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Stand out from matrix: Ultra-sensitive LC–MS/MS method for determination of histamine in complex biological samples using derivatization and solid phase extraction

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ABSTRACT

The determination of low abundant endogenous components is a challenge for the clinical samples. Histamine, a crucial endogenous component, fulfils various regulatory and mediatory functions in human, and the change of content is a critical index for the diagnosis of some diseases, especially allergy, asthma, and anaphylactic shock. However, it is challenging to detect histamine because of the low stability and concentration in complex biological samples. Here we developed an ultra-sensitive and accurate LC–MS/MS quantification method based on derivatization, isotope dilution, and solid phase extraction. The derivatization of histamine with diisopropyl phosphite (DIPP) not only enhanced the retention on the LC column but also improved the ionization efficiency. Next, solid phase extraction was applied to remove the interference, which finally resulted in standing out of the trace histamine from the high contents of the matrix. The lowest limit of quantification (LLOQ) was 0.1 pg/mL that is enough low to determine the histamine in one cell and low nano-liter of serum. This approach was successfully applied for the quantification of histamine in clinical serum samples of asthma patients and mast cell treated with chemicals modulating histamine release.

1. Introduction

Histamine is a vital biogenic amine, and performs multiple effects in humans, involving the tasks of the immune and neuroendocrine systems, neurotransmission, gastric secretion, cell life and death, and development [1]. It is a potent mediator of numerous biologic reactions, and the alterations in histamine-related factors are a critical part in the cause of various diseases, such as allergy, asthma, and anaphylactic shock [2], normal and malignant lymphocytes [3], cerebral ischemia [4], urticarias [5], carcinogenesis [6]. Consequently, the determination and quantification of histamine in biologic samples are very crucial for the diagnosis of diseases. Various approaches have been used to determine histamine in different matrix samples, e.g. enzyme-linked immunosorbent assay [7], high performance liquid chromatography (HPLC) [8]. The concentration of histamine is usually low in blood [9,10]; accordingly, the mass spectrometry (MS) approaches [11–16] are widely applied for the quantification of histamine owing to its high sensitivity, specificity, and accuracy (Table 1). For instance, the lowest limit of quantitation (LLOQ) is 0.3 ng/mL in cell line [17] as well as 0.2 ng/mL in plasma samples [14] using LC–MS/MS approaches. In addition,

Abbreviations: DIPP, Diisopropyl phosphite; LLOQ, Lowest limit of quantification; HPLC, High performance liquid chromatography; MS, Mass spectrometry; SPE, Solid phase extraction; TEA, Triethylamine; IS, Internal standard; D-TSS, D-Tyrode's salt solution; DMEM, Dulbecco's modified Eagle's medium; SCIT, Subcutaneous immunotherapy; UHPLC, Ultra-high performance liquid chromatography; Q-TOF-MS, Quadrupole-time of flight mass spectrometry; QQQ-MS, Triple quadrupole mass spectrometry; dual AJS ESI, Dual Jet stream electrospray ion source; MRM, Multiple reaction monitoring; ROC, Receiver operating characteristic.

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Table 1
Reported mass spectrometry approaches for quantification of histamine in biological samples.

Sample type	Derivatization reagent	Analytical method	LOQ (ng/mL)	Volume (μL)	LOQ (fmol)	Ref.
Mast cell and rat plasma	–	LC-MS/MS	15.6	10	1393	[16]
Human urine and serum	Methyl chloroformate	GC-MS/MS	112 (1.0 μM)	1	1000 (LOD)	[11]
Mouse cerebrospinal fluid (CSF)	–	LC-MS/MS	11.2 (0.1 μM)	4	400	[12]
Human urine	–	LC-MS/MS	4.8	5	215	[13]
Cell line	–	LC-MS/MS	0.3	10	26.8	[17]
Rat CSF	Benzoyl chloride	LC-MS/MS	0.224 (2 nM)	9	18 (LOD)	[18]
Plasma	–	LC-MS/MS	0.2	5	9.0	[14]
Rat brain dialysates	Propionic anhydride	LC-MS/MS	0.0834	10	7.45	[20]
Rat CSF	Benzoyl chloride	LC-MS/MS	0.1	5	4.46	[15]
Human blood	Phenylisothiocyanate	LC-MS/MS	0.1	2	1.79	[21]
Human CSF	4-Bromobenzenesulfonyl chloride	LC-MS/MS	0.0055	5	0.25	[22]
Serum	Diisopropyl phosphite (DIPP)	LC-MS/MS	0.0001	1	0.0009	Current method

microdialysis sampling approach is usually used to monitor the change of histamine, acting as a key neurotransmitter in central nervous system, and its concentration in dialysate is rather low, e.g. about 0.8 nM in dialysate of nucleus accumbens [18]. Moreover, the half-life of histamine is short because of the rapid inactivation by histamine-*N*-methyltransferase or diamine oxidase [19], about 1 min in the extracellular fluid. Besides, the high polarity results in the difficult separation with other endogenous components. Derivatization is a suitable method to solve above problems, and several derivatization reagents have been reported, such as methyl chloroformate [11], propionic anhydride [20], benzoyl chloride [15,18], phenylisothiocyanate [21], and 4-bromobenzenesulfonyl chloride [22] (Table 1). However, the sensitivities were not enough high, the microdialysate must be collected for at least 5 min in order to determine histamine in the brain [20]. This time is approximately 5 times of half-life, which means histamine may degrade during the collection. Thus, an ultra-sensitive and accurate approach is urgent for the quantification of histamine in biological samples.

It has been reported that *N*-dialkyloxyphosphoryl derivatization could improve the response of amino acids in the mass spectrometer [23]. Similar to amino acids, there is an amine group in histamine, which makes the introduction of dialkyoxyphosphoryl group possible. In the present study, an ultra-sensitive LC−MS/MS quantification method based on diisopropyl phosphite (DIPP)-derivatization, isotope dilution, and solid phase extraction (SPE) was developed. The LLOQ was 0.1 pg/mL, which is enough low to determine histamine in one cell and low nano-liter serum.

2. Material and methods

2.1. Chemicals and reagents

Histamine, histamine-α,α,β,β-d_4 dihydrochloride (histamine-d_4), and CCl_4 were purchased from Sigma-Aldrich (St. Louis, MO) and used without further purification. DIPP and absolute ethanol were obtained from Alfa Aesar Chemical Ltd (Lancashire, United Kingdom). Triethylamine (TEA), MS grade acetonitrile, methanol, and water were provided by Tedia (Fairfield, OH). Oasis MCX 3cc (60 mg) cartridge and 96-well μElution plate were produced by Waters Corporation (Milford, MA).

2.2. Preparation of solutions

The stock solutions of histamine and histamine-d_4 were prepared by dissolving the corresponding standards in water (MS grade) at a concentration of 10 μg/mL. Two series of working solutions were prepared to construct two calibration curves in different ranges, and the concentrations of histamine in series 1 were 20, 10, 5, 2.5, 0.5, 0.1, 0.05, and 0.01 ng/mL with 1 ng/mL of histamine-d_4 as internal standard (IS), while the concentrations in series 2 were 32, 16, 8, 2, 0.5, 0.1, and 0.02 pg/mL with 1 pg/mL of histamine-d_4 as IS. Two reaction solutions for *N*-phosphorylation labeling were prepared by mixing the corresponding reagents according to the following volume to volume ratios (A) ethanol−TEA (1:1) and (B) DIPP−CCl_4 (1:5). All solutions were kept at −20 °C for further use.

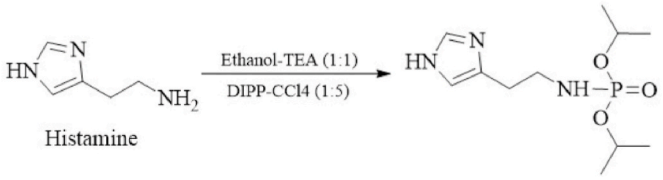

Fig. 1. Derivatization of histamine with DIPP.

2.3. Sample preparation

A modified Atherton-Todd reaction was used for *N*-phosphorylation derivatization (Fig. 1). Briefly, the individual working solution of histamine, diluted serum or cell culture supernatant (50 μL) was mixed with histamine-d_4 (2 μL), followed by drying with nitrogen gas. Then, the residue was dissolved in 10 μL H_2O and reacted with solution A (10 μL) and solution B (5 μL) for 1 min at room temperature. After drying with nitrogen gas, the residue was dissolved in 10 μL of 0.1% formic acid-containing H_2O and extracted by Waters 96-well μElution plate as follows. The cartridges were conditioned with methanol (100 μL) and equilibrated by 0.1 N HCl (100 μL). Then above reaction products were loaded onto the plate and washed with 100 μL of 0.1 N HCl and 100 μL of methanol successively followed by eluting with 100 μL of 5% ammonia-containing methanol to provide the analytes. Finally, the trap solution was removed using nitrogen and the products were dissolved in 50 μL methanol prior to LC−MS/MS analysis.

2.4. Primary mast cell culture

Peritoneal fluid from anesthetized male SD rat (300 ± 20 g) was collected by washing the peritoneal cavity with D-Tyrode's salt solution (D-TSS). D-TSS (15 mL) was injected into the peritoneal cavity, and the abdomen was gently massaged for approximately 5 min. The peritoneal cavity was carefully opened, and the fluid containing peritoneal cells was aspirated by Pasteur pipettes. The peritoneal cells were sedimented by centrifugation at 4 °C, 300 g for 10 min and resuspended in 0.75 mL TSS. Then 3.5 mL of 1.1 g/mL Percoll was added and gently mixed, and 0.5 mL TSS was added flat on the surface, centrifuged at 4 °C, 130 g for 10 min, the cells remained at the bottom of the Percoll gradient were collected. The collected cells were washed for 3 times with 3 mL of TSS by centrifugation at 4 °C, 200 g for 10 min. The cells, which contained mast cell above 90% identified by Toluidine Blue staining, were re-suspended in 90% Dulbecco's modified Eagle's medium (DMEM) and seeded in streaming tube (40,000 cells/mL/tube). Different concentrations of sinomenine, C48/80 or Triton X-100 were added to drug group, while DMEM was added to control group. All cells were incubated at 37 °C for 30 min, and then the supernatants were collected.

2.5. Serum samples of asthma patients and desensitized patients

A total of 45 serum samples were collected from 15 healthy children and 30 children with allergic asthma. Of the allergic asthma samples, 15 were collected from patients who had not received treatment, while 15 had received *Dermatophagoides pteronyssinus* subcutaneous immunotherapy (SCIT) for half a year (n = 6), one year (n = 4), and two years (n = 5), respectively. All patients completed questionnaires on the history of demographics and medical examination, and fulfilled the criteria of Allergic Rhinitis and its Impact on Asthma for allergic rhinitis. The serum was prepared by centrifuging at 3000 *g* for 10 min at 4 °C and kept at −80 °C. Then, 2 μL serum samples were collected and participated with 100 μL cold methanol followed by centrifugation at 13,000 rpm for 5 min at 4 °C. The extraction was repeated 2 times and the combined supernatants were dried under a nitrogen stream. The residue was stored at −20 °C before derivatization.

2.6. LC−MS conditions

An Agilent 1290 Ultra-high Performance Liquid Chromatography (UHPLC) consisting of an autosampler, thermostatted column compartment, and binary pump and equipped with a Thermo Syncronis aQ column (2.1 × 100 mm; 1.7 μm) was employed for the separation of components. The column temperature was maintained at 40 °C. The flow rate was 0.3 mL min^{-1} without any flow splitting, and the injection volume was 1 μL. The mobile phase comprised of 0.1% acetic acid and 20 mM ammonium acetate (A) and 0.1% acetic acid-containing acetonitrile (B) with the following gradient, 0–0.5 min: 5% B, 0.5–4.5 min: from 5% to 25% B, 4.5–6.5 min: from 25% to 95% B, 6.5–6.99 min: 95% B; 7 min: 5% B. The optimization of separation and derivatization was conducted on an Agilent 6550 quadrupole-time of flight mass spectrometry (Q-TOF-MS), while the quantification was conducted on an Agilent 6490 iFunnel triple quadrupole mass system (QQQ-MS) with a dual Jet Stream electrospray ion source (dual AJS ESI) in positive mode. The quantification was carried out by multiple reaction monitoring (MRM) mode with two transitions for each labeled compound, i.e. *m/z* 276.1 → 111.9 (quantifier) and 276.1 → 94.9 (qualifier) for histamine-DIPP and *m/z* 280.1 → 115.9 (quantifier) and 280.1 → 98.9 (qualifier) for histamine-d_4-DIPP at the collision cell energy of 30 eV. Other MS parameters were optimized by using the labeled histamine and set as follows: gas temperature at 225 °C, gas flow at 13 L/min, nebulizer pressure at 25 psig, sheath gas temperature at 275 °C, sheath gas flow at 12 L/min, capillary at 4000 V, nozzle voltage at 350 V.

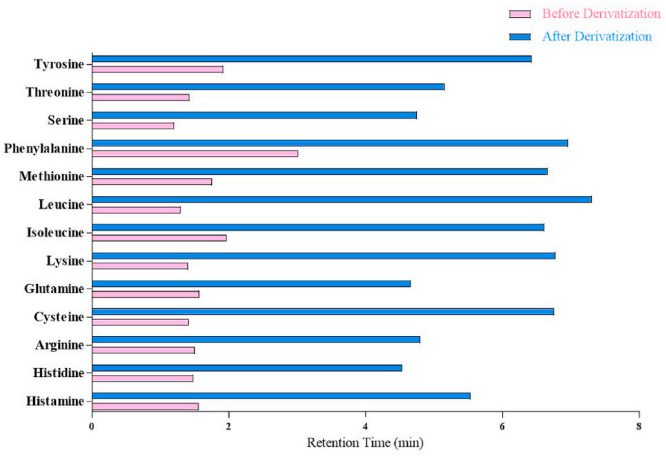

Fig. 2. Retention times of histamine and amino acids in DMEM without derivatization and after derivatization.

2.7. Method optimization

The reaction time was optimized by collecting the reaction solution at different times (1, 2, 5, 10, 15, 17, 20, and 30 min) followed by LC−MS analysis. The effect of SPE was evaluated by three groups of experiments, i.e. no SPE purification, MCX cartridge purification, and HLB cartridge purification. Four kinds of ultra-performance liquid chromatography columns, Waters Acquity UPLC BEH C18 (2.1 × 100 mm; 1.7 μm), Agilent Eclipse C18 (2.1 × 100 mm; 1.7 μm), Thermo Syncronis aQ (2.1 × 100 mm; 1.7 μm), and Phenomenex Luna Omega (2.1 × 100 mm; 1.6 μm), were compared to obtain better separation and MS response.

2.8. Method validation

The calibration curves were constructed by plotting the peak area ratios of histamine-DIPP (*m/z* 276.1 → 111.9) to the internal standard of histamine-d_4-DIPP (*m/z* 280.1 → 115.9) against the concentrations. The ratio of the quantifier and qualifier ions was applied for the confirmation of histamine-DIPP and histamine-d_4-DIPP, and if the ratio exceeds ±30% of the corresponding standard, the peak will not be considered as histamine-DIPP or histamine-d_4-DIPP. The repeatability and reproducibility were separately assessed using the intra-day and inter-day variations determined from replicate analyses of samples at three concentrations of 0.05, 2.5, and 20 ng/mL in series 1, as well as 0.5, 2, and 16 pg/mL in series 2, respectively, on three consecutive days. Accuracy was evaluated by the percentage ratios of measured concentrations to the real concentrations of quality control samples at 0.05, 2.5, and 20 ng/mL in series 1 and 0.5, 2, and 16 pg/mL in series 2. Recovery was performed by spiking the working solutions of histamine and histamine-d_4 into diluted blank serum or DMEM at three concentrations, 0.05, 2.5, and 20 ng/mL in series 1 as well as 0.5, 2, and 16 pg/mL in series 2, respectively, and calculated by the equation of (concentration of spiked sample – non-spiked concentration)/spiked concentration × 100. Stability of histamine-DIPP in DMEM and serum was determined at 4 °C within 72 h, and calculated by the comparison of the measured concentration with the prepared concentration. The lower limit of quantitation (LLOQ) was calculated as the concentrations for which the precision is lower than 15% and the accuracy is within 100% ± 20%.

2.9. Data analysis

The data were acquired and processed with MassHunter Workstation B.06.00 (Agilent). The performance of the discriminant model was characterized by estimating the area under the receiver operating characteristic (ROC) curve (AUC) using SPSS (IBM SPSS Statistics 19.0), and the optimal cut-off value, specificity, sensitivity, and accuracy were calculated. The multivariate analysis of histamine in group discrimination was measured by t-test using GraphPad Prism 5. The difference with $p < 0.05$ was considered as significant.

3. Results and discussion

3.1. Derivatization and solid phase extraction clean-up

Histamine has high polarity, and it is poorly retained even on hydrophilic interaction liquid chromatography and amide columns. Moreover, its structure and retention on column are very similar to that of amino acids, hence high contents of amino acids in cell culture medium and biological samples largely interfere the detection of histamine, e.g. histamine at 4.2 ng/mL was buried in the peaks of amino acids in DMEM (Fig. S1A).

Derivatization of small molecules prior to mass spectrometry analysis has been widely employed to make it more suitable for qualitative and quantitative analysis in LC-MS. Along with the development of new matrices and materials, much attention has been paid to improve the

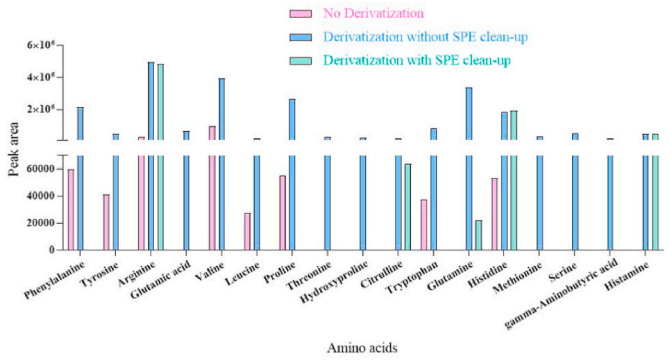

Fig. 3. MS responses of histamine and amine-containing compounds in DMEM without derivatization, derivatization without SPE clean-up, and derivatization with SPE clean-up.

sensitivity by the derivatization during the past decade. The Atherton-Todd reaction is a common method applied for improving the sensitivity of primary or secondary amines by the formation of dialkylphosphite [23,24]. There is an amine group in histamine (Fig. 1), consequently, a derivatization of histamine with DIPP was applied in this research.

The reaction condition was first optimized. The results indicated that the reaction had no significant difference when conducting for different times from 1 to 30 min at room temperature or using the common method (Fig. S2), in which the sample mixed with solution A and then solution B was added slowly in an ice-water bath followed by 30 min incubation at room temperature [24,25]. Hence, the reaction time was set at 1 min.

After derivatization, the retention time of histamine-DIPP is delayed to 5.6 min, while histamine was flushed out at about 1.5 min (Fig. 2 and S1). Although the amino acids in the DMEM were also derivatized, their retention times were different to histamine-DIPP (Fig. 2), which resulted in standing out of histamine from the matrix (Fig. S1). At the same time, the MS response also significantly increased after derivatization (Fig. 3), because the introduced neutral phosphoryl group had high gas-phase affinity [25,26].

However, other co-eluted components still influence the determination of histamine, thus, four different columns were tried to separate them. While a Thermo Syncronis aQ column gave better result, the interference could not be eliminated completely. Therefore, a clean-up procedure was conducted to remove them. Two kinds of SPE columns, Oasis HLB and MCX, were tested. HLB is a polymeric SPE sorbent and widely used to purify the compounds with acidic, basic, or neutral properties from a wide spectrum of matrices. However, the result for the purification of histamine-DIPP was not satisfied. Considering there is an alkaline imidazole group in histamine, the Oasis MCX, a mixed-mode cation-exchange polymeric sorbent column should be a better choice. It can absorb histamine and alkaline components in acidic condition to remove the impurities or other acidic and neutral components in biological samples due to the dual modes of retention, ion exchange and reversed phase. Then the weak alkaline components, e.g. amino acids, can be eluted out with methanol, while histamine could not be flushed out until stronger basic solution, 5% ammonia-containing methanol is applied. As expected, the impurities and most of amino acids were removed or dramatically decreased except arginine and histidine, while the peak area of histamine had no significant difference (Fig. 3 and S1). The strong retention of arginine and histidine should be due to the existence of basic group, guanidine and imidazole, respectively. In addition, citrulline and glutamine had also relative weak retention due to the carbamoyl amino and amide groups. Whatever, the remaining amino acids had different retention times and MS characterization, and had no interference for the determination of histamine.

Table 2
Precision, accuracy, and recovery of histamine in DMEM and human serum samples.

Series	Spiked conc. (pg/mL)	Precision		Accuracy (%)	Recovery (%)	
		Intra-day variation (%)	Inter-day variation (%)		Serum	DMEM
Series 1	20,000	5.11	7.91	105.80	96.27	96.05
	2500	0.13	0.49	88.01	94.59	96.73
	50	1.50	3.06	103.53	95.74	99.27
Series 2	16	1.12	1.94	102.93	93.26	96.15
	2	3.71	4.78	110.83	86.78	89.77
	0.5	10.21	14.29	108.75	81.33	83.49

3.2. Development of quantification approach

The quantification method was developed using UHPLC−QQQ−MS/MS. The transitions of *m/z* 276.1 → 111.9 and 276.1 → 94.9 were selected for the quantification and qualification analyses, respectively. In order to accurately quantify the content, histamine-d_4, an isotope labeled histamine, was employed as IS. And the ratios of histamine at *m/z* 276.1 → 111.9 to histamine-d_4 at *m/z* 280.1 → 115.9 were set as Y-variations for the construction of calibration curve.

Calibration curve and sensitivity. To cover a wide concentration range of histamine, two calibration curves with different concentration of histamine-d_4 as IS were constructed. Good linearities with r^2 of 0.9987 and 0.9979 were obtained by weighted least-squares regression (weighting 1/x) in the range from 0.01 to 20 ng/mL and from 0.1 to 32 pg/mL, and the equations were $y = 0.97x + 0.031$ and $y = 1.11x - 0.029$, respectively. The LLOQ was considered as the lowest concentration at the calibration curve with the precision and accuracy of $\leq \pm 15\%$ and 80–120%, i.e. 0.1 pg/mL, while histamine at 0.02 pg/mL could also be detected. It was around 278 times lower than that reported before [15, 20–22] (Table 1).

Precision and accuracy. Inter-day and intra-day variations at three concentrations in series 1 and 2 were determined to assess the precision, and the variations were less than 15%. The accuracies at three concentrations were between 88% and 111%. High recoveries (81%–100%) were obtained at high, medium, and low concentration spiked in diluted serum and DMEM, respectively, which implied that other components in the real samples had no evident influence on the whole procedure, including the reaction, SPE clean-up and LC−MS analysis (Table 2).

Stability. Samples were stable at 4 °C within 72 h. The measured concentrations were between 90% and 107% of the prepared concentrations.

3.3. Application

The developed method was applied to determine histamine in mast cells and serum samples of asthma patients.

Histamine analysis in rat primary mast cell culture. Mast cell is a kind of granulocyte and contains many granules. After being stimulated by pathogens or other allergens, mast cell releases the mediators, e.g. histamine, to defense them by degranulation. In the present study, two reagents of C48/80 and triton X-100, which promote the release of histamine, were first used to assess the feasibility of this method. By comparison with the control, C48/80 and triton X-100 evidently induced the release of histamine about 2 and 3 times, respectively (Fig. 4A). Then, this method was further employed to determine the effect of sinomenine, a medicine used to treat rheumatoid arthritis in clinic, on the histamine release. Occasional allergy cases of sinomenine have been reported [26], which might be related to the cell degranulation [27]. Using this new developed method, histamine released into the medium was determined. It was found that the release of histamine increased along with the concentrations of sinomenine from 1 to 400 μM (Fig. 4B). The number of cell was about 40,000/well/tube, accordingly

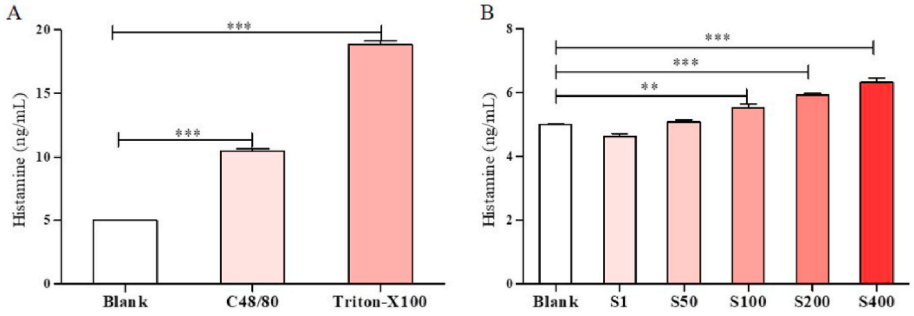

Fig. 4. Histamine release in (A) C48/80 and triton X-100 treated cell line and control; (B) Sinomenine treated cell line at 1, 50, 100, 200, and 400 μM and control. **, $p < 0.01$, ***, $p < 0.001$ compared with blank.

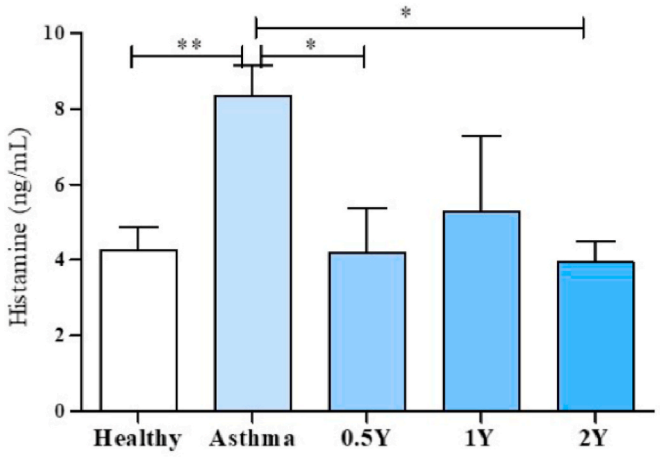

Fig. 5. Histamine contents in asthma patients and de-sensitization treatment patients after 0.5 year (0.5Y), 1 year (1Y) and 2 years' (2Y) treatment. *, $p < 0.05$; **, $p < 0.01$ compared with healthy group.

the average release amount of each cell was calculated to be around 0.125 pg/mL, which is higher than the LLOQ. It means that the sensitivity is enough to determine the histamine released by one cell.

Histamine analysis in serum samples of asthma patients. Asthma, a complex and increasingly prevalent airway syndrome, is most often related to an allergic phenotype. SCIT is effective to treat allergic asthma. Histamine is a popular inflammatory mediator intimately associated with the pathologic allergy [28]. The above-established method was applied to determine the contents of histamine in asthma patients and desensitization treatment patients. The content of histamine was found to increase in asthma patients compared with healthy controls, and decrease after half a year (0.5 Y), one year (1 Y) and two years' (2 Y) SCIT treatment (Fig. 5). We found that the content of histamine in serum ranged between 1 and 14 ng/mL in serum, which means that the low nano-liter of serum was enough for the determination the content of endogenous histamine.

4. Conclusions

An ultra-sensitive UHPLC-QQQ-MS/MS approach was developed to quantify histamine in biological samples. This method, adopting DIPP as the derivatization reagent, improves the ionization efficiency and the hydrophobicity. Furthermore, MCX SPE purification removes most of the impurities and decreases the interference. Finally, the LLOQ reached to 0.1 pg/mL, which is sensitive enough to detect the histamine in one cell and low nano-liter of serum.

Credit Author Statement

Xiaolan Hu: Methodology, Investigation, Writing-Original draft preparation. **Xiqing Bian**: Methodology, Investigation, Writing-Original draft preparation. **Wan-Yi Gu**: Methodology, Investigation. **Baoqing Sun**: Instruction, Resources. **Xiang Gao**: Methodology. **Jian-Lin Wu**: Conceptualization, Supervision, Project administration, Writing-Review & Editing. **Na Li**: Conceptualization, Supervision, Funding acquisition, Writing-Review & Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2020.122056.

References

[1] A. Pino-Angeles, A. Reyes-Palomares, E. Melgarejo, F. Sanchez-Jimenez, Histamine: an undercover agent in multiple rare diseases? J. Cell Mol. Med. 16 (9) (2012) 1947–1960. https://doi/10.1111/j.1582-4934.2012.01566.x.
[2] C.A. Akdis, K. Blaser, Histamine in the immune regulation of allergic inflammation, J. Allergy Clin. Immunol. 112 (1) (2003) 15–22, https://doi.org/10.1067/mai.2003.1585.
[3] M.R.-D.E. Schneider, M. Arock, M. Dy, Trends in histamine research: new functions during immune responses and hematopoiesis, Trends Immunol. 23 (5) (2002) 255–263, https://doi.org/10.1016/s1471-4906(02)02215-9.
[4] W.W. Hu, Z. Chen, Role of histamine and its receptors in cerebral ischemia, ACS Chem. Neurosci. 3 (4) (2012) 238–247, https://doi.org/10.1021/cn200126p.
[5] M.F. Hide, D. M, C.E. Grattan, J. Hakimi, J.P. Kochan, M.W. Greaves, Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria, N. Engl. J. Med. 328 (22) (1993) 1599–1604. https://doi/10.1056/NEJM199306033282204.
[6] X.D. Yang, W. Ai, S. Asfaha, G. Bhagat, R.A. Friedman, G. Jin, H. Park, B. Shykind, T.G. Diacovo, A. Falus, T.C. Wang, Histamine deficiency promotes inflammation-associated carcinogenesis through reduced myeloid maturation and accumulation of CD11b+Ly6G+ immature myeloid cells, Nat. Med. 17 (1) (2011) 87–95. https://doi/10.1038/nm.2278.
[7] A.I. Ujike, M. Ono, T. Yuasa, T. Yoshino, M. Fukumoto, J.V. Ravetch, T. Takai, Modulation of immunoglobulin (Ig)E-mediated systemic anaphylaxis by low-affinity Fc receptors for IgG, J. Exp. Med. 189 (10) (1999) 1573–1579. https://doi/10.1084/jem.189.10.1573.
[8] T. Yoshitake, F. Ichinose, H. Yoshida, K.-i. Todoroki, J. Kehr, O. Inoue, H. Nohta, M. Yamaguchi, A sensitive and selective determination method of histamine by HPLC with intramolecular excimer-forming derivatization and fluorescence

detection, Biomed. Chromatogr. 17 (8) (2003) 509–516, https://doi.org/10.1002/bmc.264.
[9] R.H.D. Jackson JA, S. Neathery, C. Revard, Histamine levels in health and disease, J. Orthomol. Med. 13 (4) (1998) 236–240.
[10] R.Y. Lin, L.B. Schwartz, A. Curry, G.R. Pesola, R.J. Knight, H.S. Lee, L. Bakalchuk, C. Tenenbaum, R.E. Westfal, Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study, J. Allergy Clin. Immunol. 106 (1 Pt 1) (2000) 65–71. https://doi/10.1067/mai.2000.107600.
[11] H.F. Kvitvang, T. Andreassen, T. Adam, S.G. Villas-Boas, P. Bruheim, Highly sensitive GC/MS/MS method for quantitation of amino and nonamino organic acids, Anal. Chem. 83 (7) (2011) 2705–2711. https://doi/10.1021/ac103245b.
[12] M.E. Blanco, O.B. Mayo, T. Bandiera, D.P. Tonelli, A. Armirotti, LC-MS/MS analysis of twelve neurotransmitters and amino acids in mouse cerebrospinal fluid, J. Neurosci. Methods 341 (2020), 108760, https://doi.org/10.1016/j.jneumeth.2020.108760.
[13] F. Gosetti, E. Mazzucco, M.C. Gennaro, E. Marengo, Simultaneous determination of sixteen underivatized biogenic amines in human urine by HPLC-MS/MS, Anal. Bioanal. Chem. 405 (2–3) (2013) 907–916, https://doi.org/10.1007/s00216-012-6269-z.
[14] J. Liu, L. Wang, W. Hu, X. Chen, D. Zhong, Development of a UHPLC-MS/MS method for the determination of plasma histamine in various mammalian species, J. Chromatogr. B 971 (2014) 35–42. https://doi/10.1016/j.jchromb.2014.08.043.
[15] H. Tsutsumi, K. Yonemitsu, A. Sasao, Y. Ohtsu, S. Furukawa, Y. Nishitani, Cerebrospinal fluid neurotransmitter levels and central nervous system depression in a rat drug overdose model, Toxicol. Mech. Methods 30 (2) (2020) 139–145, https://doi.org/10.1080/15376516.2019.1672122.
[16] K.C. Chimalakonda, E. Pang, J.L. Weaver, K.E. Howard, V. Patel, M.T. Boyne, 2nd, Development and validation of a liquid-chromatography tandem mass spectrometry method to determine in vitro and in vivo histamine release, J. Pharmaceut. Biomed. Anal. 102 (2015) 494–499, https://doi.org/10.1016/j.jpba.2014.10.016.
[17] J. Koyama, S. Taga, K. Shimizu, M. Shimizu, I. Morita, A. Takeuchi, Simultaneous determination of histamine and prostaglandin D2 using an LC-ESI-MS/MS method with positive/negative ion-switching ionization modes: application to the study of anti-allergic flavonoids on the degranulation of KU812 cells, Anal. Bioanal. Chem. 401 (4) (2011) 1385–1392. https://doi/10.1007/s00216-011-5200-3.
[18] P. Song, O.S. Mabrouk, N.D. Hershey, R.T. Kennedy, In vivo neurochemical monitoring using benzoyl chloride derivatization and liquid chromatography-mass spectrometry, Anal. Chem. 84 (1) (2012) 412–419, https://doi.org/10.1016/j.jpba.2019.04.025.
[19] L.N. Maintz N, Histamine and histamine intolerance, Am. J. Clin. Nutr. 85 (5) (2007) 1185–1196. https://doi/10.1021/ac202794q.
[20] E. Bourgogne, F.X. Mathy, D. Boucaut, H. Boekens, O. Laprevote, Simultaneous quantitation of histamine and its major metabolite 1-methylhistamine in brain dialysates by using precolumn derivatization prior to HILIC-MS/MS analysis, Anal. Bioanal. Chem. 402 (1) (2012) 449–459. https://doi/10.1093/ajcn/85.5.1185.
[21] K.Y. Kim, H.J. Kwon, S.H. Cho, M. Nam, C.W. Kim, Development and validation of a highly sensitive LC-MS/MS method for in vitro measurement of histamine concentration, J. Pharmaceut. Biomed. Anal. 172 (2019) 33–41, https://doi.org/10.1007/s00216-011-5224-8.
[22] M. Croyal, Y. Dauvilliers, O. Labeeuw, M. Capet, J.C. Schwartz, P. Robert, Histamine and tele-methylhistamine quantification in cerebrospinal fluid from narcoleptic subjects by liquid chromatography tandem mass spectrometry with precolumn derivatization, Anal. Biochem. 409 (2011) 28–36, https://doi.org/10.1016/j.ab.2010.09.045.
[23] Y. Chen, J. Zhang, J. Chen, X.Y. Cao, J. Wang, Y.F. Zhao, Sensitivity improvement of amino acids by N-terminal diisopropyloxyphosphorylation in electrospray ionization mass spectrometry, Rapid Commun. Mass Spectrom. 18 (4) (2004) 469–473. https://doi/10.1002/rcm.1356.
[24] X. Chen, D. Gao, F. Liu, X. Gao, S. Wang, Y. Zhao, H. Liu, Y. Jiang, A novel quantification method for analysis of twenty natural amino acids in human serum based on N-phosphorylation labeling using reversed-phase liquid chromatography-tandem mass spectrometry, Anal. Chim. Acta 836 (2014) 61–71. https://doi/10.1016/j.aca.2014.05.053.
[25] X. Gao, X. Bi, J. Wei, Z. Peng, H. Liu, Y. Jiang, W. Wei, Z. Cai, N-phosphorylation labeling for analysis of twenty natural amino acids and small peptides by using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, Analyst 138 (9) (2013) 2632–2639, https://doi.org/10.1039/c3an00036b.
[26] T.W. Kok, P.Y. Yue, N.K. Mak, T.P. Fan, L. Liu, R.N. Wong, The anti-angiogenic effect of sinomenine, Angiogenesis 8 (1) (2005) 3–12. https://doi/10.1007/s10456-005-2892-z.
[27] L. Huang, J. Pi, J. Wu, H. Zhou, J. Cai, T. Li, L. Liu, A rapid and sensitive assay based on particle analysis for cell degranulation detection in basophils and mast cells, Pharmacol. Res. 111 (2016) 374–383. https://doi/10.1016/j.phrs.2016.05.033.
[28] P.J. Dunford, S.T. Holgate, The Role of Histamine in Asthma, Histamine in Inflammation, Springer2010, pp. 53-66.