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Original Article

Photoinitiators Induce Histamine Production in Human Mast Cells

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Photoinitiators are used in the manufacture of many daily products, and may produce harmful effects due to their cytotoxicity. They have also been detected in human serum. Here, we investigated the histamine-producing effects in HMC-1 cells and the inflammatory cytokine release effects in RAW264 cells for four photoinitiators: 1-hydroxycyclohexyl phenyl ketone; 2-isopropylthioxanthone; methyl 2-benzoylbenzoate; and 2-methyl-4′-(methylthio)-2-morpholinopropiophenone. All four promoted histamine production in HMC-1 cells; however, they did not significantly affect the release of inflammatory cytokines in RAW264 cells. These findings suggest that these four photoinitiators induce inflammatory cytokine-independent histamine production, potentially contributing to histamine-mediated chronic inflammation *in vitro*.

Key words: photoinitiator, ink, injection, histamine, inflammation

Photoinitiators are an indispensable component in a wide range of products that enrich human life, including resin-based dental adhesives [1], inks [2], adhesives [3], and sunscreens [4]. As a result, most people are in daily contact with photoinitiators.

2-isopropylthioxanthone (2-ITX) is a well-known photoinitiator that has been classified by the European Food Safety Authority (EFSA) as a potential hazard to human health, and that has been detected in milk, yoghurt, and juices [5]. Subsequent research revealed that the presence of 2-ITX in these foods was due to its migration from printing ink on the food containers [6, 7]. 2-ITX has varying effects on hormones: it is anti-estrogenic [8], aryl hydrocarbon receptor (AhR)-agonistic, and it has anti-androgenic and anti-estrogenic potencies [9], as well as estrogenic activity [10]. Expanding on the earlier detections in printing ink, our previous studies detected photoinitiators in the injection solutions from plastic containers [11-13]. Potential routes for photoinitiator contamination thus include polymerization reactions during the production of plastic containers, and ink during printing. As further evidence of the former contamination route, an injection solution containing photoinitiator 2-methyl-4′-(methylthio)-2-morpholinopropiophenone (MTMP) was shown to induce cell death via the caspase pathway [14], and photoinitiators in an injection solution were shown to exhibit estrogen-like activity [15]. In our recent study, the photoinitiator MTMP in an injection solution exhibited mutagenicity [16]. Given the ubiquity of photoinitiators, there are serious concerns regarding its associated health hazards.

Previous studies have reported that photoinitiators not only exhibit cytotoxicity and genotoxicity [17-19], but can also cause skin disorders such as allergic contact

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dermatitis [20,21], photoallergic contact urticaria, and facial erythema [22]. The purpose of this study was to investigate the underlying mechanisms of the effects in skin disorders by examining the effect of photoinitiators on histamine production using human mast cells (HMC-1), and on the release of inflammatory cytokines using the cell line RAW264.

Methods and Materials

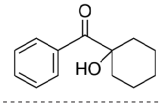
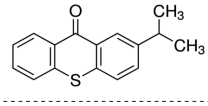
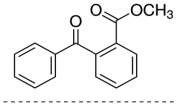
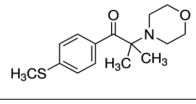
Reagents. 1-hydroxycyclohexyl phenyl ketone (1-HCHPK), dimethyl sulfoxide (DMSO), penicillin, streptomycin, alpha-thioglycerol, lipopolysaccharides (LPS) from Escherichia coli O55: B5, and compound 48/80 were purchased from Sigma-Aldrich (Tokyo). 2-ITX, methyl 2-benzoylbenzoate (MBB), and MTMP were purchased from Tokyo Chemical Industry Co. (Tokyo). Iscove's modified Dulbecco's medium (IMDM), minimum essential medium (MEM), non-essential amino acids solution (NEAA), and fetal bovine serum (FBS) were acquired from Life Technologies Japan (Osaka, Japan); histamine enzyme immunoassay (EIA) kits were purchased from Bertin Pharma (Paris); and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and N, N-dimethylformamide were obtained from Wako Pure Chemical Industries (Osaka). The mouse interleukin (IL)-6 antibody pair and mouse tumor necrosis factor (TNF)-α antibody pair were acquired from Thermo Fisher Scientific (Cleveland, OH, USA). The photoinitiators and compound 48/80 were dissolved in DMSO. MTT was dissolved in phosphate buffered saline. The final DMSO concentration in the culture medium was 0.1%. Information on the photoinitiators used in this study is presented in Table 1.

Cell culture. The HMC-1 cell line used in this study was derived from a patient with mast cell leukemia and was kindly provided by Dr. Steven P. Van Nurden. HMC-1 cells are widely used in studies on human mast cell function because they exhibit various key characteristics of tissue mast cells, such as expression of histamine. The HMC-1 cells were cultured in IMDM supplemented with 10% (*v*/*v*) heat-inactivated fetal bovine serum, 100 units/ml penicillin, 100 μg/ml of streptomycin, and 0.01% *v*/*v* alpha-thioglycerol. Cells were maintained at 37°C in an incubator in a water-saturated atmosphere containing 5% (*v*/*v*) CO_2.

The mouse macrophage-like cell line RAW264, which is used to assess inflammatory cytokine release, was obtained from the RIKEN BioResource Center (Ibaraki, Japan), and maintained in MEM supplemented with 10% (*v*/*v*) heat-inactivated fetal bovine serum, 100 units/ml penicillin, 100 μg/ml of streptomycin, and 1% *v*/*v* NEAA. Cells were maintained at 37°C in an incubator in a water-saturated atmosphere containing 5% (*v*/*v*) CO_2.

Cell viability assays. The HMC-1 cells were transferred to 96-well plates (20,000 cells/well), treated with a photoinitiator (1-HCHPK, 2-ITX, MBB, or MTMP) and/or compound 48/80, and cultured at 37°C in an incubator in a water-saturated atmosphere con-

Table 1 Information of photoinitiators in this study

Analyte	CAS No.	Chemical name	cLog P	cLog S	Chemical structure
1-HCHPK	947-19-3	1-hydroxycyclohexyl phenyl ketone	2.441	−3.176	
2-ITX	5495-84-1	2-isopropylthioxanthone	5.027	−5.287	
MBB	606-28-0	methyl 2-benzoylbenzoate	3.224	−3.857	
MTMP	71868-10-5	2-methyl-4′-(methylthio)-2-morpholinopropiophenone	2.126	−2.824	

taining 5% (*v*/*v*) CO_2 for 24 h. The RAW264 cells were transferred to 96-well plates (100,000 cells/well), treated with a photoinitiator (1-HCHPK, 2-ITX, MBB, or MTMP), and cultured at 37°C in an incubator in a water-saturated atmosphere containing 5% (*v*/*v*) CO_2 for 24 h. For the negative control wells, DMSO was added instead of a photoinitiator, and the cells were incubated as described above.

Cell viability was assessed using the MTT assay [23], and was expressed as a percentage of the absorbance value determined for control cultures using the equation

Cell survival rate (%) = [(As-Ab)/(Ac-Ab)] ×100,

where As, Ac and Ab are the absorbance of the sample, the negative control, and the blank, respectively.

Measurement of histamine levels. Histamine levels, including those derived from HMC-1 cells, were assessed using a histamine EIA kit according to the manufacturer's protocol. The cells (1×10^5 cells/ml) were incubated with compound 48/80 or a photoinitiator for 30 min at 37°C in an incubator with 5% (*v*/*v*) CO_2 [24]. Cells were then cooled on ice to stop the reaction and pelleted by centrifugation at 1,200 rpm for 3 min at 4°C before the supernatants were collected and used to measure the concentration of histamine. The absorbance was measured at 414 nm using a multimode microplate reader (FlexStation 3; Molecular Devices, San Jose, CA, USA).

The effect of each compound on histamine release was expressed as the ratio of the histamine concentration of the relevant sample to that of negative control cultures:

Effect on histamine release = [histamine release (sample)/histamine release (negative control)].

Measurement of inflammatory cytokine concentrations. The cells (1×10^6 cells/ml) were incubated with LPS (10 ng/ml) or a photoinitiator for 24 h at 37°C in an incubator with 5% (*v*/*v*) CO_2. Thereafter, IL-6 and TNF-α levels in the culture medium of RAW264 cells were determined by enzyme-linked immunosorbent assay (ELISA) using the mouse IL-6 antibody pair and mouse TNF-α antibody pair according to the manufacturer's protocol.

Statistical analysis. Cell viability and inflammatory cytokine concentrations were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's test. Histamine levels were analyzed using one-way ANOVA, followed by Tukey's test. The significance level was set at $p<0.05$.

Results

Cell viability. The effects of compound 48/80 and photoinitiators on the proliferation of HMC-1 cells were determined using the MTT assay. As shown in Fig. 1, exposure to compound 48/80 (1-100 μg/ml) produced no significant cytotoxicity; however, marked cytotoxicity was detected at 500 μg/ml ([$F(5,30)=25.4$, $p<0.01$]). As shown in Fig. 2, exposure to 1-HCHPK, 2-ITX, or MTMP at 10^{-10}–10^{-4} M produced no significant cytotoxicity, but marked cytotoxicity was detected at 10^{-3} M (1-HCHPK: [$F(8,45)=5.362$, $p<0.01$]; 2-ITX: [$F(8,45)=10.456$, $p<0.01$]; and MTMP: [$F(8,45)=7.267$, $p<0.01$]). In contrast, treatment with MBB (10^{-10}–10^{-3} M) caused no significant cytotoxicity.

The effects of photoinitiators on the proliferation of RAW264 cells were then determined. Exposure to 1-HCHPK, 2-ITX, MBB, or MTMP at 10^{-10}–10^{-4} M produced no significant cytotoxicity (Fig. 3), but marked cytotoxicity was detected at 10^{-3} M (1-HCHPK: [$F(8,41)=10.328$, $p<0.01$]; 2-ITX: [$F(8,40)=42.994$, $p<0.01$]; MBB: [$F(8,41)=13.333$, $p<0.01$]; and MTMP: [$F(8,41)=268.162$, $p<0.01$]).

Histamine production in HMC-1 cells. To investigate the effects of the photoinitiators on histamine release from HMC-1 cells, histamine levels were measured. Treatment with compound 48/80 (positive control: 50 μg/ml) increased histamine release from HMC-1 cells. In addition, each photoinitiator (10^{-4} M) significantly increased histamine release from HMC-1 cells compared to the control (1-HCHPK: [$F(4,10)$

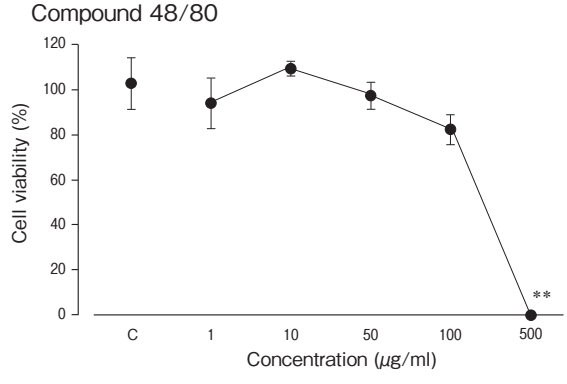


Fig. 1 Effect of compound 48/80 on cell viability. The percentage of viable cells was determined using the MTT assay. Error bars represent the mean ± SD for six independent experiments. $^{**}p<0.01$ indicates significant difference from the respective control. C, control.

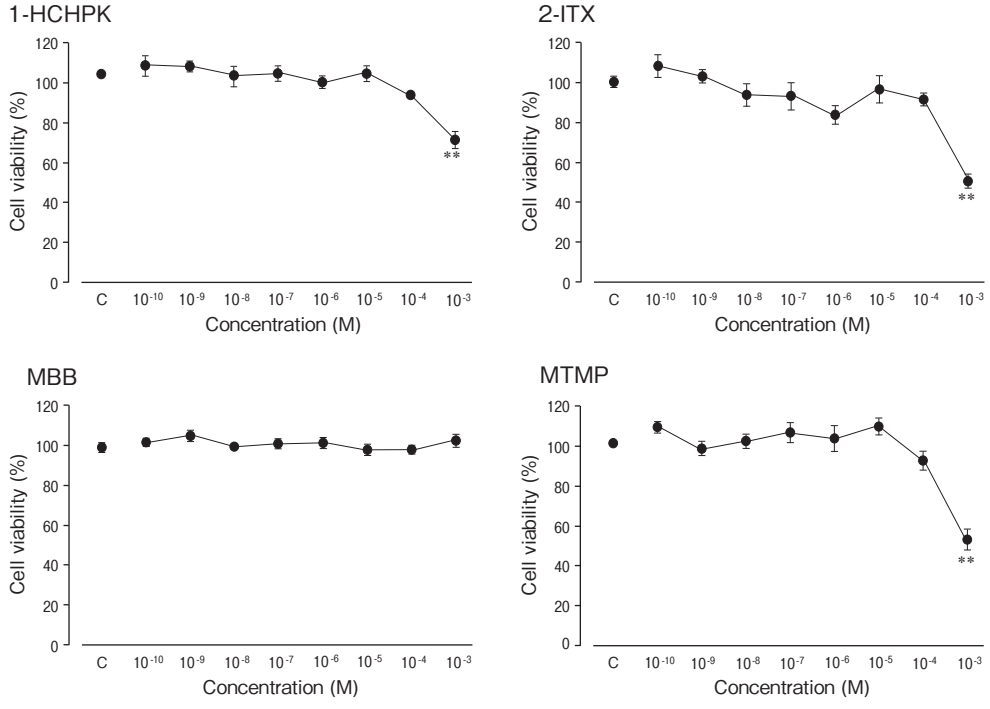


Fig. 2 Effects of 1-HCHPK, 2-ITX, MBB, and MTMP on HMC-1 cell viability. The percentage of viable cells was determined using the MTT assay. Error bars represent the mean ± SD for six independent experiments. $^{**}p<0.01$ indicates a significant difference from the respective control. C, control.

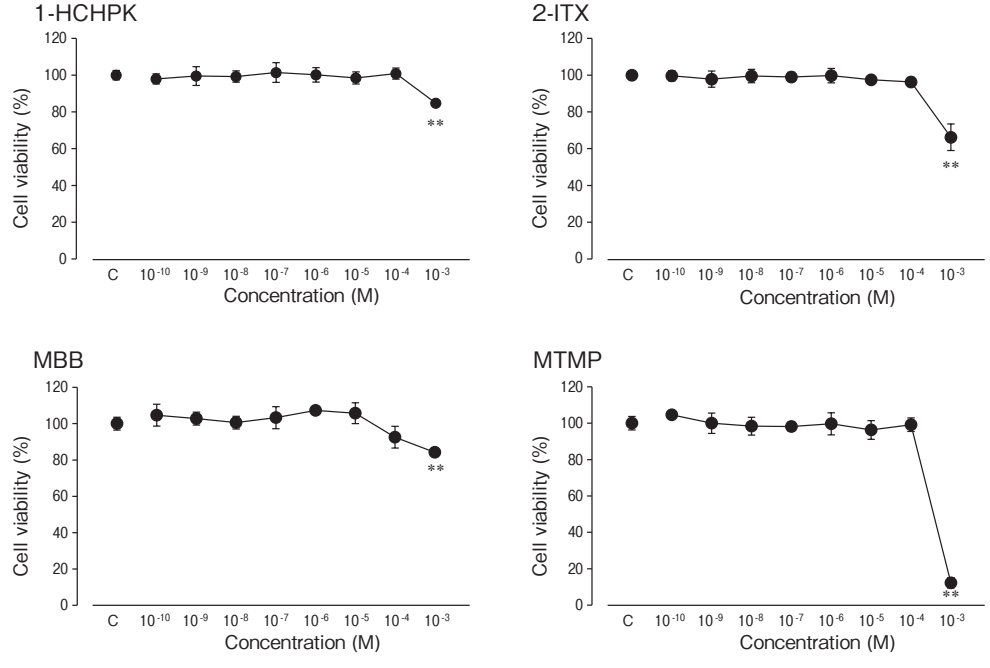


Fig. 3 Effects of 1-HCHPK, 2-ITX, MBB, and MTMP on RAW264 cell viability. The percentage of viable cells was determined using the MTT assay. Error bars represent the mean ± SD for six independent experiments. $^{**}p<0.01$ indicates a significant difference from the respective control. C, control.

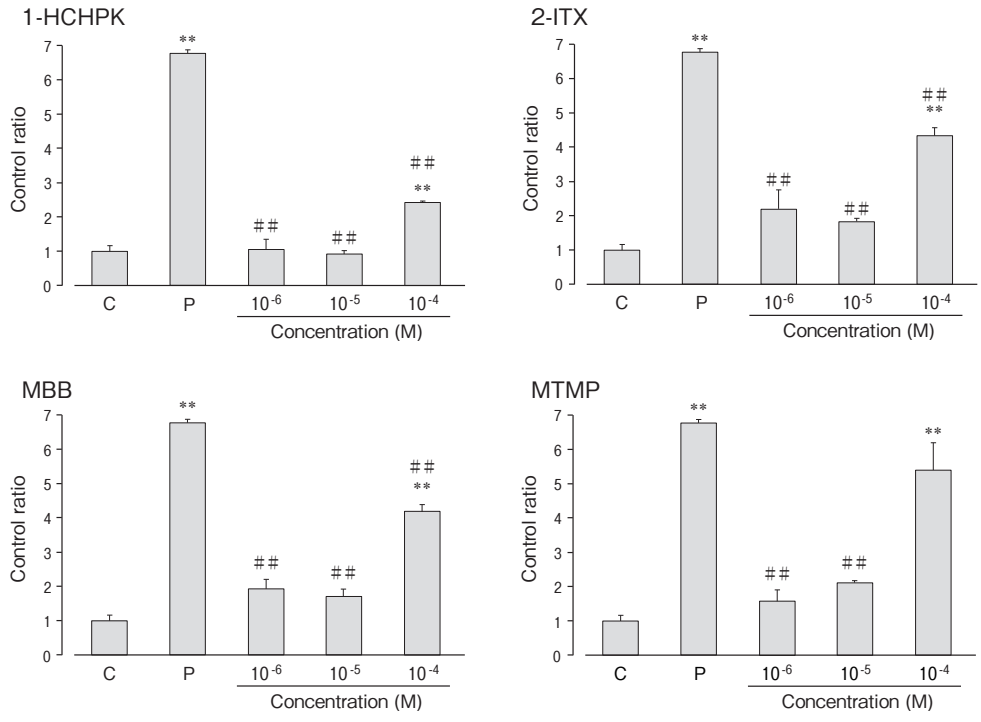


Fig. 4 Effects of 1-HCHPK, 2-ITX, MBB, and MTMP on histamine production in HMC-1 cells. Error bars represent the mean ± SD for six independent experiments. $^{**}p<0.01$ indicates a significant difference from the respective control. $^{\#\#}p<0.01$ indicates a significant difference from the respective positive control. C, control; P, positive control (50 μg/ml compound 48/80).

$=237.258$, $p<0.01$]; 2-ITX: [$F(4,10)=69.139$, $p<0.01$]; MBB: [$F(4,10)=143.330$, $p<0.01$]; and MTMP: [$F(4,10)=42.287$, $p<0.01$]). However, exposure to 10^{-4} M MTMP produced no significant increase in histamine release compared to that induced by compound 48/80 (Fig. 4).

Effect of photoinitiators on inflammatory cytokine release. To investigate the effects of photoinitiators on the inflammatory cytokine release in RAW264 cells, IL-6 and TNF-α levels were measured. In the RAW264 cell line, significant induction of IL-6 and TNF-α release was confirmed in the positive-control group treated with 10 ng/ml LPS (IL-6: [$F(5,12)=40.35$, $p<0.01$]; and TNF-α: [$F(5,12)=18.6$, $p<0.01$]). In contrast, no significant increase in IL-6 or TNF-α release was observed, even when cells were exposed to each photoinitiator (10^{-4} M) for 24 h (Fig. 5).

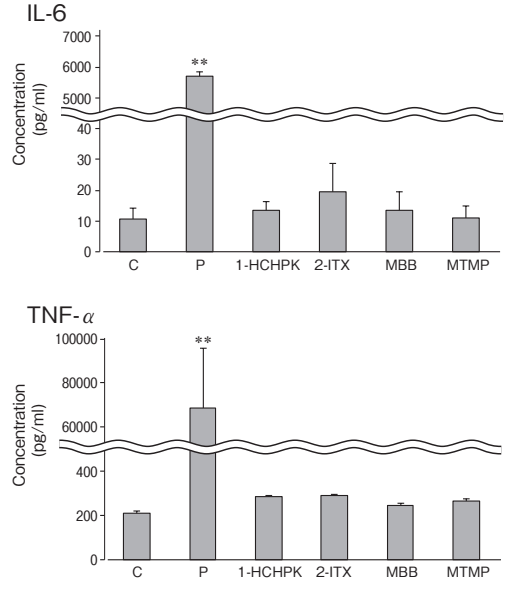


Fig. 5 Effects of 1-HCHPK, 2-ITX, MBB, and MTMP on inflammatory cytokine release in RAW264 cells. Error bars represent the mean ± SD for three independent experiments. $^{**}p<0.01$ indicates a significant difference from the respective control. C, control; P, positive control (10 ng/ml LPS).

Discussion

In the present study, we demonstrated that the four selected photoinitiators induced histamine production

in HMC-1 cells. However, none of the photoinitiators affected the release of IL-6 and TNF-α in RAW264 cells. This suggests that photoinitiators cause skin disorders by inducing histamine production, rather than inflammatory cytokine release. In addition, it should be noted that the photoinitiator concentrations used in this experiment (10^{-4} M) were within the range previously detected in injection solutions (10^{-5} to 10^{-4} M) [11-13], and were thus suitable for an examination of exposure risk.

Mast cells are involved in immune responses such as histamine release when activated by immunoglobulin E (IgE) and toll-like receptors (TLRs). Many inflammatory skin diseases, including atopic dermatitis and acute urticaria, are mediated by IgE-dependent mast cell activation [25]. Recent studies have suggested that TLR7 in mast cells causes IgE-independent skin inflammation [26]. However, there are currently no reports on the activation of mast cells via IgE or TLR in photoinitiators. Histamine is produced by various immune cells, including mast cells, basophils, macrophages, neutrophils, and lymphocytes [27]. It is synthesized from histidine by histidine decarboxylase (HDC) [28]. Mast cells and basophils constitutively express HDC and store histamine in their granules, whereas macrophages do not store histamine.

However, extracellular ligands, endotoxins such as LPS, and inflammatory cytokines such as IL-1 and TNF-α induce HDC expression in macrophages, leading to histamine secretion [29-31]. In experiments using RAW264 cells, HDC gene expression and histamine production were induced by various stimuli such as LPS, the endoplasmic reticulum stress inducer thapsigargin, and phorbol esters [32]. As mentioned above, cells with granules use them to store histamine, while macrophages, which lack granules, continuously secrete their newly synthesized histamine outside the cell. Consequently, the increase in histamine concentration in the surrounding tissues is lower than that due to degranulation, resulting in a relatively prolonged effect. This persistent activation of weak signals via histamine receptors likely plays a role in controlling inflammatory immune responses and pathogenesis. Furthermore, in cases of sepsis, histamine may indirectly promote inflammation by inducing cytokines and chemokines such as TNF-α, IL-1β, IL-6, and monocyte chemotactic protein (MCP)-1 [33]. These results indicate that histamine is involved in inducing the expression of inflammatory cytokines and chemokines. HDC expression is regulated by mitogen-activated protein kinases (MAPK), including extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) [34, 35].

In this study, since photoinitiators did not affect the expression of IL-6 and TNF-α, the histamine production stimulated by the photoinitiators was not due to TNF-α-induced regulation of HDC expression. In our previous study, MTMP induced expression of caspases-3/7 in a time-dependent manner in normal human peripheral blood mononuclear cells [14]. In addition, it has been reported that ERK phosphorylation in MCF7 cells is linked to apoptosis [36]. Therefore, we suggest that photoinitiator-induced histamine production involves the activation of signal transduction pathways-related growth factors. HDC is activated by caspase-9 in mouse mast cells [37]. We previously reported that MBB induces caspase-9-dependent apoptosis [13], suggesting that MBB activates HDC associated with caspase-9.

Differences in histamine production were observed among the photoinitiators. Chemicals are metabolized by the liver, which plays an important role in protecting organisms from potentially toxic chemical insults by converting lipophilic metabolites into water-soluble metabolites [38]. The four polymerization initiators examined in this study are classified as follows: 1-HCHPK and MBB are benzopenones (BZPs); 2-ITX is a thioxanthone (TX); and MTMP is an amine co-initiator (ACI).

In the human liver, BZP is metabolized by human cytochrome P450 enzymes, undergoing both Phase I and Phase II biotransformations [39, 40]. The chemical structure of MBB contains an ester bond, which is degraded by carboxylesterases [41]. Subsequently, these metabolites are either excreted in urine or bioaccumulated in the human body [39]. ITXs are metabolized in the liver by CYP1A2 and CYP3A4 [42]. In addition, 2-ITX is metabolized to epoxide metabolites [43], and these play a potential role in the toxicological properties of photoinitiators [43-45]. Although the metabolic pathways of MTMP are not well understood, the chemical structure of MTMP indicates that ketone reduction, N-dealkylation, S-oxidation, and S-demethylation are likely involved [46-49].

In keeping with this likely mechanism, beta-hydroxy-MTMP (β-OH-MTMP), beta-hydroxy-MTMP-sulfoxide (β-OH-MTMP-SO), and beta-hydroxy-MTMP-sulfone (β-OH-MTMP-SO2) have been detected in

the urine of MTMP consumers [50]. However, there are no reports on the toxicity of these metabolites. As shown in Table 1, a high cLogP value indicates high lipophilicity. Compared to the other photoinitiators, MTMP exhibited a lower partition coefficient, indicating lower lipophilicity. It is inferred that histamine production ability differs due to differences in the caspase pathway, metabolic pathways, and lipophilicity.

Allergic contact dermatitis (ACD) is associated with the activation of nuclear factor kappa B (NF-κB). NF-κB plays a crucial role in the expression of several genes involved in immune and inflammatory responses, including allergies [18-20].

The activation of caspase-1 induces the production of pro-inflammatory cytokines via nuclear translocation of NF-κB [20]. Therefore, the inhibition of MAPKs, NF-κB, and caspase-1 is a therapeutic strategy to reduce the severity of inflammatory diseases.

In recent reports, photoinitiators have been detected in human blood [51], as have the four photoinitiators investigated in this study [52, 53]. It has been suggested that the photoinitiators investigated here induce inflammatory cytokine-independent histamine production. Chronic inflammatory reactions caused by histamine in the human body cause adverse effects other than ACD [54]. Further *in vitro* and *in vivo* studies are needed to establish whether photoinitiators induce changes in the expression of key proteins and genes involved in chronic inflammation. In addition, the mechanism by which photoinitiators induce histamine production must be elucidated.

In conclusion, we demonstrated that the four selected photoinitiators promoted histamine production in HMC-1 cells. The different histamine production-promoting effects of these photoinitiators were thought to be due to differences in their chemical structures. Furthermore, the promotion of histamine production by photoinitiators may be independent of inflammatory cytokines *in vivo*.

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