and plasma TNF-α following SEA injection

As depicted in Fig. 1, an i.v. dose of SEA(30 ng/kg) induces a monophasic febrile response in rabbits, with the Tco maxima 300 min post-injection (Fig 1, top). The early phase of the fever is greatly accompanied by remarkable elevations of TNF-α in plasma. In addition, it is found that both the temperature and plasma pro-inflammatory cytokines elevations induced by SEA injection are dose-dependently reduced by pretreatment with curcumin (5-40 mg/kg, i.p.) one hour before the SEA injection (Table 1 and Table 2). An appropriate control injection of curcumin (40 mg/kg, i.p.) or olive oil (1 ml/kg, i.p.) causes an insignificant change in Tco or plasma levels of these pro-inflammatory cytokines. We found that SEA induced significant change in Tco and plasma levels of TNF-α and curcumin significantly attenuated the SEA -induced febrile and inflammatory response ($P<0.05$).

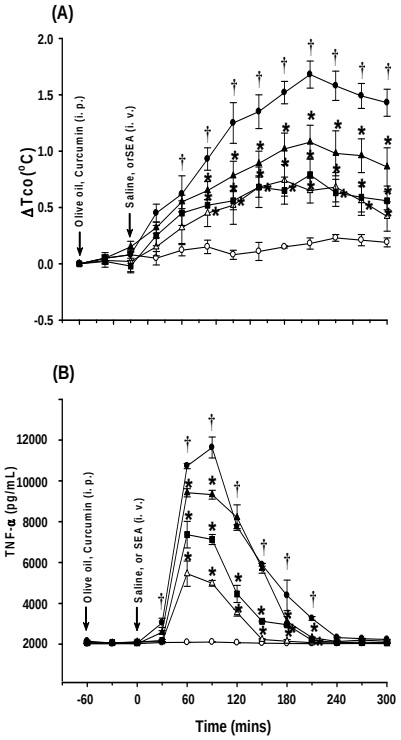

Fig. 1.

Fig. 1. Mean ± S.E.M. changes in core temperature (Tco) (A), and serum levels of TNF-α (B) in rabbits injected intraperitoneally (i. p.) with either olive oil plus saline (i. v.)(○) (n=6), olive oil (i. p.) plus SEA(i. v.) (30 ng/ kg) (●) (n=6), Curcumin at 40 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (△) (n=6), Curcumin at 20 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (■) (n=6), and Curcumin at 5 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (▲) (n=6). †P<0.05, significantly different from corresponding control values (olive oil plus saline group); *P<0.05, significantly different from corresponding control values (olive oil plus SEA group) (ANOVA followed by Dunnett's test).

Curcumin reduced the increased levels of Tco and hypothalamic glutamate and hydroxyl radical following SEA injection

Fig.2 showed the effects of systemic administration of curcumin one hour before the SEA injection on the peak Tco elevation and hypothalamic glutamate and hydroxyl radical elevation in response toSEA injection in rabbits. It can be seen from the figure, the temperature elevations and hypothalamic glutamate and hydroxyl radical elevation in response to SEA (30 ng/kg, i.v.) are dose-dependently reduced by pretreatment with curcumin (5-40 mg/kg, i.p.) one hour before the SEA injection. An appropriate control injection of curcumin or olive oil caused an insignificant change in hypothalamic release of both glutamate and 2,3-DHBA. We found that SEA induced significant change in Tco and hypothalamic levels of glutamate and hydroxyl radicals and curcumin significantly attenuated theSEA -induced febrile and oxidative stress response (P<0.05).

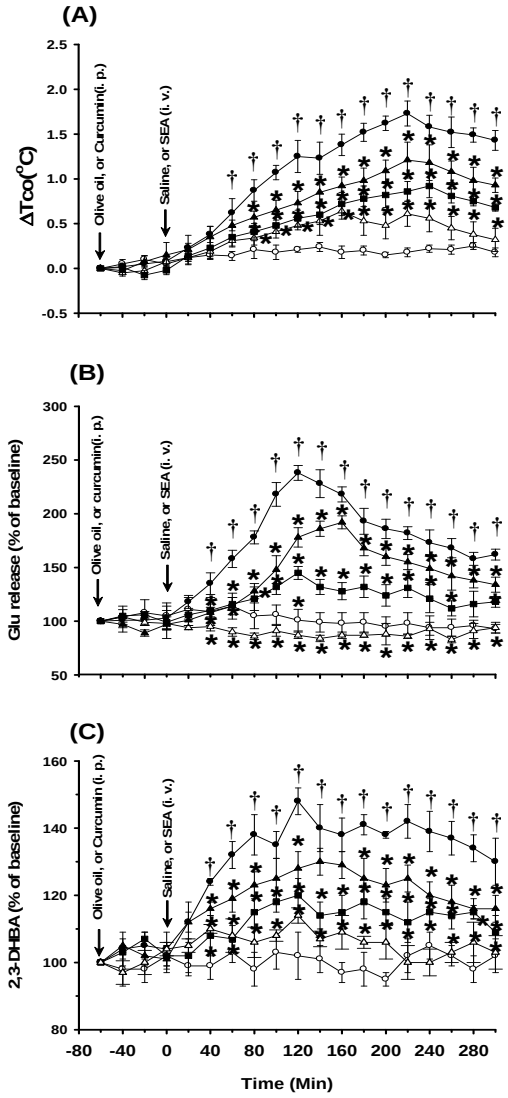

Fig. 2.

Fig. 2. Mean ± S.E.M. changes in core temperature (Tco) (A), and glutamate (Glu) release (B), and 2,3-dihydroxylbenzoic acid (2,3-DHBA) generation (C) in preoptic anterior hypothalamus (POAH) with intraperitoneal administration (i. p.) of either olive oil plus saline (i. v.) (○) (n=6), olive oil (i. p.) plus SEA(i. v.) (30 ng/ kg) (●) (n=6), Curcumin at 40 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (△) (n=6), Curcumin at 20 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (■) (n=6), and Curcumin at 5 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (▲) (n=8). †P<0.05, significantly different from corresponding control values (olive oil plus saline group); *P<0.05,

significantly different from corresponding control values (olive oil plus SEA group) (ANOVA followed by Dunnett's test).

Curcumin reduced the increased levels of hypothalamic PGE_2 produced by SEA

Fig. 3 depicts the effects of pretreatment with curcumin (5-40 mg/kg, i.p.) one hour before an i.v. dose of SEA (30 ng/kg, i.v.) on the increased hypothalamic PGE_2 level in rabbits. It can be seen from the figure that the SEA-induced PGE_2 overproduction is reduced significantly by curcumin ($P<0.05$).

The present study shows that curcumin may cause attenuation of SEA fever by reducing overproduction of the TNF-α pro-inflammatory cytokines in rabbits. The contention is supported by many investigations. For example, LPS-induced overproduction of TNF-α in both monocytes and alveolar macrophages can be inhibited by curcumin in a concentration and a time dependent manner (Abe et al., 1999). Both the fever and the increased levels of TNF-α in the supernatant fluids obtained from the staphylococcal enterotoxin A-stimulated human peripheral blood mononuclear cells can be decreased by incubating staphylococcal enterotoxin A-peripheral blood mononuclear cells with curcumin (Shao et al., 2004).

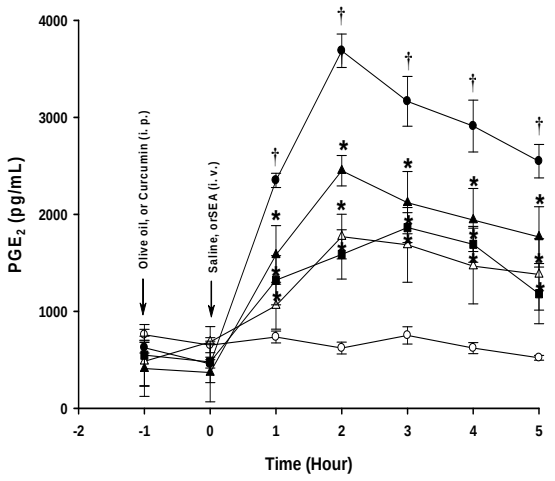

Fig. 3.

Fig. 3. Mean ± S.E.M. changes in hypothalamic levels of PGE_2 in rabbits injected with olive oil (i.p.) plus saline (i.v.) (○) (n=6), olive oil (i. p.) plus SEA(i. v.) (30 ng/ kg) (i. v.) (●) (n=6), Curcumin at 40 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (△) (n=6), Curcumin at 20 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (■) (n=6), and Curcumin at 5 mg/kg (i. p.) plus SEA(i. v.) (30 ng/ kg) (▲) (n=6). $^{\dagger}P<0.05$, significantly different from corresponding control values (olive oil plus saline group); $^{*}P<0.05$, significantly different from corresponding control values (olive oil plus SEA group) (ANOVA followed by Dunnett's test).

Our previous result (Huang et al., 2001) and present results have demonstrated that glutamate release in the anterior hypothalamus of rabbit brain is attributable to the fever by SEA. Probably, the most striking finding of the current study is that curcumin may inhibit the increase of glutamate, hydroxyl radicals and PGE_2 in the hypothalamus and reduce SEA-induced fever in rabbits. Our results indicate that curcumin may cause antipyresis by inhibiting glutamate-hydroxyl radicals-PGE_2 pathways in the hypothalamus. The hypothesis is supported by several investigations. Curcumin has been shown to be a more potent free radical scavenger than vitamine E (Zhao et al., 1989), and protects oxidative injury in vascular endothelial cells by increasing hemeoxygenase formation (Mottechini et al., 2000). Curcumin has been shown to down regulate the production of pro-inflammatory cytokines, such as TNF-α in myelomonocytic cells after LPS exposure (Strasser et al., 2005) and inhibit the activation of transcription factors nuclear factor-κB and activator protein-1, which regulate the genes for proinflammatory mediators and protective antioxidant genes (Chan, 1995; Surh et al., 2000). Curcumin is also reported to suppress LPS-induced cyclooxygenase-2 expression by inhibiting NF-κB activity in the BV-2 microglia cells (Kang et al., 2004).

In summary, as demonstrated in the current results, pretreatment with curcumin one hour before an i.v. dose of SEA significantly reduced the SEA-induced overproduction of circulating TNF-α, and hypothalamic glutamate, hydroxyl radicals, and PGE_2. These findings suggest that systemic administration of curcumin may exert its antipyresis by inhibiting the glutamate-hydroxyl radicals-PGE_2 pathways in the hypothalamus and circulating pro-inflammatory cytokines accumulation during SEA-induced fever.

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在實驗性發燒模式中薑黃素可透過減少下視丘麩胺酸-氫氧自由基-前列腺素E_2及循環中腫瘤壞死因子-α 而達到解熱作用

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摘要

證據顯示全身性給予金黃色葡萄球菌腸毒素A (staphylococcal enterotoxin A, SEA)除了可增加循環中的腫瘤壞死因子-α(tumor necrosis factor-α, TNF-α)、介白質-2、干擾素及發燒外，並可在兔子下視丘誘導麩胺酸的產生。目前的研究主要是分析薑黃素是否可透過減少兔子循環中發炎性細胞激素及下視丘麩胺酸、氫氧自由基及前列素E_2的產生，而達到解熱的作用。微透析探針經立體定位埋入兔子下視丘前視區，並用來分析麩胺酸、氫氧自由基及前列腺素E_2。靜脈給予SEA(30 ng/kg)可增加肛溫及下視丘麩胺酸、氫氧自由基的產生，並伴隨血清中TNF-α的增加。在SEA靜脈注射前一小時腹腔給予薑黃素(5-40 mg/kg)可減少SEA在循環中誘導產生的TNF-α及腦中的麩胺酸、氫氧自由基及前列腺素E_2。這些證據顯示全身性給予薑黃素可透過抑制下視丘麩胺酸-氫氧自由基-前列腺素E_2途徑及循環中的TNF-α，而達到抑制SEA的發燒。

關鍵字：薑黃素、金黃色葡萄球菌腸毒素 A、腫瘤壞死因子-α、麩胺酸、氫氧自由基、前列腺素 E_2

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