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Physiological Doses of Volatile Organic Compounds Emitted by the Skin under Psychological Stress Impact Skin Functions

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Abstract

Background: A previous *in vivo* study analysing the volatilome—the complete set of volatile organic compounds (VOCs) emitted by an organism—identified 17 compounds that were increasingly released by the skin during psychological stress. **Objective:** As stress is known to accelerate skin ageing, and many VOCs have detrimental effects on the skin, we selected three of the 17 identified VOCs and assessed their effects following a single exposure to physiological doses. **Materials and methods:** Using reconstructed human epidermis, we focused on changes in the expression of genes and proteins related to inflammation, epidermal differentiation, and oxidative stress. **Results:** Each of the three VOCs induces changes in gene and protein expression. Two VOCs, heptadecane and 2,6,10,14-tetramethylpentadecane, induce inflammation and affect epidermal differentiation, although the specific markers influenced and the timing of these changes differ between the two compounds. The third VOC, 2-hydroxyethyl acetate, inhibits inflammation but increases the expression of genes and proteins involved in epidermal differentiation and oxidative stress defence. **Conclusion:** While each VOC has distinct effects, all impact functions critical to the proper functioning of the skin. These findings suggest that stress-modulated skin VOCs could be a, yet, unsuspected factor linking the brain and the skin and impacting skin functions.

Keywords

Psychological Stress, Volatile Organic Compounds, Skin, Epidermal Differentiation, Inflammation, Oxidative Stress

1. Introduction

The volatilome refers to the complete set of volatile organic compounds (VOCs)

emitted by an organism [1]. In healthy humans, VOCs are released from breath, skin, urine, saliva, breast milk, and blood, collectively forming a complex mixture comprising thousands of compounds [2]. Breath is the most significant of these sources, with 1488 VOCs identified in 2021, followed by the skin, which emits 623 VOCs [3].

The skin volatilome originates from three endogenous sources: eccrine, sebaceous, and apocrine glands [4]. The distribution of these glands, varying across body regions, results in distinct VOC profiles. These VOCs are produced by endogenous biochemical reactions, and the composition of the volatilome varies between individuals, reflecting genetic background, diet, and lifestyle [2] [5]-[7]. In addition, VOCs are generated by skin-resident microorganisms, some of which metabolise sweat and sebum [8]. As the skin is the interface with the external environment, its volatilome also reflects environmental exposures and the use of cosmetic products [9] [10]. Consequently, the skin volatilome constitutes a complex mixture of VOCs from both endogenous and exogenous origins.

Similarly, to the breath volatilome analysis [11] [12], the study of the skin volatilome offers a non-invasive method to disease diagnosis [13]. It has also proven valuable in monitoring psychological stress [14]-[17]. Initial works identified a limited number of differentially emitted compounds under stress [14]-[16]. More recently, 17 VOCs were found to be increasingly emitted in response to psychological stress, several of which had not been previously reported [17].

Stress not only alters the skin's VOC profile but also directly affects the skin itself. Beyond its involvement in various dermatological conditions and pathologies [18]-[20], stress has also been implicated in skin ageing [21]. It rapidly triggers the production of glucocorticoids via the hypothalamic-pituitary-adrenal (HPA) axis and induces catecholamine release by the autonomic nervous system [18]. The skin, possessing functional peripheral HPA and catecholaminergic systems, responds with impaired barrier function [22], compromised stratum corneum integrity [23], and diminished innate and adaptive immune responses [24] [25]. However, the nature of the stress—acute or chronic—modulates its effects. While acute stress responses are tightly regulated through feedback mechanisms, chronic stress leads to habituation, attenuating HPA axis activity and heightening sensitivity to new stimuli [26]. This ultimately weakens immunoprotection, increasing susceptibility to infection and exacerbating allergic and inflammatory conditions [27].

While the impact of glucocorticoids and the autonomic nervous system on the skin's stress response is well-documented, the production of specific VOCs in this context raises questions about their potential role. In studies of extrinsic ageing, many VOCs—alongside UV radiation—have been shown to promote oxidative stress, leading to macromolecular damage, cellular senescence, and visible signs of ageing [28] [29]. This suggests that stress-induced VOC production may represent an unrecognised mechanism contributing to skin damage.

To explore this hypothesis, the effects of physiological doses of three stress-

modulated VOCs were evaluated: heptadecane, 2,6,10,14-tetramethylpentadecane, and 2-hydroxyethyl acetate [17]. Besides their increased release under stress, the rationale behind this selection was the commercial availability of these compounds and, for heptadecane and 2-hydroxyethyl acetate, a prior identification within the skin volatilome [15]. The impacts of these three VOCs on reconstituted human epidermis (RHE) were evaluated by assessing the expression of genes and proteins involved in inflammation, epidermal differentiation, and oxidative stress.

2. Materials and Methods

2.1. Reconstituted Human Epidermis (RHE) and Treatment

Upon receipt, 11-day-old *in vitro* human epidermis (8 mm in diameter), reconstructed from normal human keratinocytes cultured on a collagen matrix (EpiSkin™, France), were placed at the air-liquid interface of MGCM growth medium (EpiSkin, France) in 24-microwell plates. Each well contained 3.4 ml of medium, covering a surface area of 190 mm^2.

Following a 24-hour acclimatisation period (day 12), treatment started by adding physiological doses of volatile compounds to the culture medium, namely the dose emitted over a 10-minute period by the forehead skin of subjects exposed to psychological stress [17]. The three compounds tested were heptadecane (CAS number: 629-78-7; tested concentration: 31.25 ng/ml prepared from a DMSO stock solution diluted 6.25×10^5 folds), 2,6,10,14-tetramethylpentadecane (CAS number: 1921*70-6; tested concentration: 6.25 ng/ml prepared from an ethanol stock solution diluted 6.25×10^6 folds), and 2-hydroxyethyl acetate (CAS number: 542-59-6; tested concentration: 6.25 ng/ml prepared from an water stock solution) [17]. RHEs maintained in culture medium deprived of VOC were used as control. RHEs (one per condition and time point) were sampled one- and five-hours post-treatment, and the culture medium was frozen for subsequent analysis.

2.2. Preparation of RNA, Reverse Transcription, and Real-Time qPCR

For each condition and time point, one RHE fragment was ground using a Precellys Homogeniser in the presence of RLT lysis buffer. Lysates were clarified by centrifugation, and RNA was extracted using the RNeasy Micro Kit (Qiagen, Germany). Following quantification, RNA was reverse transcribed into cDNA using RT^2 First Strand Kit (Qiagen, Germany).

Real-time quantitative PCR (RT-qPCR) reactions (one per condition) were performed using the RT^2 SYBR® Green qPCR Mastermixes (Qiagen, Germany) and a LightCycler® 480 (Roche, Switzerland). The analysis focused on 12 genes associated with inflammation (IL-1α), epidermal differentiation (AQP3, CALML5, CASP14, FLG, IVL, KRT1, KRT10, and LOR), and oxidative stress (CAT, SOD1, and SOD2). Two housekeeping genes—GAPDH (glyceraldehyde-3-phosphate dehydrogenase) and YWHAZ (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta)—were used as internal standards. Relative expres-

sion levels were calculated using $2^{-\Delta\Delta Ct}$, with untreated RHE at the same time point as reference. Genes were considered upregulated for $2^{-\Delta\Delta Ct}$ values greater than 1.70 and downregulated when $2^{-\Delta\Delta Ct}$ was below 0.68.

2.3. Immunohistochemical Analysis

RHE samples were fixed in formalin and embedded in paraffin. Five-micrometre-thick cross-sections were prepared, deparaffinised, and mounted on SuperFrost™ slides. After unmasking antigens (15 minutes at 94˚C in citrate buffer), cross-sections were permeabilised (10 minutes with 0.1% Triton), and saturated (2% bovine serum albumin). Dual primary labelling was performed using a rabbit anti-loricrin polyclonal antibody (ab24722, Abcam, UK) and a mouse anti-filaggrin monoclonal antibody (MA5-13440, Thermo Fisher Scientific, USA). These were respectively labelled with a goat anti-rabbit IgG conjugated to Alexa Fluor™ 546 (A-11010, Invitrogen, USA) and a goat anti-mouse IgG conjugated to Alexa Fluor™ 488 (A-11001, Invitrogen, USA). Fluorescence was observed under a Nikon Eclipse 50i fluorescence microscope. Images were acquired with a Nikon NIS Elements software, analysing 7 to 29 fields from different cross-sections of one RHE per time point/condition. Signal intensity for each marker was normalised to epidermal surface area.

2.4. Quantification of Oxidative Stress Defence Proteins

Superoxide dismutase 1 and 2 (SOD1 and SOD2) and catalase (CAT) levels were quantified in the RHE culture medium using ELISA assays (SOD1: ab119520, Abcam, UK; SOD2: HUFI01825, Ozyme, France; CAT: ABIN6730920, Antibodies-online, USA). Assays were conducted in duplicates according to the manufacturer's protocols.

2.5. Statistical Analysis

Except for qRT-PCR results, expressed as average $2^{-\Delta\Delta Ct}$ values, all results are presented as mean ± standard error of the mean (SEM). For the immunohistochemical analysis of filaggrin and loricrin, data distribution was assessed using the Shapiro-Wilk test ($\alpha < 0.1$) and results were compared using the Kruskal-Wallis test followed by *post-hoc* Dunn tests.

3. Results

3.1. Effects of Volatile Compounds on Gene Expression

To analyse the effects of volatile compounds on the skin, RT-qPCR was used to quantify expression changes in genes associated with inflammation (IL-1α: interleukin 1 alpha), epidermal differentiation (AQP3: aquaporin 3, CALML5: calmodulin-like 5, CASP14: caspase 14, FLG: filaggrin, IVL: involucrin, KRT1: keratin 1, KRT10: keratin 10, and LOR: loricrin), and oxidative stress (CAT: catalase, SOD1 and SOD2: superoxide dismutase 1 and 2). Overall, results (**Figure 1**) revealed that each VOC induced a distinct transcriptional response, with effects varying

over time.

One hour after adding heptadecane, almost all genes analysed were downregulated. Except for CALML5, all genes involved in epidermal differentiation were downregulated, ranging from −33% (IVL) to a maximum of −79% (FLG). Similarly, oxidative stress-related genes were also downregulated (CAT: −74%, SOD1: −37%, and SOD2: −38%). A noticeable difference was evidenced in inflammation, where IL-1*α* was significantly upregulated (+189%). Only a limited number of genes remained affected by five hours, with IL-1*α*, IVL, and CALML5 still downregulated (−90%, −60%, and −33%, respectively). Among the oxidative stress response genes, only SOD1 still exhibited reduced expression (−41%).

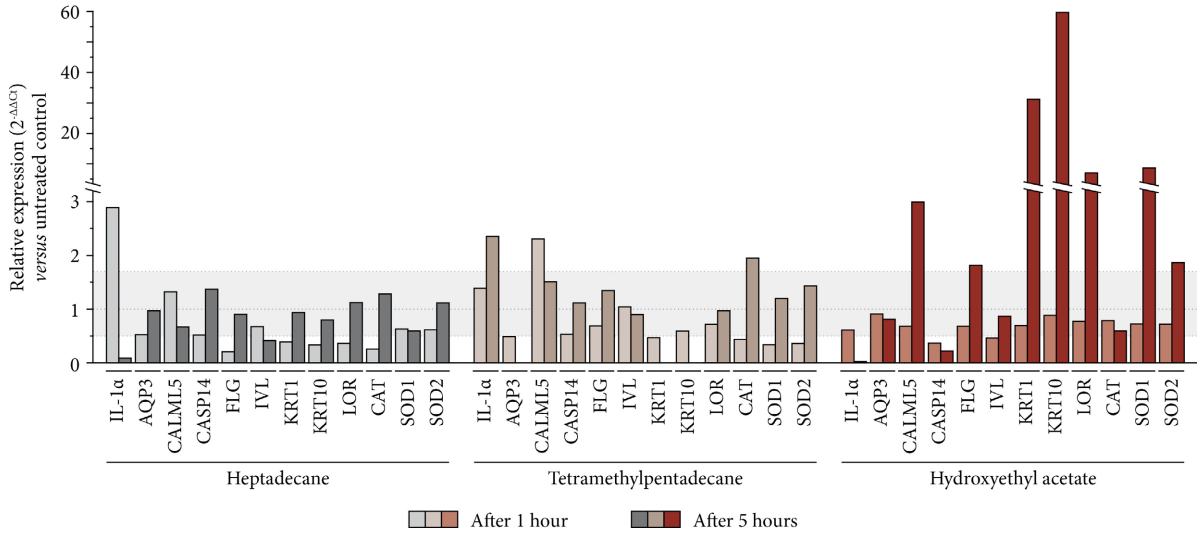

Figure 1. Relative expression ($2^{-\Delta\Delta Ct}$) of genes involved in inflammation (IL-1*α*), epidermal differentiation (AQP3, CALML5, CASP14, FLG, IVL, KRT1, KRT10, and LOR), and oxidative stress (CAT, SOD1, and SOD2) one and five hours after the addition of volatile compounds.

Tetramethylpentadecane triggered the downregulation of most epidermal differentiation genes at the one-hour time point (CASP14: −47%, KRT1: −61%, KRT10: −41%, AQP3: −51%), alongside with reductions in CAT (−57%) and SOD2 (−64%). Only one gene, CALML5, was upregulated (+135%). After five hours, the inflammation marker gene was upregulated (IL-1*α*: +135%), as was CAT (+95%). Conversely, KRT10 and AQP3 were downregulated, becoming undetectable.

Hydroxyethyl acetate had minimal early effects, with modest downregulation observed in IL-1*α* (−39%), FLG (−32%), IVL (−53%), and CASP14 (−63%). However, at five hours, a broader pattern of gene upregulation affected epidermal differentiation and oxidative stress genes. However, CASP14 and CAT were downregulated (−78% and −41%, respectively), and IL-1*α* expression was only slightly detectable.

3.2. Effects of Volatile Compounds on Filaggrin and Loricrin Proteins

We then evaluated the impact of volatile compounds on the levels of two im-

portant epidermal markers: filaggrin and loricrin. Results from a VOC-treated RHE were compared to those of an untreated RHE at the same time point (See Table 1).

Heptadecane significantly reduced filaggrin levels after one hour (−54%, $p = 0.021$), and the reduction became more pronounced after five hours (−68%, $p < 0.001$). It also impacted loricrin, but only after one hour (−39%, $p = 0.018$).

Tetramethylpentadecane had a marginal impact on filaggrin levels after one hour (−36%), though this was at the significance limit ($p = 0.065$). Still, after five hours, the negative impact was evident (−48%, $p = 0.004$). Tetramethylpentadecane had no noticeable effect on loricrin after one hour but may have reduced it after five hours (−28%, $p = 0.089$).

Table 1. Immunohistochemical quantification of filaggrin and loricrin (arbitrary fluorescence units) one and five hours after treatment with volatile compounds.

Volatile compound	Time	Filaggrin	Loricrin
Untreated	T + 1 h	17.3 ± 2.9	8.4 ± 1.3
	T + 5 h	22.0 ± 2.5	5.8 ± 0.5
Heptadecane	T + 1 h	7.9 ± 1.0*	5.1 ± 0.3*
	T + 5 h	7.0 ± 1.7***	7.3 ± 1.6
Tetramethyl pentadecane	T + 1 h	23.5 ± 1.6^{LS}	10.0 ± 0.8
	T + 5 h	11.5 ± 1.2**	4.2 ± 0.6^{LS}
Hydroxyethyl acetate	T + 1 h	18.9 ± 3.1	7.0 ± 0.9
	T + 5 h	15.0 ± 1.9^{LS}	5.3 ± 0.7

Statistical comparisons were performed using the Kruskal-Wallis test and *post-hoc* Dunn tests. Significant differences are only reported *versus* the untreated control at the same time point with LS: $p < 0.1$, *: $p < 0.05$, **: $p < 0.01$, and ***: $p < 0.001$.

Finally, hydroxyethyl acetate had a minimal impact on both filaggrin and loricrin. At most, a non-significant reduction in filaggrin was observed (−32%, $p = 0.093$).

3.3. Effects of Volatile Compounds on Oxidative Stress Defence Proteins

To assess the oxidative stress response, we also quantified the levels of SOD1, SOD2, and CAT proteins present in the RHE culture medium. Due to levels being one order of magnitude below the limit of quantification under all conditions evaluated, CAT could not be assessed. Thus, only SOD1 and SOD2 were analysed (Figure 2).

One hour post-treatment, regardless of the volatile compound added to the culture medium, no important changes in SOD1 or SOD2 protein levels were evidenced compared to the untreated control. However, by five hours, only hydroxyethyl acetate decreased SOD1 (−44.4%), while the reduction in SOD2 levels (−41.7%) was at the significance limit.

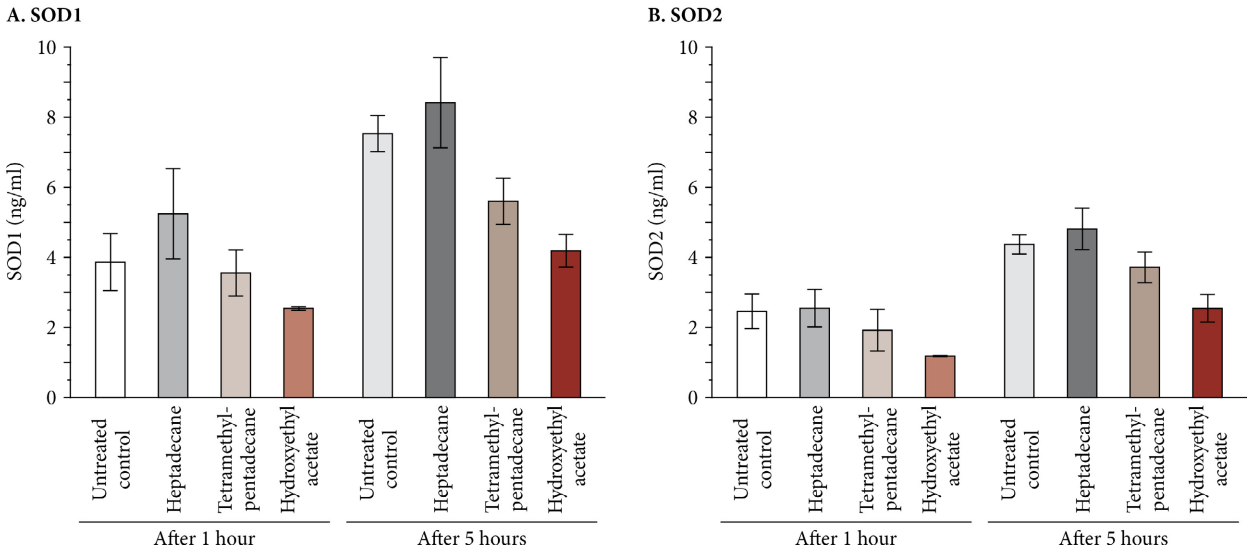

Figure 2. Quantification of (A) SOD1 and (B) SOD2 protein levels released in the culture medium one and five hours after the addition of volatile compounds.

4. Discussion

By assessing the effects of a single, relatively brief exposure to physiological doses of three VOCs emitted by the skin under psychological stress, we evidenced that each compound distinctly impacted the expression of genes and proteins involved in inflammation, epidermal differentiation, and oxidative stress. For instance, heptadecane induced the early upregulation of the inflammation marker IL-1α, whereas tetramethylpentadecane upregulated it after five hours. In contrast, heptadecane and hydroxyethyl acetate markedly reduced IL-1α expression after five-hours. Similarly, genes whose products are involved in epidermal differentiation and oxidative stress displayed varying patterns of up- or downregulation depending on the VOC. These changes were not restricted to gene expression but also occurred at the protein level in most cases. Finally, none of the VOCs exhibited a cytotoxic effect (data not shown).

However, as a preliminary analysis, limitations must be acknowledged. Analysing only IL-1α gene is insufficient to draw robust conclusions about inflammation, necessitating further experiments assessing additional genes and cytokines. Moreover, some inconsistencies were observed between RT-qPCR data and protein quantification by immunohistochemistry. While these differences could be explained by temporal delays between transcription and translation, a deeper understanding of these relations is required. In particular, assessing protein levels at later time points would help establish whether the observed mRNA variations translate into corresponding protein changes. Despite these limitations, our results reasonably suggest that the three stress-modulated VOCs impact skin functions, albeit through distinct molecular mechanisms. Consequently, an attempt to discuss their effects should consider them individually.

Heptadecane is the VOC that most rapidly affects the expression of key genes

involved in epidermal terminal differentiation, including KRT1, KRT10, FLG, and LOR, with corresponding reductions in filaggrin and loricrin protein levels. Filaggrin, keratin, and loricrin are essential structural components of the stratum corneum [30] [31]. Their interaction results in the collapse and flattening of corneocytes, providing mechanical resistance to the skin. Additionally, filaggrin proteolysis during terminal differentiation releases hygroscopic amino acids essential for stratum corneum hydration [32]. Collectively, filaggrin, keratin, and loricrin are crucial for maintaining the skin's barrier function. Interestingly, murine studies have shown that disruption of this barrier induces inflammation through upregulation of several cytokines, including IL-1α [33] [34], as we observed.

Tetramethylpentadecane also downregulates KRT1/10 expression, later upregulating IL-1α, possibly through mechanisms similar to those mentioned above for heptadecane. It also downregulates AQP3, a gene encoding the primary epidermal transporter of water, glycerol, and small solutes in the epidermis. Aquaporin-3 also contributes to cell proliferation, migration, and skin barrier maintenance [35]. Although tetramethylpentadecane also downregulates oxidative stress-related genes (CAT, SOD1, SOD2) early on, no decrease in the corresponding protein levels was detected within five hours. While SOD proteins, essential to protect cells against oxidative stress, are typically constitutively expressed [36] [37], environmental stressors such as air pollution can modulate their expression [38] [39]. Therefore, the decreased gene expression could result in decreased SOD levels, and whether such a decrease occurs after five-hour time remains to be determined. If it does, it should lead to diminished antioxidant defences, weakening resistance to oxidative stress.

Hydroxyethyl acetate elicits an entirely different effects compared to the two other VOCs. It is characterised by a marked upregulation of SOD1 and SOD2 after five hours, partially reflected at the protein level. Although poorly responsive to external stimuli, as already mentioned, SOD gene expression is triggered by the NF-κB transcription factor under oxidative stress conditions [36], suggesting that hydroxyethyl acetate could induce oxidative stress. However, the simultaneous downregulation of IL-1α and upregulation of differentiation markers (CALML5, KRT1, KRT10, LOR) runs counter to typical oxidative stress gene expression profiles, usually involving inflammation and impaired epidermal development [40]. Thus, if oxidative stress were the main driver of the hydroxyethyl acetate response, one would expect reduced KRT, LOR, and CALML5 expression. Other mechanisms must, therefore, be at play and remain to be identified.

Future research should expand this preliminary analysis by including additional genes/markers and functional assays, particularly to assess the impact on inflammation and the skin barrier function. Nevertheless, all three stress-modulated VOCs seem to affect the skin, at least the epidermis, inducing changes that can also be evidenced in response to exogenous stressors such as environmental VOCs. However, we only analysed three VOCs out of the 17 recently identified [17]. Whether the remaining 14 compounds also impact the skin remains to be determined. Moreover, the effects of stress-modulated VOCs are likely not only

due to their individual impact, but rather from their interactions. Besides, we only assessed single, relatively short exposure to VOCs. Analysing longer and repeated exposures to acute stress will be of interest. Although more complex, it will also be interesting to assess the effects of chronic stress, which results in habituation, to determine its impact on the skin volatilome and the effects of this volatilome on the skin.

5. Conclusion

Environmental VOCs pollutants are well known to compromise skin integrity, contributing to barrier dysfunction, premature ageing, and visible signs of senescence [28] [29]. It is therefore unsurprising that stress-modulated VOCs may similarly affect the skin. Stress itself is already recognised for affecting the skin through the rapid release of glucocorticoids via the hypothalamic-pituitary-adrenal (HPA) axis and catecholamines from the autonomic nervous system [18]. These responses impair barrier function, compromise stratum corneum integrity, and weaken both innate and adaptive immunity. However, the role of stress-modulated VOCs has never been considered before, and our results suggest that it may represent an additional mechanism linking stress to skin dysfunction.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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